

Phase Transformation of Anhydrous to Dihydrate Carbamazepine: Preparation and Comparative Characterization

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Anhidritten Dihidrat Karbamazepin'e Faz Dönüşümü: Hazırlanışı ve Karşılaştırmalı Karakterizasyonu

SUMMARY

Carbamazepine, an anticonvulsant drug is one of the suitable active compounds for the study of crystal and polymorphism. Hydrate formation or dehydration of a given hydrate may affect the overall performance of the ultimate formulations and it has been estimated that more than 30 % available active drug compound can form a hydrate. The anhydrous form of the compound always shows higher aqueous solubility and dissolution parameters as compared to hydrates. This ultimately led to improved bioavailability when the rate limiting step for the absorption is dissolution rate. The purpose of the present investigation was to compare various techniques for the formation of Carbamazepine dihydrate from anhydrites and also to discriminate crystal forms of Carbamazepine by Melting point, FTIR, DSC, Powder X-ray diffractometry analysis, NMR, scanning electron microscopy, solubility and intrinsic dissolution testing. Carbamazepine phase transformation of solid state occurs when exposed to the environmental condition, which can affect the performance of the drug and the formulations.

Key Words: Carbamazepine, dihydrate, solubility, intrinsic dissolution rate, polymorphism,

ÖZ

Antikonvülsan bir ilaç olan Karbamazepin, kristal ve polimorfizm çalışması için uygun etkin maddelerden biridir. Verilen hidratin hidrat formasyonu veya dehidrasyonu sonuç formülasyonun genel performansını etkileyebilir ve mevcut etkin maddenin %30'undan fazlasının bir hidrat oluşturabileceği tahmin edilmektedir. Bileşiğin anhidrat formu hidratlara kıyasla her zaman daha yüksek suda çözünürlük ve çözünme hızı parametreleri göstermiştir. Bu durum sonuç olarak absorpsiyon için hız sınırlayıcı adımın çözünme hızı olması durumunda biyoyararlılığın artmasına yol açmıştır. Mevcut araştırmanın amacı, anhidratlardan Karbamazepin dihidrat oluşumuna yönelik çeşitli teknikleri karşılaştırmak ve ayrıca Karbamazepin kristal formlarını Erime noktası, FTIR, DSC, Toz X-ışını difraktometre analizi, NMR, taramalı elektron mikroskopu, çözünürlük ve intrinsik çözünme hızı testi ile ayırt etmektir. Karbamazepinin katı halinin faz dönüşümü ilacın ve formülasyonların performansını etkileyebilecek çevresel koşullara maruziyet sonucu ortaya çıkar.

Anahtar Kelimeler: Karbamazepin, dihidrat, çözünürlük, intrinsik çözünme hızı, polimorfizm

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INTRODUCTION

For decades, crystal polymorphism has been a process of great concern to the pharmaceutical scientists as it may pose various challenges in drug development (Wang, 2020). The most common problem that occurs during the drug development process where water/environmental humidity is brought into contact with the drug is hydrate formation. It has been reported that more than 30 % available drugs have tendency to undergo hydrate transformation which may influence the overall performance of the formulations. The bioavailability of poorly aqueous soluble drugs may be affected on account of changes in the solubility and dissolution parameters between the hydrate and anhydrate forms. Hence, it is crucial to discover any probable hydrate form promptly in the process of development of drug (Tian, 2010). It is well known fact that hydrates always have lower solubility and a dissolution rate when compared to anhydrides due to their lower free Gibbs energy. The important aspect is that, formations of hydrates also persuade changes in flow properties and compatibility (Huang, 2022).

An alteration of active constituents in solution phase during dissolution process may be one of the common phenomenon that lead to compromising the therapeutic response of drug by decreasing the amount of drug present for absorption. And this is critical for that drug moiety which belongs to narrow therapeutic efficacy, such as Carbamazepine (CBZ). CBZ belongs to Biopharmaceutical Classification System class II and is reported to exist in at least 4 anhydrous (I, II, III & IV) and 1 dihydrate polymorphic form (Barakh Ali, 2019). Water molecule inclusion found to alter the anhydrate or lower hydrate crystal structure (Kogermann, 2008). Anhydrous forms show better water solubility and dissolution rate, which ultimately contributes to enhance bioavailability when the rate controlling step for drug absorption is dissolution (Halebian & Shires, 1989; Rodríguez-Hornedo, 2006; Byrn, 2019; Strachan, 2005 and Bhise Rajkumar, 2010).

