RESEARCH ARTICLE

Investigation of Edaravone Degradation and Stabilization through Solid Dispersions with Kollidone VA64

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Received: 19th July 2024; Revised:3rd Aug, 2024; Accepted:11th Aug, 2024; Available Online: 31st August, 2024

ABSTRACT

Edaravone (EDA) is an effective antioxidant that is easily degraded, which diminishes its therapeutic efficiency. The present study assessed the hydrolytic and oxidative degradation of edaravone and its solid dispersion with Kollidon VA 64, a water-soluble polymer. The characterization of the edaravone and solid dispersion was done by Fourier Transform Infrared Spectroscopy, X-ray diffraction, and Differential Scanning Calorimetry. The results revealed that edaravone undergoes extensive degradation under hydrolytic conditions at pH 2, 5, 7, 10 with the following respective rate constant K: 0.00983 through 0.0107, 0.01279, and up to 0.0201 min^{-1}, as well as under oxidative conditions in 3% H_2O_2 with a K of 0.00924 min^{-1}. The stability of solid dispersion with KVA 64 was greater with a reduced degradation rate constant of 0.00326, 0.00109, 0.00145, 0.00277 min^{-1} in pH 2, 5, 7, 10, respectively, and under oxidative conditions in 3% H_2O_2 with a rate constant K 0.00392 min^{-1}. The study provides valuable insights into the degradation kinetics and stabilization of edaravone using solid dispersion.

Keywords: Edaravone, Kollidon VA64, Solvent Evaporation, Solid dispersion

How to cite this article: Sadhana Gautam, Shagufta Khan. Investigation of Edaravone Degradation and Stabilization through Solid Dispersions with Kollidone VA64. International Journal of Pharmaceutical Quality Assurance. 2024;15(3): 2041-2048. DOI: 10.25258/ijpqa.15.3.140

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a unique scavenger of free radicals and the first therapeutically utilised neuroprotective for acute cerebral infarction.[1] It significantly enhances regional blood flow post-cerebral infarction by reducing brain edema. Its low molecular weight allows it to cross the blood-brain barrier, extending its therapeutic effects beyond the vascular compartment.[1] Edaravone (EDA) also shows promise in various other applications: it inhibits hepatic steatosis and apoptosis in rats and suppresses CCl4-induced elevated levels of total bilirubin, LDH, and ALT.[2] It also defends rats against cisplatin nephrotoxicity.[3] and reduces the precursors of free radicals and their metabolites in rats with burn injuries.[4] In a hemorrhagic shock model, EDA was found to reduce bacterial translocation and intestinal neutrophil lipid peroxidation.[5] Additionally it also safeguards mice by blocking peroxynitrite production against methamphetamine-induced neurotoxicity in the striatum.[6] Furthermore, edaravone prevents liver injury and improves survival in LPS-treated rats by inhibiting inflammatory cell recruitment, and cytokine expression, and increasing 4-hydroxynonenal-modified proteins in the liver.[7] In an acute Crohn's disease model in rats, EDA was found to reduce the histological damage, ulcer index and oxidative damage markers, ameliorating mesenteric indomethacin-induced small intestine ulcers.[8] It also holds promise for the treatment of various lung disorders.[9] including ischemia/reperfusion (I/R) injury, sepsis, and fibrosis.[10] Despite its therapeutic potential, edaravone's weak solubility and stability hinder its suitability for oral administration, and thus far, an oral formulation has not been clinically successful.[11] There are some investigations on the development of complexes of EDA and conformers to enhance their solubility and stability. Patel and Wairkar used bile salts as conformers to create EDA's amorphous dispersions to improve their stability and solubility.[12] Zeng et al created an inclusion complex of EDA with hydroxypropyl-β-cyclodextrin (HP-β-CD) by a freeze-drying method that significantly improved the EDV's solubility and bioavailability.[13] Jindal explored the formation of EDA inclusion complexes with β-CD using microwave irradiation and, demonstrated increased stability and efficacy.[14] Teng et al attempted to design a temperature-sensitive hydrogel (TGS) containing an inclusion complex of EDA and borneol (EDV-BP TSG), providing controlled release and enhanced therapeutic effects.[15] Rahim et al explained the molecular interactions and stability of the β-cyclodextrin/EDV complex using advanced computational techniques including PM3, DFT, HF, and various ONIOM2.[16] Parikh et al developed EDA-loaded lipid-based nanosystems, accomplishing improved drug delivery and neuroprotective effects.[17] These advancements unveiled a variety of approaches and innovative methods to upheave EDA's therapeutic capability. However, there is a handful of research on EDA's degradation behavior under stress conditions and approaches for its stability improvement. Consequently, it is vital to conduct thorough stability

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Table No. 1: EDA content in EDA-KVA64-SD

Ratio of EDA: KVA64	Nature of solid dispersion	Weight in mg of EDA per 100 mg EDA-KVA64-SD
1 : 1	White free-flowing powder	20.05±0.25

studies on EDA and identify methods to enhance its stability. In the current investigation, the degradation behavior of EDA under stress conditions was examined and to enhance its stability, solid-state amorphization with Kollidon VA64 was utilized as a stabilization technique.

