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# L-Proline as Co-Crystal Forming Amino Acid for Enhanced Dissolution Rate of Lamotrigine: Development of Oral Dispersible Tablet

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**ABSTRACT**

Lamotrigine is an antiepileptic drug with slow dissolution rate which can reduce its oral bioavailability. In addition, it was reported to have first pass metabolism. Accordingly, the aim of this work was to enhance its dissolution rate utilizing co-crystallization technique to be suitable for incorporation in oral dispersible/disintegrating tablets (ODT). L-proline was selected as co-crystal co-former for enhancing dissolution in addition to its beneficial anticonvulsant properties. Formulations containing lamotrigine and L-proline at different molar ratios were prepared using ethanol assisted co-grinding. The prepared formulations were characterized using FTIR, X-Ray powder diffraction, differential scanning calorimetry and dissolution studies. The formulation recorded the highest dissolution rate was incorporated in fast disintegrating tablet/ODT for buccal use. Characterization techniques suggested the formation of lamotrigine-l-proline co-crystals with 1:2 molar ratio being optimum for interaction. This interaction resulted in significant enhancement in dissolution rate with the ratio of lamotrigine to proline at molar ratio of 1:4 showed greatest dissolution rate (% DE= 80.57). The prepared tablet utilizing lamotrigine and L-proline at molar ratio of 1:4 showed fast disintegration and rapid dissolution rate compared with control tablet containing lamotrigine alone. The study suggested L-proline as an efficient co-crystal co-former for enhancing dissolution rate of lamotrigine for buccal delivery.

**Keywords**: Lamotrigine; L-proline; Co-crystallization; Dissolution efficiency; Oral dispersible tablet

## INTRODUCTION

Lamotrigine is antiepileptic drug of phenyltriazine class. It is sometimes prescribed to treat dipolar syndrome. When taken orally, lamotrigine is subjected to extensive hepatic first pass metabolism that reduces its oral bioavailability (Mashru *et al*., 2005). Solubility of lamotrigine is considered pH dependent. Though its solubility at buccal pH value (6.8) is low, its partition coefficient would favor its transport through buccal mucosa (Patel *et al*., 2011; Srinija and Lakshmi, 2016). The dissolution rate of hydrophobic active pharmaceutical ingredient (API) such as lamotrigine can be hastened adopting various techniques. Among the reported strategies are micronization, addition of solubilizing agent, formation of inclusion complexes, and solid dispersion with hydrophilic polymer(s) (Srikanth *et al*., 2010; Pankaj *et al*., 2011; Essa and Dwaikat, 2015). Another emerging strategy draws the attention of scientific researchers is the modification of the crystalline structure of API via co-crystallization approach. Formation of co-crystals of API with inert co-former results in alteration of its crystal lattice structure. The obtained product usually shows weaker intramolecular bonding compared to that present in the parent compound. The advantage of co-crystallization is the capability to alter the physicochemical characteristics of APIs without affecting their pharmacological benefits via non-covalent interactions with one or more co-formers. This can enhance drug dissolution rate to a great extent (Arafa *et al*., 2016, 2018; Karagianni *et al*., 2018). Co-processing may result in amorphization, this process is termed co-amorphousization. The latter process is another approach for enhancing the dissolution rate of many APIs (Dengale *et al.,* 2016; Abdelquader *et al*., 2018). A variety of inert co-formers are reported.


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Oxalic acid, benzoic acid, tartaric acid and urea are examples of these co-formers (Nalte *et al*., 2015; Budiman *et al*., 2016). Additionally, some pharmaceutical excipients such as sugars (e.g. sucralose and xylitol) have been employed as co-crystal co-formers with promising results (Arafa *et al*., 2016, 2018)