Conversion of a hydrate to anhydrate or vice versa is of great importance as this may lead to the change in various physicochemical properties leading to altered dissolution profile and bioavailability (Suo, 2021). As reported previously, CBZ Dihydrate is generally prepared by two different techniques, water suspension and the crystallization method (Khoo, 2009). The present investigation describes a study of the four different types of solution mediated transformation of CBZ anhydrate (CBZ-A) to CBZ dihydrate (CBZ-D), with the goal to identify the rate controlling parameters for such transformation.

MATERIALS AND METHODS

Preparation of CBZ dihydrate form

CBZ-D were prepared by four different techniques to understand the changes in various physicochemical properties and compared with CBZ-A. The samples obtained were meticulously stored in desiccators at 75% RH to maintain their integrity.

Lyophilization: (CBZ-DL)

To prepare CBZ -D, CBZ -A(form-III) was suspended in deionized water and agitated for 48 h. The obtained slurry was filtered and the obtained solid residue were dried by using Lyophilization techniques (0 °C and 2500 mTorr for about 6 h) (Ma, 2020).

Water Ethanol Method: (CBZ-DE)

About 15 g of CBZ -A dissolved in 400 mL of a (3:1 w/w) boiling water- ethanol solution. After cooling of prepared mixture in water bath for about 14 h, the obtained crystals were collected by filtration (Kachrimanis & Griesser, 2012).

Suspension Method: (CBZ-DS)

CBZ-A was suspended in distilled water with continuous stirring at room temperature for 24 h. The resultant crystals were vacuum filtered and meticulously stored in desiccators (Wadher, 2021; Murphy, 2002).

Cooling Crystallization Method: (CBZ-DC)

CBZ-D form was prepared by modified approach

described by Rodriguez HN et. al (Rodríguez-Hornero, 2006). About 500 mg of CBZ-A was dissolved in deionized water (1L), the solution was refluxed for 1 h at 65 °C with continuous stirring. The resultant solution was cooled down to room temperature, filtered and washed in triplicate with water, and dried in vacuum oven at 30° C for about 48 h.

Characterization

Melting Point

Melting point of all dihydrate and anhydrate samples was evaluated using the conventional Capillary Tube Method.

Fourier transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy study generally carried out to identify polymorphic forms. The FTIR spectrum of the CBZ and its dihydrates are recorded over the region on 4000-400 cm⁻¹ using instrument FTIR – Alpha IIE, Model No. 286,5124 (Bruker Series) (Khajir, 2021).

Differential Scanning calorimeter (DSC)

DSC (A STAR, DB V16.40: METTLER) was used for the studies. The appropriate quantity of sample was placed into an aluminum pan and heated over a temperature range of 30–300°C, at a rate of 10 K/min under N₂ purge at 50 mL/min (Zhou, 2019).

Powder X-ray diffractometry (PXRD)

PXRD diffractograms of CBZ and its dihydrate were determined to identify the solid state of CBZ (Barakh, 2019). On a Siemens D5000 diffractometer, experiments of variable-temperature XRPD were carried out with CuK α radiation of 1.541. Powder samples were provided in a stainless steel holder's hollow. The heating of the sample was done from 30 to 200 °C in an Anton Paar, 589775 sample holders using an Anton Paar TTK2-HC controller at 10 °C min⁻¹. All the data was gathered at 10°C intervals between 3° and 40° 2 θ in 0.05° 2 steps with a count rate of 3 s/step (Yutani, 2019).

Nuclear Magnetic Resonance Spectroscopy (NMR)

A Spect PROBHD apparatus running at 300 MHz was used to obtain the ¹H NMR spectra of CBZ-A and its dihydrate. The 1D and 2D spectra recording was done with standard software. All the resonance bands were referred to tetramethylsilane as an internal standard after the material was dissolved in DMSO-d₆ (Apirh, 2020).

Solubility Analysis and Intrinsic Dissolution Rate

The shake agitation technique was used to determine solubility (Murphy,2002). An excess quantity of sample was added in about 100.0 ml distilled water with continuous shaking (100 rpm, at 37±1 °C for 72 h). About 2 ml Samples were withdrawn at different time intervals and analyzed by UV-Vis spectrophotometer at 265 nm. The whole procedure was carried out in triplicate. The rotating disk method was used to determine intrinsic dissolution rate by placing the sample in 400 ml of dissolution medium (demonized water) at 37±1 °C for 180 minutes and 100 rpm in USP-II paddle apparatus. Exactly 5.0 mL aliquot was withdrawn and spectrophotometrically analyzed at wavelength of 265 nm (Mawazi, 2021). throughout the experiment, the sink conditions were maintained.