MATERIAL AND METHOD

Chemicals and Reagents

Edaravone (EDA) was procured from M/s. Samrudh Pharmaceuticals. Boisar, Mumbai, India. Polymer Kollidon VA 64 received from Trans Chem Corporation Pharma Private Limited Mumbai, India. Methanol, ethanol, and HPLC grade water were obtained from LOBA Chemie, Mumbai, India.

Instrumentation and chromatographic conditions

Chromatography was completed by the Shimadzu HPLC System (Jasco Corporation, Koyto, Japan), comprising of the HPLC pump with Quaternary (Gradient System), UV detector, and 30w high-resolution UV lamp and C18 column (4.6 mm × 250 mm × 5µm). Compounds were separated at room temperature (25 ± 2°C) on the C18 reversed-phase column, with Methanol: Distilled water: TEA (70:30:01 V/V/V) mobile phase, at a 1.0 ml/minute flow rate. Prior to use, the mobile phase was sonicated and filtered through a 20 µm filter paper. The wavelength for detection was set at 243 nm.

Standard solution preparation

Stock solution of 1 mg/ml was prepared by dissolving accurately weighed 10 milligrams of EDA in 10 ml of methanol. Furthermore, standard solutions in the concentration range of 0.50 to 10.00 µg/ml were obtained by diluting the stock solution with the mobile phase.

Preparation of solid dispersions with Kollidon VA64 (KVA64)

Solid dispersion was prepared by solvent evaporation method with EDA and polymer Kollidon VA64 in different ratios (1:1, 1:2 and 1:3). In a Petri dish EDA and KVA64 were dissolved in a sufficient amount of methanol and the solvent was eliminated by evaporation at room temperature.[18] Solid dispersion (EDA-KVA64-SD) having