Amino acids were largely investigated as co-former to many APIs. Structurally, amino acids are promising candidates as co-formers because they possess functional groups capable of forming hydrogen bonds with other molecules. L-proline is considered as the most fruitful amino acid employed as co-former. L-proline is reported to build a flexible, but strong, interaction with other compounds based on zwitterionic co-crystal formation due to charge-assisted hydrogen bonding that add value to its co-former ability (Nugrahani *et al*., 2021). Importantly, L-proline was also reported to improve the permeability through gastrointestinal tract of many drugs such as indomethacin and acetazolamide (Song *et al*., 2019; Wang *et al*., 2020). The use of L-proline as co-crystal co-former has been widely investigated to increase the solubility of many drugs such as naproxen (Tumanova *et al*., 2018), ibuprofen (Othman *et al*., 2016), flurbiprofen (Silva *et al*., 2016) and chlorothiazide (Teng *et al*., 2020). In addition, L-proline was reported to have anticonvulsant properties which will be beneficial if it is combined with antiepileptic agent such as lamotrigine (Sarhan *et al*., 1989).

Accordingly, the objective of this work was to investigate the effect of co-processing of lamotrigine with proline on the dissolution rate of the drug. The goal was to prepare lamotrigine oral dispersible tablets (ODT) with rapid release in the oral cavity, for subsequent absorption by buccal mucosa to minimize pre-systemic degradation.

## MATERIALS AND METHODS

Lamotrigine was supplied as a gift sample by Apex, Cairo city, Egypt. L-proline, croscarmellose sodium, crospovidone, magnesium stearate, mannitol and avicel PH 102 were obtained from Sigma for Pharmaceutical Industries, Quesna, Egypt. Ethanol (99 % ethyl alcohol), potassium dihydrogen phosphate and sodium hydroxide (pharmaceutical grade) were purchased from EL Nasr Pharmaceuticals Chemicals CO., Cairo, Egypt.

### Spectrophotometric quantification of lamotrigine

Lamotrigine stock solution was prepared by dissolving 50mg of the drug in ethanol to obtain a concentration of 1mg/ml. Exact volumes of the stock was appropriately diluted with potassium dihydrogen phosphate pH 6.8 solution to obtain lamotrigine concentrations of 20, 30, 35, 40 and 50 µg/mL. The absorbance of each concentration was recorded spectrophotometrically at 267 nm. The standard curve was then constructed by plotting the absorbance values obtained as a function of the corresponding concentration.

### Preparation of lamotrigine co-crystals

Lamotrigine co-crystals were prepared by liquid assisted grinding with L-proline. The used process was adopted from published work with slight modification (Essa *et al*., 2019; Elkholy *et al*., 2020). The calculated amounts of lamotrigine and L-proline at different molar ratios were mixed in mortar then ethanol was added drop by drop till the formation of thick slurry. The slurry was exposed to continuous kneading until evaporation of ethanol. This process was repeated four more times. Each mixture was left at ambient temperature (25°C) overnight for drying prior to packaging in an airtight container till used (Table I).

To elucidate the importance of the adopted technique, physical mixture containing the drug and L-proline at 1:4 molar ratio was prepared by gentle mixing with a spatula in a mortar.

### Solid state characterization

### Fourier–transform infrared spectroscopy (FTIR)

The FTIR spectra of lamotrigine, L-proline and their co-kneaded mixtures were obtained by employing Bruker Tensor 27 equipment (Ettlingen, Germany). The technique based on KBr diffuse reflectance mode. Each formulation was mixed with potassium bromide (spectroscopic grade) and compressed into discs using hydraulic press. The disks were scanned from 4000 to 400$cm^{-1}$. Data analysis was performed using DLATGS IR detector.

### Differential scanning calorimetry (DSC)

Thermal events of the pure components and their mixtures were examined using Differential Scanning Calorimeter (DSC) (Perkin Elmer DSC 6 module, Waltham, MA).