Scanning Electron Microscopy (SEM)

The SEM was used to evaluate the solid state transition of CBZ A and its dihydrated sample residuals following solubility and dissolution experiments. A ZEISS EVO HD 15 scanning electron microscope was used to obtain SEM micrographs. The samples were mounted on aluminum pin stubs with the help of self adhesive carbon mounts. Under vacuum, SEM pictures of the mounted samples were taken with a FEI Quanta 400 SEM (Diya Labs, Mumbai) and XTM microscope control software V 2.3. To get the SEM pictures, the electron beam was accelerated at a voltage of 10.00 kV (Pagire, 2017; Pagire, 2017).

RESULTS AND DISCUSSION

Melting Point

The melting point of CBZ A, CBZ DS, CBZ DE, CBZ DC, AND CBZ DL was found to be 177 °C, 168°C, 161°C, 165°C, and 169°C respectively which complies with the melting point reported in Literatures (Grzesiak, 2003).

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of CBZ-A and CBZ-D showed absorption bands of a range of functional groups as depicted in Figure 1. The spectrum of **CBZ A** exhibited characteristic peaks at 3584 (-NH valence vibration), 1678 cm^{-1} (-CO-R vibration), and 1383 cm^{-1} (C-NH₂ stretching vibration) which were corresponding to those previously reported by Douroumis D et

al. (Douroumis, 2007). 3500–3392, 1731–1629, and 1427–1317 cm^{-1} are the three primary zones for recognizing and differentiating CBZ polymorphs. **CBZ DS** depicted peaks at 3499, 1681, and 1410 cm^{-1} . **CBZ DE** confirmed peaks at 1677, and 1401 cm^{-1} . **CBZ DC** confirmed peaks at 3440, 1684, and 1411 cm^{-1} , and **CBZ DL** showed peaks at 1674 and 1398 cm^{-1} respectively. CBZ A showed a sharp band at 3463 cm^{-1} , while CBZ-DH showed a doublet band at 3431 cm^{-1} might be due to the stretching vibration of heterocyclic amine. N-H groups stretching vibration was observed at 3152 cm^{-1} for CBZ-A and 3178 cm^{-1} for CBZ-DH. The O-H stretching at 3278 cm^{-1} was found in both CBZ-A and CBZ-D. This adds to the structural differences between the dihydrate and anhydrate forms, making it easier to identify between the anhydrate and different dihydrate forms of CBZ using IR spectra.