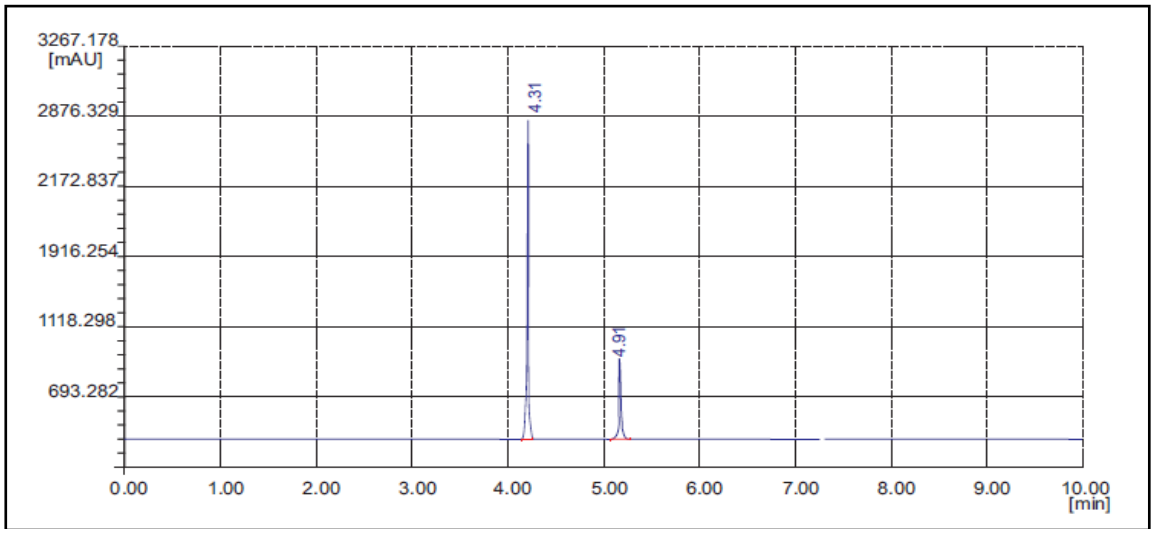

Figure No. 1: HPLC Chromatogram of EDA in 0.01N HCL (pH2) at 30 minute

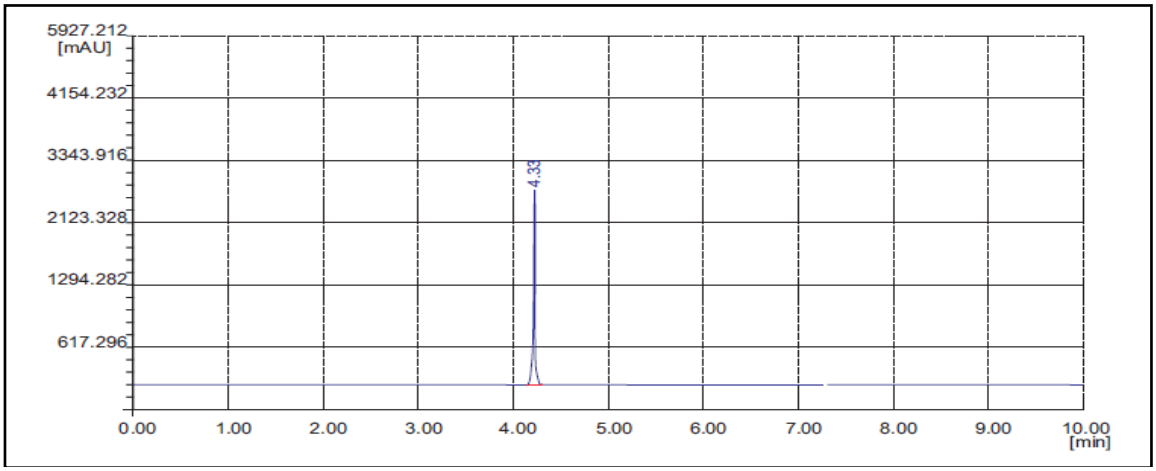

Figure No. 2: HPLC Chromatogram of EDA-KVA64-SD in 0.01N HCL (pH2) at 90 minute

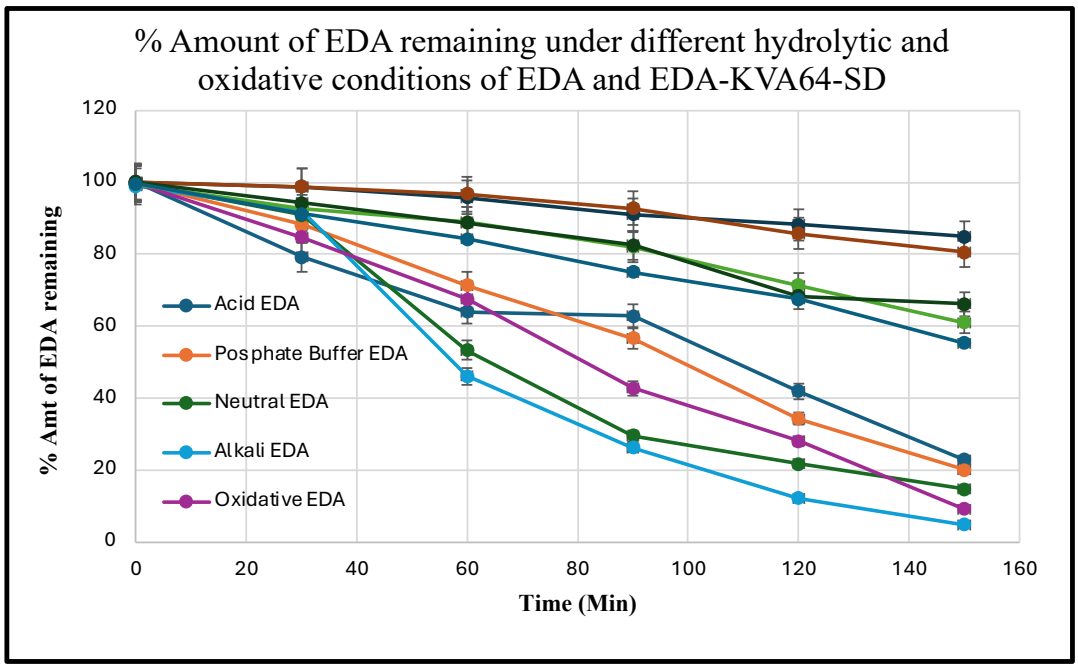

Figure No. 3: Time verses % Amount of EDA remaining under different hydrolytic and oxidative degradation of EDA and EDA-KVA64-SD