Table I. Compositions of different formulations of lamotrigine (L) prepared using proline (P), expressed as molar and weight ratios. the dissolution parameters, denoted as percentage amount released after 5 minutes (Q5) and percentage dissolution efficiency (% DE), are also listed.

| Formula | Lamotrigine | Proline | Q5 (%) | DE (%) |
|---|---|---|---|---|
| Lamotrigine | 25 | _ | 12.54 ± 2.32 | 30.22 ± 4.73 |
| Physical mixture | 25 | 44.95 | 35.04 ± 1.21 | 44.21 ± 0.85 |
| LP 1:1 | 1 (256.09) | 1 (115.13) | 37.73 ± 2.5 | 57.8 ± 2.76 |
| LP 1:2 | 1 (256.09) | 2 (230.26) | 43.88 ± 3.25 | 69.39 ± 1.9 |
| LP 1:3 | 1 (256.09) | 3 (345.39) | 55.97 ± 2.54 | 71.52 ± 1.27 |
| LP 1:4 | 1 (256.09) | 4 (460.52) | 77.82 ± 4.83 | 80.57 ± 2.43 |

-Values between brackets represent the weight ratios in mg; Values of Q5 and DE (%) represented as mean ± SD; Values for physical mixture is presented as weight ratios

Table. II Master formula for lamotrigine oral disintegrating tablets, together with *in vitro* dissolution parameters and results of quality control test.

| Ingredients | Test tablets | Control tablets |
|---|---|---|
| LP 1:4 | 69.95 | - |
| Lamotrigine | - | 25 |
| Proline | - | 44.95 |
| Avicel | 71.05 | 71.05 |
| Mannitol | 80 | 80 |
| Croscarmellose sodium | 12 | 12 |
| Crospovidone | 12 | 12 |
| Magnesium stearate | 5 | 5 |
| Total tablet weight | 250 | 250 |
| Q5 (%) | 83.9 ±1.57 | 45.46 ± 3.47 |
| Q60 (%) | 89.75 ± 0.3 | 63.19 ± 1.98 |
| Dissolution efficiency (% DE) | 82.2 ± 0.32 | 52.99 ± 2.02 |
| Hardness (kp) | 5.3±0.5 | 5.8±0.2 |
| Disintegration time (min) | 1.0 | 1.5 |
| Wetting time (sec) | 28± 3.65 | 30±3.36 |
| Drug content (%) | 100.1±2.63 | 100.7 ±3.09 |

This weight of LP 1:4 formulation is equivalent to the dose of the drug (25mg); Q5 and Q60 are the percentage drug released after 5 and 60 min, respectively

The information generated from this instrument was used to understand amorphous and/or crystalline properties of the tested samples. Powder equivalent to 2-3 mg of each test sample was carefully placed in aluminum pan before crimping the lid. The samples were heated at a temperature range of 30-400$^{o}$C with a heating flow rate of 10$^{o}$C /min. This was performed under a continuous flow of nitrogen gas (20 ml/min). The data gathering and analysis were performed using Pyris software.

**Powder X-ray diffraction (PXRD)**

The crystalline structure of lamotrigine and potential co-crystal was monitored using PAN analytical X-Ray diffractometer (model X'Pert PRO, Netherlands). The equipment is supplied with secondary monochromator, CuKa radiation (λ = 1.542 Å) operated at 45 KV and current of 35 mA. Collection of the data was performed at ambient temperature using 2 theta (2Θ) scan axis. A scanning range of 3 to 63° and scanning step size of 0.02 was employed.

**Dissolution studies**

The dissolution rate of the prepared formulations and pure drug were assessed. The later was used as negative control. The dissolution studies employed USP dissolution tester type II apparatus (Copley Scientific, Dis 6000, Nottingham, UK). The dissolution was performed in 500 ml of phosphate buffer PH 6.8 maintained at 37±1°C, with stirring rate of 50 rpm. Similar dissolution condition was employed previously (Srinija *et al*.,

2016). Samples equivalent to 25mg of lamotrigine were placed in the dissolution vessels. Aliquots (5ml each) were collected for 60 min and replenishing with new dissolution medium after each sample. The collected samples were filtered using a 0.45µm Millipore filter, before lamotrigine quantitation by spectrophotometric assay at 267 nm. The dissolution profiles were constructed by plotting the percentage cumulative amount released as a function of time. These profiles were used to compute the dissolution parameters that were presented as the amount of drug liberated after 5min (Q5) and the dissolution efficiency (DE). The later was computed according to Khan, by calculating the area under dissolution profile at time (t) expressed as the percentage of the rectangle area supposing 100% dissolution within similar time range (Khan, 1975). Further comparison was performed using the similarity factor test. Employing the following equation (Kour *et al*., 2015):

$$F2 = 50.log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}\right\}.100$$

Where F2 is the similarity factor, n is the number of data points, Rt is the percentage amount of the reference dissolved at time t, while Tt is amount dissolved from the test sample (%) at the same time.