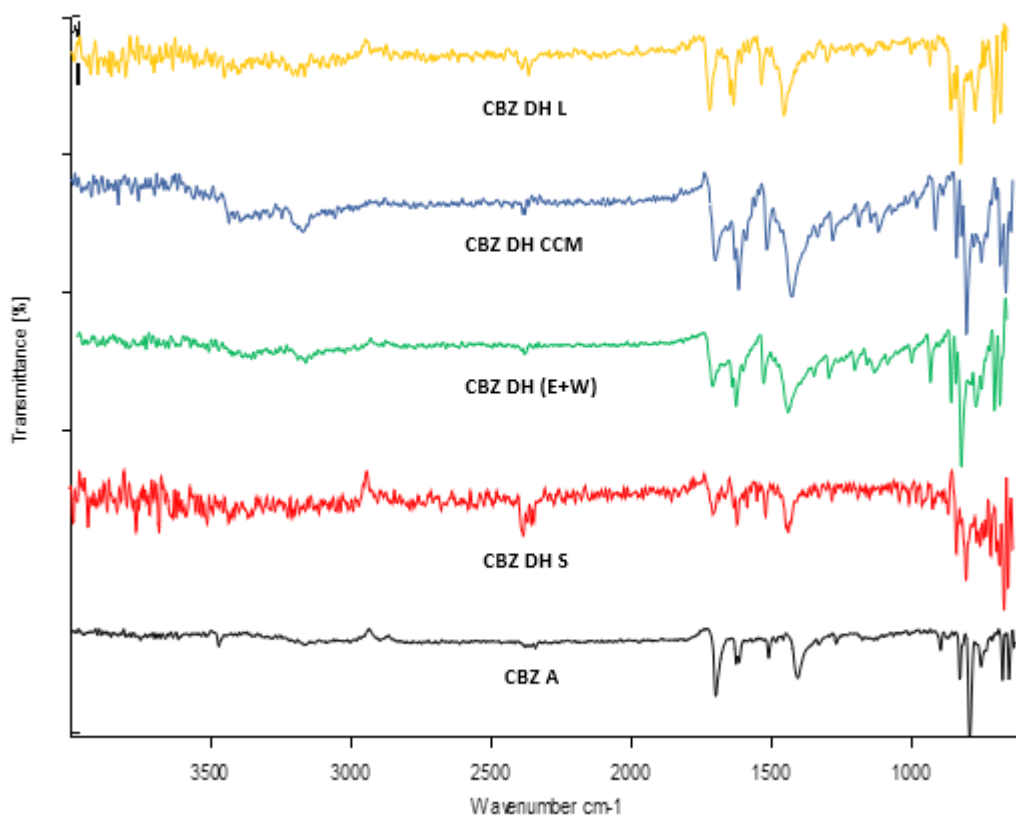


Figure 1. FTIR spectra for the anhydrate and Dihydrate forms of CBZ.

Differential scanning calorimeter (DSC) studies

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug (CBZ A) and its dehydrates (Figure 2). The DSC curve of CBZ-A revealed an initial endothermic peak at 175.64°C, with one exothermic and a strong endothermic peak at 191.35°C, indicating the normal thermal behavior of CBZ A with melting and crystallization. CBZ DS (Suspension Method) form has a wide endotherm at 176.25°C and an endothermic melting peak at 194.30°C. The endotherm of CBZ dihydrate produced with CBZ DE was wide across the range of 50-80 °C, with a peak at 75.98 °C owing to

water loss, but no endothermic melting peak was detected. Similarly, due to water loss, CBZ DC generated by the cooling crystallization Method displayed a wide endotherm across the range of 50-80 °C with a peak at 73.60 °C, however endothermic melting did not occur. However, no exothermic peak was seen in the CBZ dihydrate generated using the Lyophilization (CBZ DL) Method, rather a pronounced endothermic peak was observed at 231.30°C. The melting point of carbamazepine dihydrate generated by various techniques ranged from 70 to 160 degrees Celsius, according to DSC analysis. These results were consistent with the findings of previous reports (Barakh, 2019; Deng, 2017).