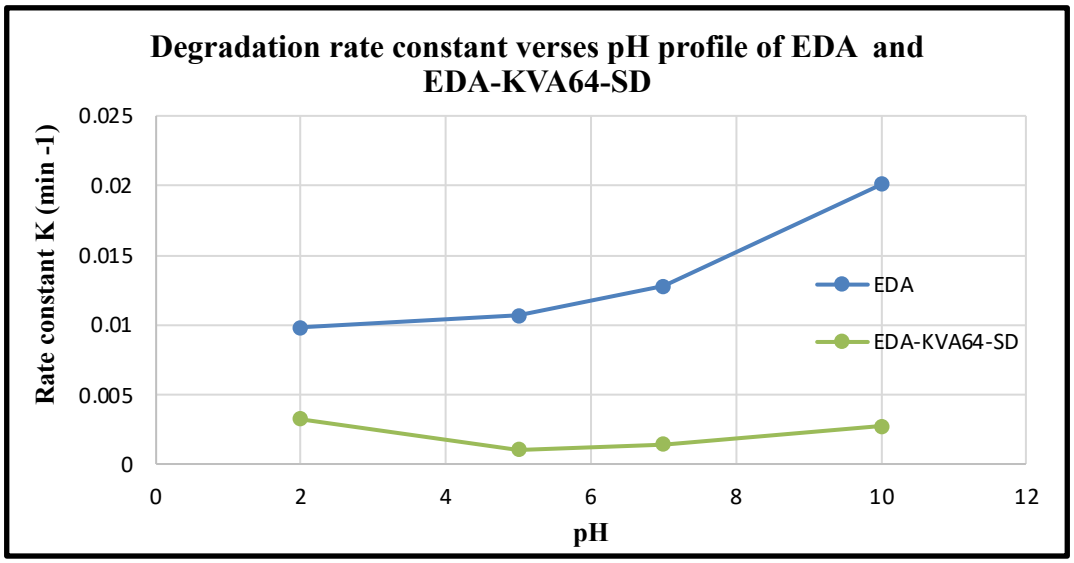

Figure No. 4: Degradation rate constant K (min $^{-1}$) verses pH profile of EDA and EDA-KVA64-SD

1:1 ratio of EDA and KVA64 produced white, free flowing solid, therefore it was stored in desiccators (over silica gel) for 48 hours, then crushed and used for further investigation. The EDA content of solid dispersion was estimated by dissolving 100 mg of EDA-KVA64-SD in 100 ml methanol. The resulting solution was properly diluted and analysed by HPLC according to the method prescribed previously. (Table No. 1)

Solution state degradation rate determination of EDA and EDA-KVA64-SD

Hydrolytic and oxidative degradation

Hydrolytic degradation of EDA and EDA-KVA64-SD was carried out by using 0.01N HCL (pH2), Phosphate buffer (pH 5), water (pH 7), 0.01N NaOH (pH 10), and oxidative degradation by using 3% H_2O_2 in water (pH 4.5).[19] Ten mg of EDA and weight of EDA-KVA64-SD equivalent to 10 mg of EDA were added to the mentioned various solvents at room temperature for different degradation conditions. For the analysis, 0.1 ml of the solution was withdrawn after every 30 minutes and diluted using 10 ml mobile phase to obtained final concentration of 1.0 µg/ml. The chromatograms were recorded under the above conditions after injected 10 microliters of the resultant solution into the HPLC system. (Figure No. 1, 2 3, 4 and 5)

Characterization of EDA-KVA64-SD

Fourier Transform Infrared Spectrophotometer (FTIR)

The FTIR spectra of EDA, KVA 64, and EDA-KV64-SD were analyzed using an FTIR spectrophotometer (FTIR-8400 S, Shimadzu Corporation, Kyoto, Japan) to examine the interaction between the EDA and KVA64, as well as to characterize the EDA-KVA64-SD. The samples were