**Preparation of oral dispersible tablets (ODT)**

Formulation showed best enhancement in drug dissolution (formula LP 1:4) was used to prepare ODTs (test tablets). For comparison, tablets containing unprocessed drug and l-proline at the same ratio (control tablets) was also prepared. Tablets were prepared to contain 25 mg of lamotrigine according to the master formula (Table II). Direct compression technique, using Royal Artist rotary press tablet machine, was used employing rounded flat surface punches of 12mm size (Kapadia Industrial Estate, BLDG, Mumbai, India). The compaction force was adapted to produce tablets having a hardness of circa 5-6 kp.

**Evaluation of ODT**

**Quality control tests**

All investigations were conducted according to United States Pharmacopeial specifications, 2000 (USP, 2000). The weight uniformity test was performed by measuring the mean weight of 20 tablets. The weight of each tablet was referred to this mean value. According to tablet weight of 250 mg, the allowed percentage deviation was ±7.5%. Tablets are considered to comply to the specification if no more than two tablets are outside the limit, and none differs by more than twice that limit.

To ensure drug consistency in all tablets, content uniformity test was conducted. The test involved 10 tablets random selected. Each tablet was crushed in mortar using pestle and then dispersed in ethanol to solubilize the drug with the aid of sonicator. The insoluble excipients were separated by centrifugation. Drug concentration in the clear supernatant was determined using UV spectrophotometric assay. The acceptable limit is where drug content of at least nine tablets lies in the range of 85–115% of the stated amount of lamotrigine. The 10$^{th}$ tablet should not contain less than 75% or more than 125% of the labeled content.

As there is no compendial way of disintegration time assessment for ODTs other than the pharmacopeial disintegration test, tablet disintegration time was done in 900 ml distilled water employing Copley Scientific disintegration tester (Model: NE4-COP, UK). Six tablets were loaded in the basket assembly. The time for complete disintegration of each tablet was recorded.

The mechanical property was confirmed by conducting conventional tablet hardness test on 10 tablets using Erweka hardness tester. Lamotrigine in vitro release was evaluated using the same dissolution conditions used for testing co-grinded mixtures.

**Wetting time**

This test estimates the speed by which ODT gets wet by water penetration through it. This reflects tablet hydrophilic properties, obtained from the used excipient, as well as its porosity. A filter paper was placed in a petri dish and wetted by distilled water (about 6.0ml). Allura red powder (dark brown) was gently sprinkled over the tablet surface. The tablets were then carefully placed on the wet filter paper. The wetting time was noted as the time lapse till the appearance of red color on the tablet surface. The test was conducted using four tablets for each batch and the average wetting time was calculated (Jain and Naruka, 2009).

## RESULTS AND DISCUSSION

**Spectrophotometric quantification of lamotrigine**

Lamotrigine was quantified in the dissolution samples using UV spectrophotometry. Calibration curve was constructed and was linear

in concentration range from 20 to 50 ❍g/ml. Y= 0.0144 (± 0.00032) X-0.022 (± 0.00726) is the equation of lamotrigine calibration curve. The intraday and interday RSD values were in the range of 0.156 to 3.15% and 0.48 to 3.8%, respectively, confirming the precision of the assay. The lower limit of lamotrigine detection was computed to be 1.66 µg/ml and the limit of quantitation was calculated to be 5.04 µg/ml.