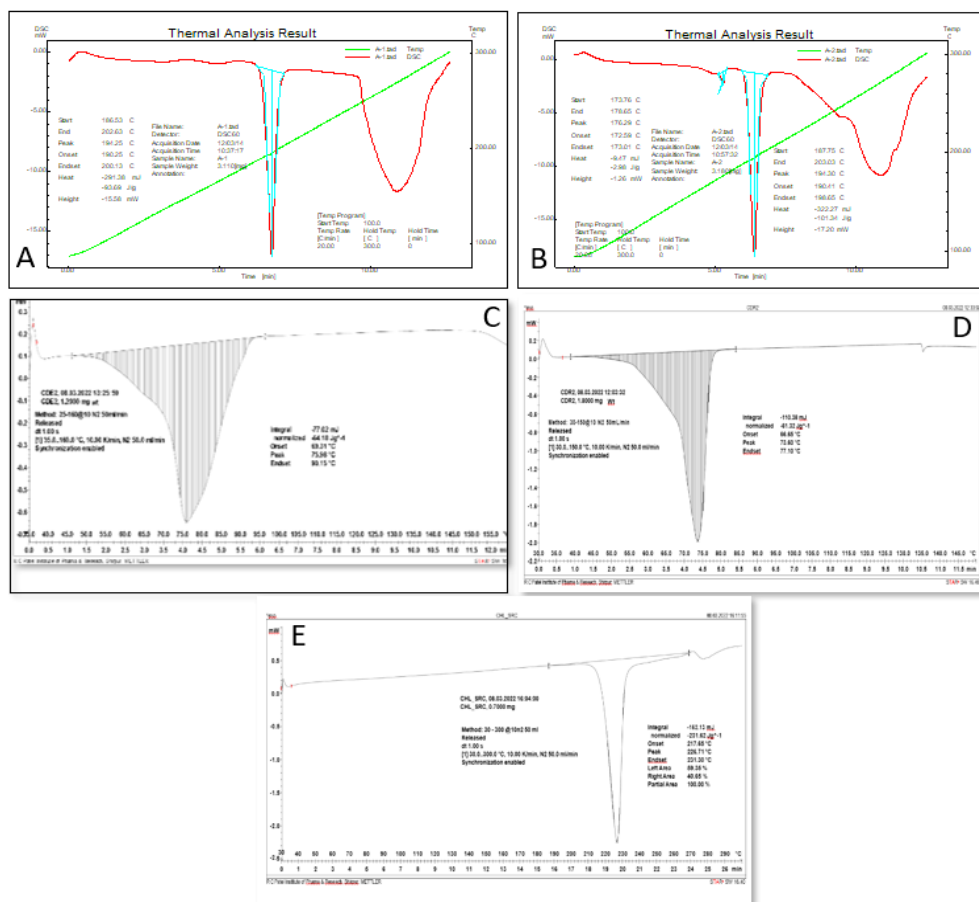


Figure 2. DSC thermograph of different sample of CBZ: a) CBZ-A, b) CBZ-DS, c) CBZ -DE, d) CBZ-DC, e) CBZ-DL.

Powder X-ray diffractometry (PXRD)

XRPD was used to describe CBZ anhydrate form A and CBZ dihydrate generated by various ways, as shown in the figure 3. The nature of dihydrate changes on heating was revealed using XRPD data collected at various temperatures. All of the dehydrate diffraction patterns were computed at temperatures ranging from 30 to 170 degrees Celsius. The XRPD patterns on all of the CBZ crystals were unique. The anhydrate of form, CBZ A showed distinct peaks at 12.198/36.296

two-theta degrees. The Suspension Method produced CBZ dehydrate (CBZ DS) with typical peaks in the range of 10.086-24.030 two-theta degrees. Similarly, peaks in the range of 8.958-26.734 two-theta degrees were seen in CBZ dihydrate produced using the Water Ethanol Method (CBZ DE). CBZ dihydrate produced by Cooling Crystallization Method (CBZ D CC) showed peaks in the range of 9.967-24.792 two-theta degrees. Dihydrate of CBZ made by Lyophilization Method (CBZ DL) showed peaks in range of 8.981-24.827 two-theta degrees.

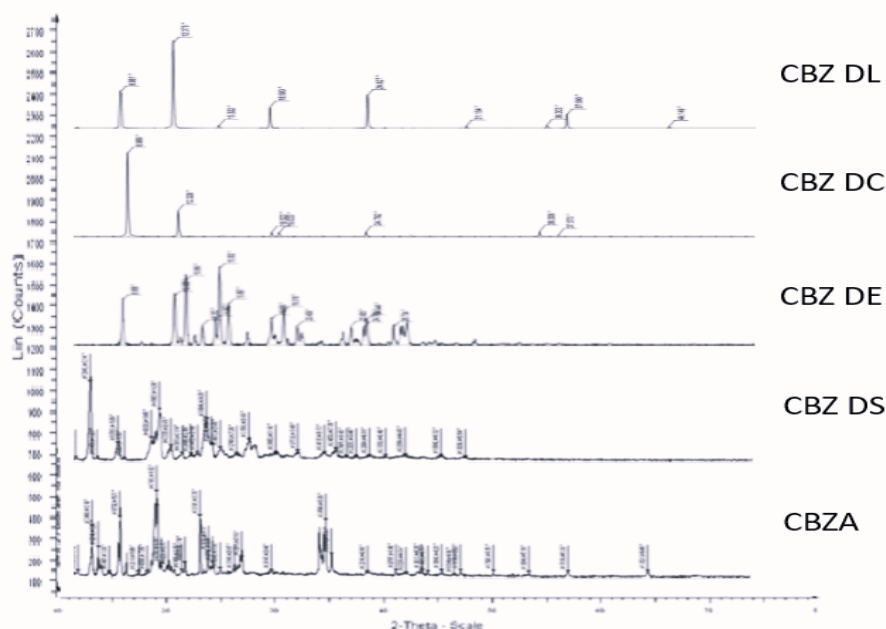


Figure 3. X-ray Diffractogram of different samples of CBZ Anhydrate and CBZ Dihydrate

Nuclear Magnetic Spectroscopy (NMR)

The CBZ-A and four CBZ-D forms have been investigated by ^1H NMR (Figure 4). The NMR spectra of **CBZ-A** showed eight peaks of C-H at 7.437, 7.431, 7.405, 7.4387, 7.368, 7.363, 7.333, 7.329 ppm and N-H peak at 6.942 ppm (Figure 3A). The NMR spectra of **CBZ DS** prepared by suspension method showed eight peaks of C-H at 7.489, 7.462, 7.434, 7.407, 7.391, 7.371, 7.334, 7.273, ppm & N-H at 6.9443 ppm and additional prominent chemical shift at 1.828 ppm. Sup-

plementary singlet which resonates at δ 6.9443 ppm is consigned to the olefinic protons at 10 and 11 positions.