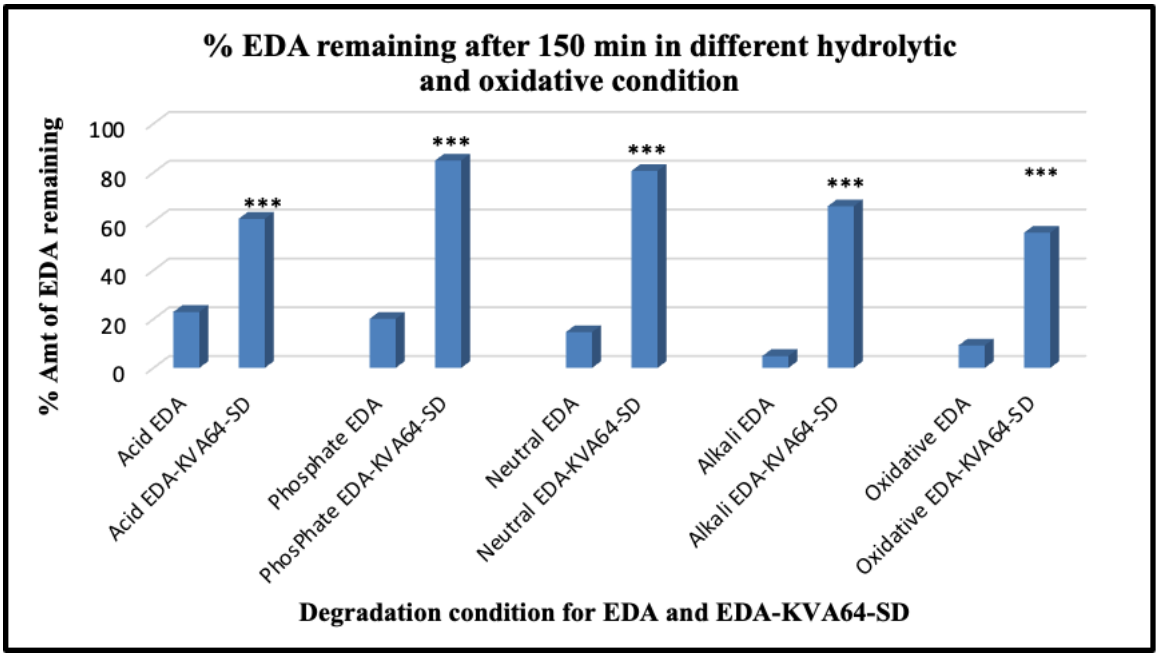

Figure No. 5: % EDA remaining after 150 minute in different hydrolytic and oxidative condition
***EDA-KVA64-SD showed significant difference ($p<0.01$) with respect to EDA in all the conditions tested.

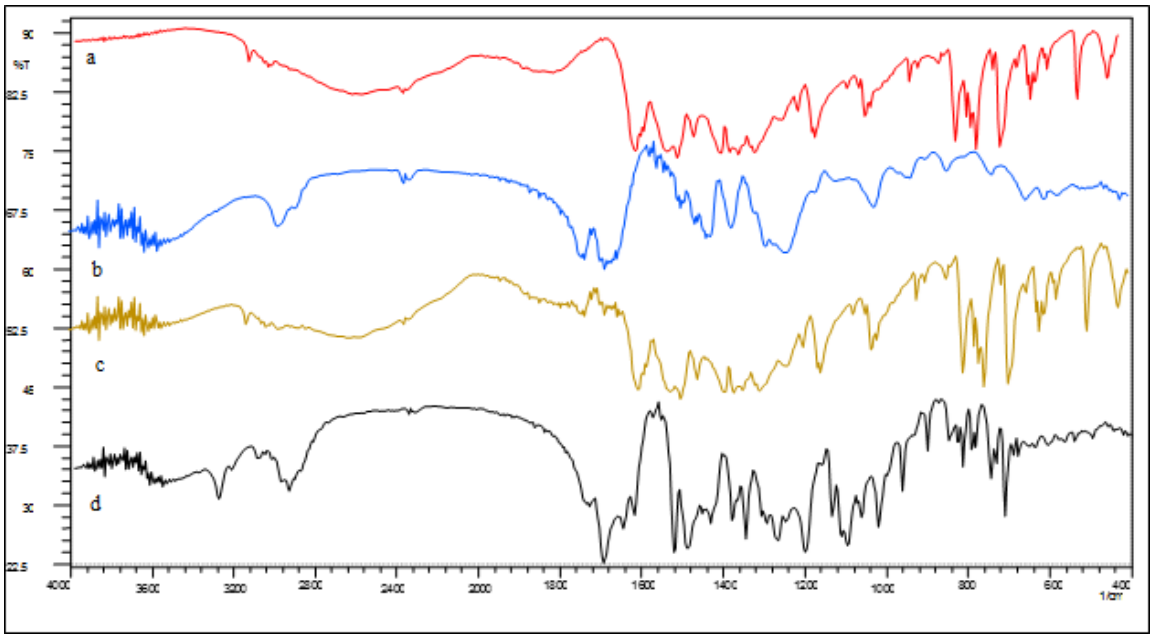

Figure No. 6: FTIR spectrum of a) EDA, b) KVA64, c) Physical mixture of EDA and KVA64 d) EDA-KVA64-SD

produced in KBr discs (2.0 mg sample in 200 mg KBr) and the 400-4000 cm^{-1} sampling range was used. (Figure No. 6)

X-ray powder diffraction (XRD)

The crystallinity of the powder EDA, KVA64, and EDA-KVA64-SD was assessed using High-resolution X-ray diffraction (HR XRD, Malvern Panalytical, Worcestershire, United Kingdom). The analysis was conducted under conditions of 40 kV voltage and 40 mA current at room temperature. A scanning rate of 0.1°/sec was applied across a 2θ range from -100° to 1600°. (Figure No. 7)

Differential Scanning Calorimetry (DSC)

DSC analysis was conducted on EDA, KVA64, and EDA-KVA64-SD using a differential scanning calorimeter (DSC 60, Shimadzu Corporation, Kyoto, Japan). The samples were sealed in aluminum pans and placed alongside an empty reference pan on a thermoelectric disk within a furnace. The measurements were conducted at a pressure range of 0.0001 to 1,000 psi, with a heating rate varying from 0.01 to 100°C per minute. (Figure No. 8)