**Characterization of the prepared formulations**

**Fourier Transform Infrared Spectroscopy (FTIR)**

Structural changes in lamotrigine after co-grinding with L-proline were assessed using FTIR spectroscopy. FTIR was performed for lamotrigine, L-proline and the prepared formulations. Figure 1 shows the recorded FTIR spectra. The spectrum of lamotrigine reflected the characteristic peaks of the drug at 3449 and 3322 $cm^{-1}$ (for N-H stretch), at 3214$cm^{-1}$ (for C-H aromatic stretch) and at 1623 $cm^{-1}$ for N-H bending. This data agrees with previously reported one for lamotrigine (Chappa *et al*., 2019).

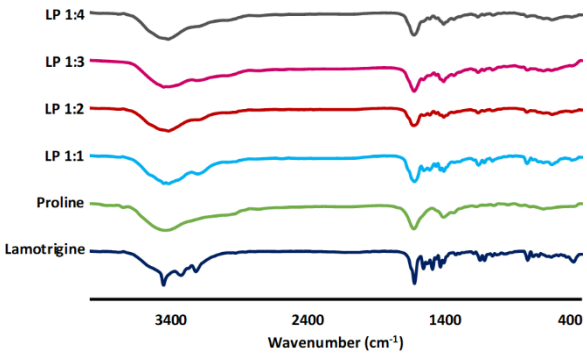


Figure 1. FTIR spectra of pure lamotrigine, L-proline, and the prepared formulations (Table I).

The FTIR spectrum of L-proline unveiled the C=O stretching at 1625 $cm^{-1}$ and COO stretching at 1409 $cm^{-1}$ which are characteristic for L-proline. The absorption band of C=O stretching was broad and appeared at lower wave number than expected for carboxylic acid carbonyl groups. This can be attributed to possible intermolecular hydrogen bonding. Similar peak assignments were reported by other researchers (Nugrahani *et al*., 2020).

Wet co-grinding of lamotrigine and L-proline at different molar ratios produced FTIR spectrum which shows alterations in the peaks corresponding to N-H bending of lamotrigine and C=O stretching of L-proline. Both absorption bands were fused and appeared as sharper peak than that corresponding to the C=O of proline. This change implies possible interaction which disrupted the intermolecular hydrogen bonding of proline. The recorded change was evident in formulations containing lamotrigine and L-proline at molar ratios of 1:1 and 1:2. This absorption band exhibited broadening at the higher molar ratios of proline (1:3 and 1:4) which suggests the existence of excess proline that underwent intermolecular hydrogen bond formation. This may indicate that optimum ratio for interaction between lamotrigine and L-proline is the molar ratio of 1:2. Similar behavior was reported with other drugs and co-formers and was explained in similar manner (Arafa *et al*., 2016; Arafa *et al*., 2018, Cho *et al*., 2022).

**Differential scanning calorimetry (DSC)**

Lamotrigine, L-proline and the prepared formulations at various molar ratios were characterized utilizing differential scanning calorimeter (Figure 2). The DSC traces of pure lamotrigine shows a sharp endothermic peak at 218.27°C with the onset at 214.73°C and the endset at 223.03°C which confirms lamotrigine crystallinity. Similar thermal behavior of lamotrigine was stated by other investigators (Chappa *et al*., 2019).

The thermogram (Figure 2) of L-proline showed sharp endothermic peak with broad shoulder appearing at higher temperature value. The Tm of the sharp endotherm was 234.73°C (onset of 231.32°C and endset of 239.97°C). This thermal pattern can be assigned for melting with decomposition and this agree with the previously reported thermal behavior for L-proline (Shimpi *et al*., 2014).

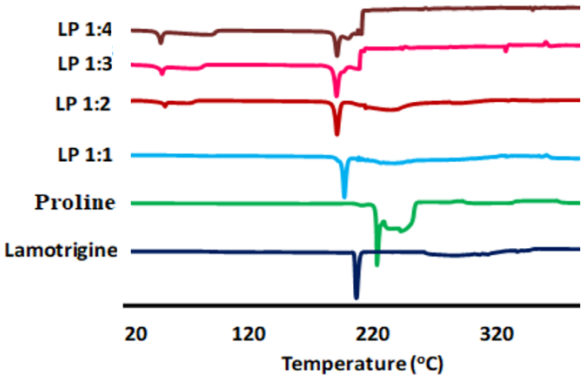


Figure 2. DSC thermograms of pure lamotrigine, L-proline, and the prepared formulations (Table I).