The NMR spectra of **CBZ DE** prepared by Water Ethanol Method showed eight peaks of C-H at 7.470, 7.458, 7.424, 7.394, 7.380, 7.368, 7.354, 7.341 & N-H at 6.998 ppm. A singlet resonates at δ 5.55 signify the 2 protons of the amino group. A singlet which resonates at δ 6.998 ppm is assigned to the olefinic protons at 10 and 11 positions. The NMR spectra of **CBZ CC**

dihydrate prepared by Cooling Crystallization method showed eight peaks of C-H at 7.474, 7.460, 7.429, 7.399, 7.385, 7.373, 7.359, 7.345 & N-H at 7.002 ppm. A singlet resonates at δ 5.23 representing the two protons of the amino group. An additional singlet which resonates at δ 7.002 ppm is assigned to the olefinic protons at positions 10 and 11. The NMR spectra of

CBZ-D prepared by Lyophilization method (CBZ DL) showed eight peaks of C-H at 7.474, 7.461, 7.430, 7.399, 7.386, 7.373, 7.359, 7.346 & N-H at 7.003 ppm. A singlet resonates at δ 5.34 representing the two protons of the amino group. One more singlet which resonates at δ 7.003 ppm may be due to the olefinic protons at 10 and 11 positions.

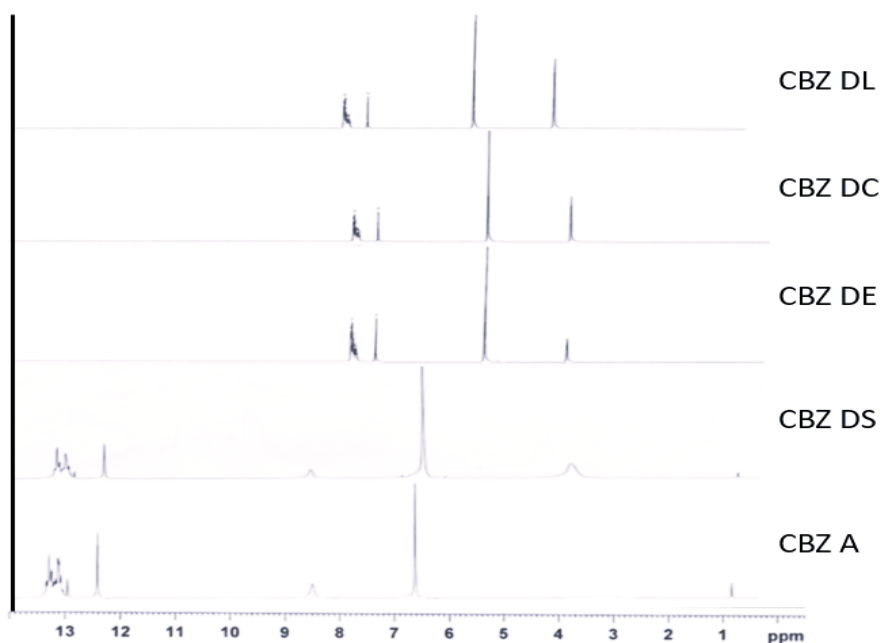


Figure 4. Comparison of NMR Spectrum of CBZ A, CBZ DS, CBZ DE, CBZ DC and CBZ DL.