Accelerated Stability Testing

For the accelerated stability study samples of EDA-KVA64-SD, were kept at $25^0C\pm 2^0C$ and 60% ± 5% relative humidity (RH) and at $40^0C\pm 2^0C$ and 75% ± 5% RH in stability chamber (WIL198, Wadegati Labequip) for six months. For analysis, 10 mg equivalent to EDA, the sample of solid dispersion was withdrawn and added to 100 ml

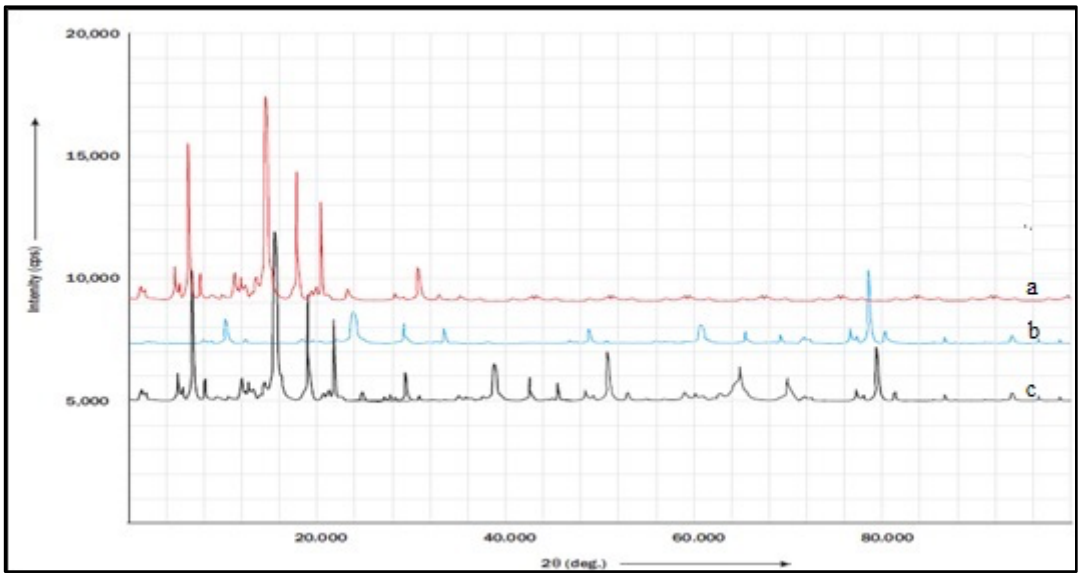

Figure No. 7: XRD of a) EDA, b) KVA64 and c) EDA-KVA64-SD

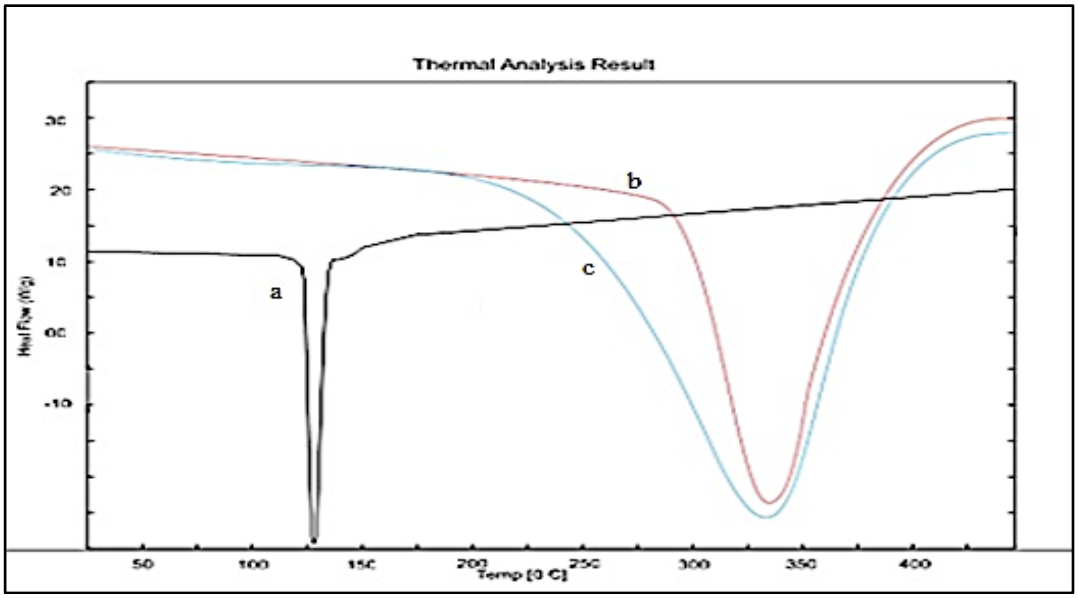

Figure No. 8: DSC Thermo gram of a) EDA, b) KVA64 and c) EDA-KVA64-SD

mobile phase. For analysis, 0.1 ml solution was taken out and treated with 10 ml mobile phase to produce 1.0 µg/ml concentration. The chromatograms were recorded after injecting 10 microliters of the resulting solution into the HPLC system. (Table No. 2)