Ethanol assisted processing of lamotrigine with L-proline at different molar ratio resulted in modified thermal pattern with the modification depended on the tested molar ratio of drug to L-proline (Figure 2). For all ratios, new endothermic peak was observed at Tm of 208.63, 202.73, 202.27, 202.74$^{o}$C for LP 1:1, LP 1:2, LP 1:3, LP1:4, respectively. It is known that melting point of a compound has significant indication because of its relationship with water solubility and vapor pressure. The melting point has actually been directly connected to the log of solubility (Thenge *et al*., 2023). The broad peak shoulder that was observed in pure L-proline started to re-appear in the formulations containing lamotrigine and L-proline at ratio of 1:3 and 1:4 indicating the presence of excess L-proline. These results revealed the formation of new crystalline form (supposed to be co-crystal) with the optimum ratio for interaction between lamotrigine and L-proline 1:2. Similar thermal behavior was recorded for other drugs and co-formers and was explained in the same way (Basavoju *et al*., 2008; Wang *et al*., 2013; Sanphui and Rajput, 2014; El-Gizawy *et al*., 2015; Arafa *et al*., 2016, Nugrahani *et al*., 2018).

**Powder X-ray Diffraction (PXRD)**

Powder x-ray diffractometry was adopted to assess the crystalline pattern of lamotrigine, L-proline and their formulations (Figure 3). Lamotrigine diffractogram confirms its crystallinity as it shows diffraction peaks which are characteristic for lamotrigine. These diffraction peaks were observed at 9.52, 11.44, 12.52, (14.11, 14.2) .16.69, 17.53, 18.04, 19.63, 20.65, 22.95, 23.74, 25.75, 26.38, 26.8, 28, 28.45, 28.96, 29.68, 31, 31.72 and 33.3$^{o}$. This diffractogram is similar to that reported by other investigators (Kuang *et al*., 2020). For pure L-proline, the recorded diffractogram includes many diffraction peaks at 2 theta values of 8.85, 15.25, 18, 19.69, 21.43, 22.81, 24.85, 30.7, 32.29, 34.12, 34.95, 36.67, 39.94, 43.69 and 46.25$^{o}$. This confirms its crystalline nature and agrees with the previously published data (Nugrahani *et al*., 2020).

Processing of lamotrigine with L-proline in presence of ethanol at various molar ratios produced different diffractograms with the observed diffraction peaks depends on the employed molar ratio (Figure 3). For all the tested formulations, the diffractograms showed new peaks compared with the diffractograms of drug and amino acid. Examples of the newly emerged diffraction peaks include those recorded at 7.31, 13.58, 21.8 and 23.54. This supports our previous supposition of formation of new crystalline species (co-crystal). The diffraction peaks that were recorded at 8.68, 19.21 and 34.72$^{o}$ in the diffractogram of L-proline disappeared after processing with lamotrigine at molar ratios of 1:1 and 1:2 which indicates complete interaction with L-proline. These diffraction peaks started to show again in the diffractogram of the formulations containing drug and L-proline at molar ratios of 1:3 and 1:4 indicating the presence of excess L-proline. These data in addition to the recorded DSC data prove the formation of co-crystal between lamotrigine and L-proline with the molar ratio of 1:2 being the optimum ratio for interaction. Similar strategy was followed in identification of the optimum co-crystallization ratio between drugs and co-formers (Wang *et al*., 2013; El-Gizawy *et al*., 2015; Arafa *et al*., 2016, Nugrahani *et al*., 2018).