Solubility and Intrinsic dissolution test

The solubility and intrinsic dissolution profile are depicted in Table 1. Initially CBZ A was found to have a higher intrinsic dissolution rate ($39.6 \pm 0.8 \mu\text{g}/\text{min}/\text{cm}^2$) but consequently it was shown a lesser dissolution on account of the quicker conversion to dihydrate form. The Intrinsic dissolution rate (IDR) of All the prepared dehydrates showed a lower IDR than CBZ A as shown in table 1. Solubility of CBZ A is higher and faster than all the Dehydrate form of CBZ. The same findings were confirmed by many researchers (Barakh, 2019; Strachan, 2005) The graphical plot of amount of drug dissolved vs time for the CBZ-A and CBZ-DH showed a linear relationship and the in-

trinsic dissolution rate was calculated by initial slope method and the results showed in table 1. CBZ A has been shown to undergo a phase change to the dihydrate form. This transformation results in a change in slope of the concentration time profile (Fig. 1). Hence, the dissolution rate of CBZ(A) was calculated from the initial linear portion of concentration-time profile (Barakh, 2019; Jensen, 2017). CBZ exhibited two distinct slopes as, the initial slope (anhydrous phase dissolution) and the final slope (dihydrate phase dissolution) (Jensen, 2017). During disk dissolution in aqueous media, CBZ -A form was found to dissolve more and faster than the CBZ-DH form, which was in accordance with the results obtained from solubility

studies. The results were as expected as per the previous finding that hydrated crystal forms are more stable in aqueous medium than anhydrites. There might be an alteration in the intermolecular force of

interactions within the hydrate crystal due to inclusion of water into the crystal lattice and hence hydrate is found to be more thermodynamically stable than anhydrate (Wang, 2020).

Table 1. Solubility and Intrinsic dissolution of CBZ at 37°C

CBZ Form	IDR* ($\mu\text{g}/\text{min}/\text{cm}^2$)	Solubility($\mu\text{g}/\text{ml}$)
CBZ A	39.6 \pm 0.9	451.0 \pm 6.2
CBZ DS	17.6 \pm 0.6	246.3 \pm 3.7
CBZ DE	16.5 \pm 0.3	243.3 \pm 2.8
CBZ DC	16.9 \pm 0.4	253.9 \pm 1.6
CBZ DL	19.1 \pm 0.4	283.3 \pm 1.7

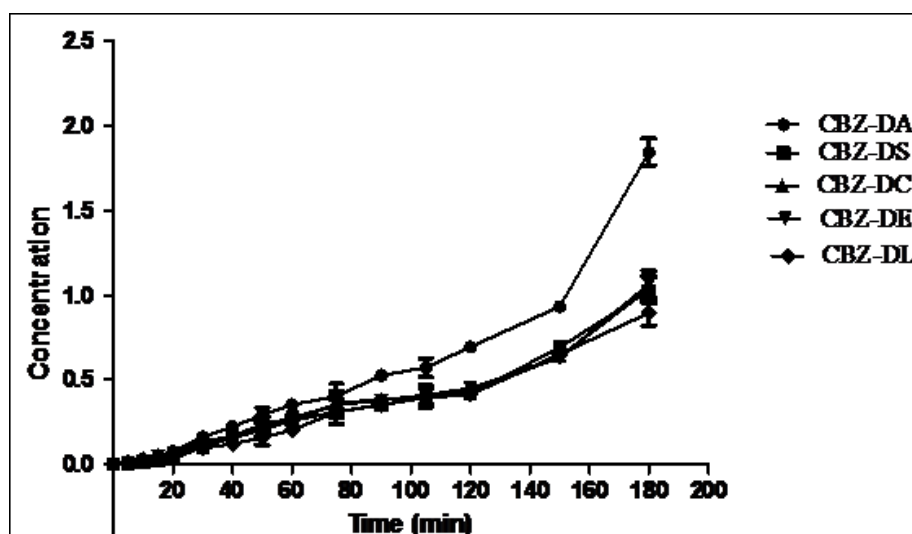


Figure 5. Concentration parameters during the dissolution of anhydrous CBZ A, CBZ DS, CBZ DE, CBZ DC and CBZ DL

Scanning Electron Microscopy

The SEM micrographs of CBZ-A and CBZ-D were presented in figure 6. CBZ-A appeared as a very small prismatic shape morphology (Figure 6A), while changes to needle shape when converted to dihydrate as depicted in figure 6. The disparity of morphology for CBZ forms might be linked with the packing behavior of the carboxamide dimer units²⁸ Formation of hydrates also stimulate alteration in properties such as, flowability and compatibility. For example, CBZ-A can show prism shape morphology, changing to needle shaped when forming CBZ -DH (Huang, 2022; Kogermann, 2008).

There have been many factors that are of prime concern in the exploration of anhydrate and hydrate systems and an understanding of this conversion could be utilized to control the phase transformation of CBZ during the process, storage, and formulation development. From the results obtained, the processing operations which could affect the conversions and the rate controlling parameters for such transformation may be crystallization, cooling, grinding, drying and solvent effect. The results also showed that agitation speed, presence of solvent (water) and temperature can accelerate the transformation of CBZ. The results obtained are in accordance with the findings of other researchers.