Statistical Analysis

Results of stability evaluation of EDA and EDA-KVA64-SD were compared by repeated measures AVONA with Tukey-Kramer Multiple Post-Adhoc comparison test when $P < 0.05$. (Figure No.8)

RESULT AND DISCUSSION

Hydrolytic and oxidative degradation of EDA and EDA-KVA64-SD

Hydrolysis may be trigger by a pH range from acidic to basic using different buffer conditions.[20] Hydrolytic study shows that degradation of EDA was less under lower pH conditions as shown by low K value (0.00983 min^{-1}). Since EDA is a weak acid, at a lower pH it remains in a unionized form, which reduces the concentration of EDA anions, stabilizes EDA to some extent, and thus degrades less.[21] EDA can be ionized under basic conditions and undergo rapid degradation. Due to its phenol-like structure and weakly acidic nature, with a pKa value of 7, EDA ionizes in a basic environment.[17] The degradation rate constant increases as the pH rises. Although the keto form of EDA is stable[21], in water, EDA exists primarily in its enol form and as an anion, which means it becomes unstable at a pH of 7 or higher. EDA degrades more significantly in neutral to alkaline pH, likely due to the nucleophilic attack by hydroxide ions, leading to the opening of the pyrazoline ring.[22] Reactive anions and cations are formed during the oxidative breakdown of medicinal compounds through an

electron transfer mechanism.[20] Electron transfer can cause oxidation of EDA because of its phenol-like structure.[23]
EDA degrades in 3% H_2O_2 (pH 4.5) with a rate constant (K) of 0.0.00924 min^{-1}, which is similar to the degradation rate constant observed under acidic condition. This may be due to the formation of an EDA peroxyl radical or a harsh oxidative environment that increases the degradation rate by forming a dione of EDA.[11] In hydrolytic and oxidative study of EDA-KVA-SD it observed that degradation rate decreases in all pH conditions. (Figure No.4) Kollidon VA64 exhibited significantly greater intermolecular interactions with active pharmaceuticals because of intrinsic binding sites (C=O) spread throughout the polymeric chains, and their capacity to form hydrogen bonding between active pharmaceutical ingredient and polymer. These interactions are critical for keeping pharmaceuticals supersaturated in aqueous and biorelevant dissolving environments as well as avoiding nucleation and crystallization.[24] Under all the pH conditions tested, KVA 64 was more effective in protecting EDA against hydrolysis. This could be explained by the fact that KVA64 contains two hydrogen acceptors, which are derived from the acetate structure and the C=O groups of the pyrrolidone ring. Furthermore, compared to the acetate group, the pyrrolidone C=O group is a stronger hydrogen bond acceptor. [25] Upon analyzing the EDA-KVA-SD using IR data, it was noted that there were no carbonyl peaks present. However, when examining the IR data of the KVA64 and EDA, strong peaks in the range of 1760-1660 cm^{-1} of for carbonyl of pyrrolidone ring of KVA64 and 1750-1735 cm^{-1} for ester in KVA64 were identified. These observations implies interactions between the KVA64 and EDA through hydrogen bonding. However, it is known that KVA64 has more carbonyl groups as it contains 6 parts of vinyl pyrrolidone and 4 parts of vinyl acetate[26], consequently, it was inferred that more hydrogen bonding is involved in the formation of a stable interaction when EDA is in the solid dispersion with KVA64. This implies that EDA forms a more stable interaction with the polymer KVA64, likely due to the increased number of hydrogen bonds with the oxygen in the carbonyl group. The higher stability of EDA-KVA64-SD may also be explained by the fact that Kollidon VA64 is a 6:4 linear random copolymer of N-vinylpyrrolidone and vinyl acetate, of which vinyl acetate makes Kollidon VA 64 more hydrophobic and less hygroscopic. Kollidon VA 64 has a lower glass transition temperature, making it more plastic. This makes it a good and an ideal polymer matrix for solid dispersions.[27] EDA-KVA64-SD degrade in 3% H_2O_2 (pH 4.5) with rate constant (K) 0.00392 min^{-1} which is significantly less than the rate constant of pure EDA i.e. 0.00924 min^{-1} ($p<0.001$). It reflects that KVA64 stabilizes EDA by retaining 55% of pure EDA in solid dispersion up to 150 minutes. (Figure No. 3, 5) The reason could be the same as explained above i.e. owing to the greater number and stronger hydrogen bonds between EDA and KVA64, there could be smaller molecular mobility of EDA in the EDA-KVA64-SD.