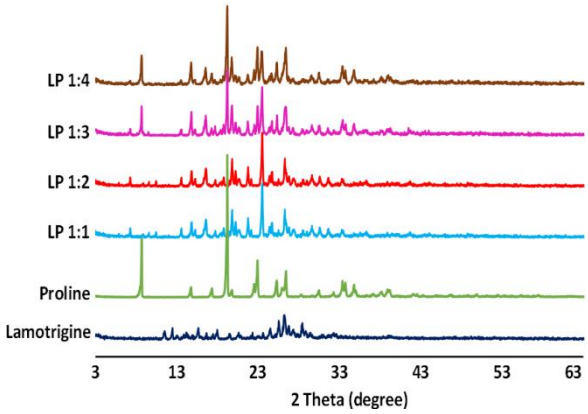


Figure 3. X-ray diffraction pattern of pure lamotrigine, L-proline, and the prepared formulations (Table I).

**Dissolution studies**

Lamotrigine dissolution rate was studied from the unprocessed lamotrigine and the prepared products with L-proline to assess the influence of co-crystallization process on dissolution rate of lamotrigine (Figure 4). These profiles were used to calculate the overall dissolution efficiency of lamotrigine (% DE) and % of the drug dissolved in the first 5 min (% Q5). The dissolution profile (Table I) of pure lamotrigine showed that only 12.54 % of the loaded dose dissolved in the first five minutes and 58.4 % dissolved after one hour. This slow dissolution rate was verified by the recorded low DE value which was only 30.2 %. Such poor dissolution behavior could be accredited to the lipophilic nature of

Lamotrigine being categorized as Class II drug by the Biopharmaceutic Classification System (BCS). These dissolution data seem to coincide with those previously reported for lamotrigine (Khan, 1975).

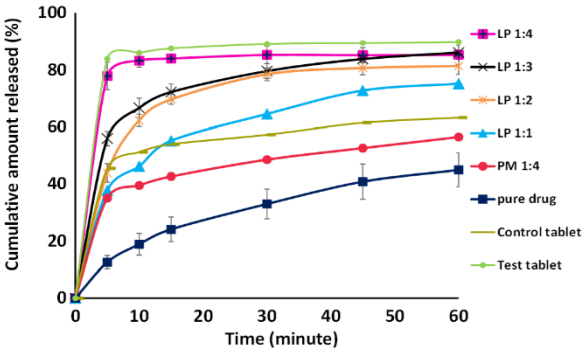


Figure 4. The dissolution profile of pure lamotrigine, the prepared formulations and the prepared tablets (Table I).

Development of co-crystal of lamotrigine with L-proline resulted in significant increase in lamotrigine dissolution rate with the recorded Q5 values were 37.73%, 43.88%, 55.97% and 77.82% for the formulations comprising the drug and L-proline at molar ratios of 1:1, 1:2, 1:3 and 1:4, respectively. The calculated DE values were 57.8%, 69.39%, 71.52% and 80.57% for the same formulations in the same order. Such enhancement in drug dissolution can be attributed to the formation of co-crystals, as reflected by the results of physical state characterization, that favors fast drug dissolution owing to its weaker crystalline structure. The solvation of the API in the co-crystal structure is the reason for enhancing solubility. Because hydrophobic BCS Class II drugs are frequently solubility-limited by reduced solvent-solute interactions, this is the primary method of increasing solubility in water. The incorporation of a polar, water-soluble molecule into the crystalline structure of a hydrophobic API can improve its solvation i.e. co-crystal solubility is related to the co-former solubility. This is due to improved solvation with a co-former having a higher solubility (Thenge *et al*., 2023). Similar explanation was reported with other hydrophobic drugs with poor aqueous solubility (Arafa *et al*., 2016; Arafa *et al*., 2018). Increasing the molar ratio of L-proline even higher than the optimum ratio for co-crystal formation resulted in further increase in lamotrigine dissolution rate. This can be accredited to the ability of L-proline to alter the pH value in the microenvironment around drug particles. Taking the pKa of proline into consideration, it can increase the pH of the diffusion layer which can subsequently augment of the dissolution rate of the weakly acidic lamotrigine (Nugrahani and Jessica, 2021). This was confirmed from the dissolution profile of the physical mixture of lamotrigine and L-proline at molar ratio of 1:4 which showed enhanced dissolution rate compared with pure drug. Noteworthy, the recorded enhancement in the physical mixture which contained proline at the highest tested ratio was lower than that recorded with the corresponding co-processed formulation. This indicates that the dissolution enhancement after co-processing is due to the co-crystallization process with pH change providing additional effect. The buffering effect of amino acid was highlighted in literature and was shown to hasten the dissolution of acidic drugs (Elkholy *et al*., 2020). For comparison between the dissolution pattern of unprocessed lamotrigine and the tested preparations similarity factor (f2) was calculated. The test confirms dissimilarity between pure lamotrigine dissolution behavior either processed or unprocessed and the prepared formulations (f2 ranged from 8–20%). Similarity factor test revealed that the formulations comprising lamotrigine with L-proline at 1:4 molar ratio had higher dissolution rate than the formulations containing lamotrigine and L-proline at lower molar ratios. Accordingly, lamotrigine and L-proline co-crystal at molar ratio of 1:4 (LP 1:4) was utilized for preparation of fast disintegrating tablet preparation.