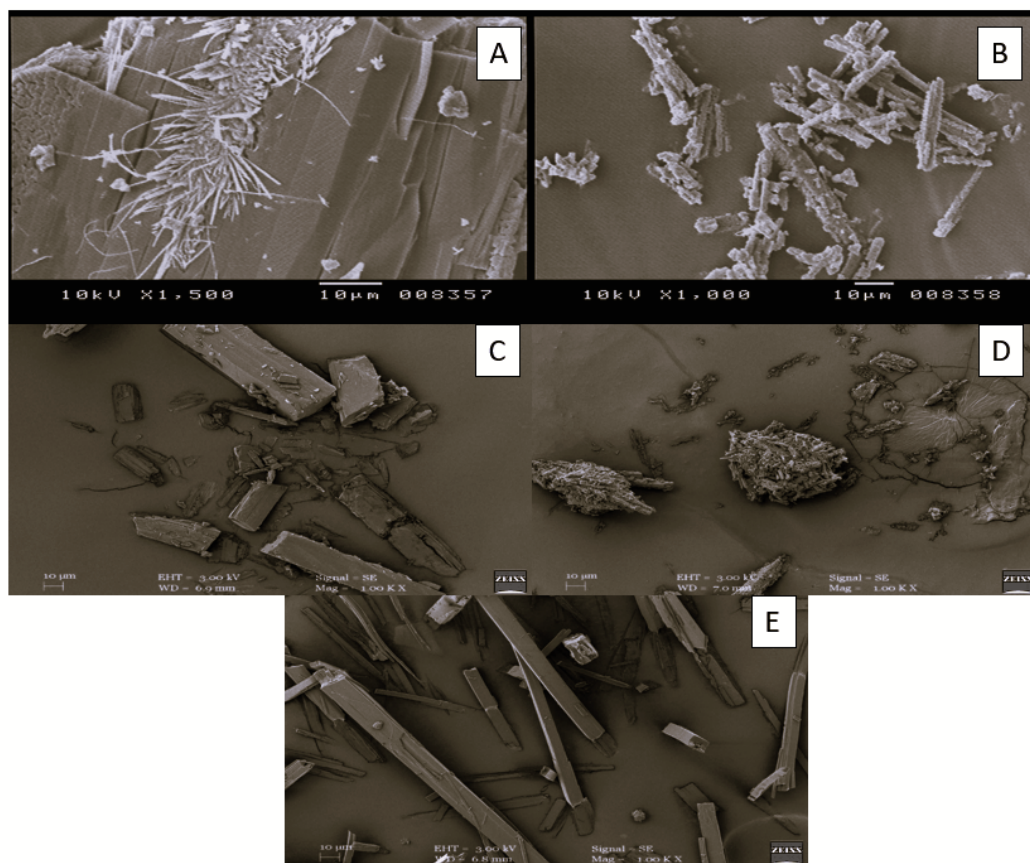


Figure 6. Scanning Electron Microphotographs of CBZ a) CBZ A, b) CBZ DS, c) CBZ DE, d) CBZ DC, e) CBZ DL.

Drying operations such as freeze drying (desolvation) could be the processing operation responsible for the solid phase transformation. The grinding of CBZ anhydrous had an impact on the transformation which also revealed novel crystal faces and functional groups, which might alter the pace of change kinetics of anhydrous monoclinic polymorph of CBZ anhydrous to dihydrate crystal form by solution mediated phase transformation.

CONCLUSION

Carbamazepine (CBZ) is available as anhydrous and dihydrate forms, and each has different solubility, dissolution profile, and ultimately therapeutic effectiveness. There have been many factors that are of prime concern in the exploration of anhydrate and hydrate systems and an understanding of this conversion

could be utilized to control the phase transformation of CBZ during the process adaptation, storage, and formulation development. Hence further investigational research is necessary to understand the precise mechanism in the wake of the difference in alteration tendency between the anhydrate and dihydrates.

CONFLICT OF INTERESE

The authors declare that there is no conflict of interest

AUTHOR CONTRIBUTION STATEMENT

KW and VR conceived and designed the experiments; KH and VR performed the experiments, analyzed the data and wrote the manuscript; MU, and ST performed the statistical analysis of the study. All authors contributed to critical revision of the manuscript.

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