Characterization of EDA-KVA64-SD

FTIR

The FTIR spectrum of EDA shows aromatic C-H , C=O and C=C stretching at 3128, 1647, and 1598.88 cm^{-1} respectively and the aliphatic C–H stretching at 3020.32 and 3029.96 cm^{-1}.All the results are concordant with the given data in analytical report of EDA. (Figure No. 6 a) The FTIR spectrum of KVA64 shows aliphatic C-H stretching at 2918.1, 2972.1 cm^{-1}, C=O stretching of ester at 1733.89 cm^{-1}, and C=O stretching of pyrrolidone ring at 1645.17 cm^{-1}. (Figure No. 6 b) The physical mixture showed some changes between wave numbers 2000 cm^{-1} to 2800 cm^{-1}. It indicates a temporary interaction between EDA and KVA64. However, some peaks of EDA were noticeable in spectra of physical mixture like C=N, C=C, and C-H aromatic stretching at 1650, 1598 and 3128 cm^{-1} respectively. (Figure No. 6 c) Infrared spectrum of EDA-KVA64-SD reflects retention of characteristic peaks of EDA like aromatic C-H and C=C stretching at 3128 and 598.88 cm^{-1} respectively and aliphatic C–H stretching at 3020.32, 3029.96 cm^{-1} and C=N stretching at 1236 and 1238 cm^{-1}. Whereas absence of 1647 cm^{-1} C=O stretching of amide of EDA and 1731, 1733 cm^{-1} C=O stretching of ester of KVA64 indicates involvement of the group in hydrogen bonding. (Figure No. 6 d)

XRD

Table No. 2: % Amount of EDA remaining in different accelerated conditions

Sample	% Amount of EDA remaining			
	0 Month	1 Month	3 Month	6 Month
At $25^0C\pm 2^0C$ and 60% ± 5%				
EDA	100.00±5.0	98.92±3.95	98.86±4.85	98.68±4.93
EDA-KVA64-SD	99.46±4.97	99.99±3.97	99.86±4.92	99.62±4.83
At $40^0C\pm 2^0C$ and 75% ± 5% RH				
EDA	100.00±5.10	98.65±5.96	98.60±4.95	98.54±4.927
EDA-KVA64-SD	99.46±4.98	99.46±4.89	99.34±4.98	99.02±4.951

The physical nature of EDA in EDA-KVA64-SD was analyzed by XRD analysis. XRD spectra of pure EDA contain several intense and sharp peaks at 2θ 11, 14, 15 20, and 21 which indicate the crystalline nature of EDA whereas spectra of Kollidon VA64 show only a few peaks with weak intensities indicating the amorphous nature. Further, XRD spectra of EDA-KVA64-SD contain all the sharp and intense peaks of EDA which confirmed that EDA is retained in the crystalline form. (Figure No. 7 c)

XRD results suggest that EDA-KVA64-SD forms crystalline-amorphous (C-A) type solid dispersions as stated by Meng et al.[28]

DSC

The thermogram of pure EDA shows intense endothermic peak at 128.12°C which indicates its crystalline nature. A broad endothermic peak at 334°C revealed in the DSC of KVA64 is due to its phase transition. In the DSC thermogram of EDA-KVA64-SD, the melting endothermic peak of EDA is missing which indicates that EDA is molecularly dispersed in KVA64,[13] however, a broad peak due to the phase transition of KVA64 is retained at 329 °C. (Figure No. 8 c)

Accelerated Stability Study

Insignificant change ($p > 0.05$) was observed in the amount of EDA remaining when EDA-KVA64-SD was placed for six months under $25^0C \pm 2^0C$ and 60% ± 5% and $40^0C \pm 2^0C$ and 75% ± 5% RH with respect to initial amount of EDA in the solid dispersion.(Table No. 2)

CONCLUSION

EDA was found to undergo hydrolysis under all pH conditions. Although its degradation in acidic conditions was relatively low, it was still significant. In the pH range of 5.5 to 7, EDA almost completely degraded within 60 minutes, which poses a challenge for oral delivery. Consequently, all current formulations of EDA on the market are in injectable forms that require reconstitution. However, EDA-Kollidon VA 64 solid dispersion was effective in slowing down the hydrolytic degradation of EDA in solution, regardless of pH. Notably, Kollidon VA 64 was effective in stabilizing EDA, maintaining its stability for up to 120 minutes under acidic conditions. Therefore, the EDA-Kollidon VA64 SD developed in this study shows the potential to protect EDA from gastrointestinal degradation, thereby enhancing its oral bioavailability. This research opens the door to developing a stable solid dosage form of EDA for oral administration, which could significantly improve its clinical use.

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