**Characterization of fast disintegrating tablets**

The prepared tablets were of acceptable difference in their weight with the deviation from the average weight being less than 1%. This acceptable variation was also confirmed by the drug content uniformity test as the recovered drug was in the range of 97-103% and 98-105% of the labeled amount for the test and control tablets, respectively. The average hardness was 5.8±0.2 and 5.3±0.5 kp for the test and control tablets respectively, indicating good compressibility. Disintegration time of test and control tablets was acceptable and was recorded to be 1.5 minute for the control tablets and 1.0 minute for the test tablet. The detected wetting time values were 28 and 30 seconds for the test and control tablets, respectively. Fast disintegration and short wetting time is logic for such formulations because of the presence of super disintegrants.

To assess the impact of tablet preparation and compaction on lamotrigine dissolution rate, the dissolution of lamotrigine from the fabricated tablets was investigated. The recorded dissolution profiles of lamotrigine from the prepared tablets are shown in Figure 4. These profiles showed faster dissolution rate of lamotrigine from lamotrigine and L-proline co-crystal-based tablets compared with the control tablet containing their physical mixture. Test tablets liberated 83.9 % of the loaded amount in the first 5 min while the control tablets released only 45.46 %. Co-crystal containing test tablets showed an overall DE of 82.2% compared with 52.99% for control tablets (Table 2). These data indicate that the compression force utilized during tableting process has no negative impact on drug dissolution as revealed from the recorded high dissolution rate from the test tablets or their corresponding co-crystal formulation. Although the dissolution rate of control tablets remains unacceptable, it is important to notice that the control tablets showed better dissolution rate than the dissolution rate of pure drug powder. The enhancement in drug dissolution after formulation into tablets can be attributed to the effect of blending with carrier like Avicel which can adsorb lamotrigine on its surface reducing drug hydrophobicity. Similar data was reported and explained in the same way for hydrophobic drugs (El Maghraby and Elsergany, 2014; Arafa *et al*., 2017).

## CONCLUSION

Coprocessing of lamotrigine with L-proline using wet co-grinding technique was employed to improve the dissolution rate of the former in the buccal environment. Physical state characterization for the prepared products reflected cocrystal formation suggesting the suitability of L-proline as an efficient co-crystal co-former. Lamotrigine dissolution was markedly improved from the prepared formulations compared to the unprocessed form. The optimized co-grinded formulation was successively used for the preparation of oral disintegrating tablets. The prepared tablets showed significant increase in drug dissolution rate besides their acceptable physical properties including hardness and disintegration time. This dosage form is expected to improve lamotrigine bioavailability due to the increased chance of buccal absorption bypassing, therefore, its pre-systemic metabolism. Such buccal absorption is also expected to be augmented by the presence of L-proline owing to its reported ability to improve permeability of many APIs.

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