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Modulating nimodipine crystallinity for enhancing dissolution: development of geriatric-friendly dosage form

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ABSTRACT

Background: Instant disintegration of oral disintegrating tablets (ODTs) provides greater chance for buccal absorption, avoiding presystemic metabolism of nimodipine. In addition, ODT can be easily dispersed in suitable liquid before delivery via nasogastric tube in critical care setting. Objective: The objective was to improve nimodipine dissolution rate with the goal of developing ODTs for elderly patients, especially those experiencing neurological deficits. Methods: Drop assisted co-grinding of nimodipine with glycine (at molar ratios 1:1, 1:2 and 1:3) or tartaric acid (at molar ratios 1:0.5, 1:1, 1:2, 1:3, and 1:4) was performed. Solid state characterization and in vitro dissolution studies were employed. The optimized formulations were employed to prepare ODTs using suitable excipients. Results: The prepared formulations improved drug dissolution compared to unprocessed and wet ground nimodipine. Fourier–transform infrared spectroscopy, differential scanning calorimetry (DSC), powder X-ray diffraction and scanning electron microscopy suggested transformation of the crystalline structure after co-processing. This was due to salt formation in case of tartaric acid and formation of new crystalline species/size reduction in case of glycine. These changes were associated with dissolution enhancement. Formulations with highest release efficiency (nimodipine and glycine a molar ratio of 1:1 or nimodipine and tartaric acid at molar ratio of 1:3) were successively incorporated in ODTs which showed fast liberation of nimodipine and dissolution efficiency values of 76 ± 0.6 % and 73.3 ± 1.7 % for the tablets containing glycine or tartaric acid respectively. Conclusion: The study introduced simple co-grinding approach for dissolution enhancement of nimodipine with high scaling up
potential. The developed tablets will increase patient compliance with expected improved bioavailability.

**Keywords:** Nimodipine. Glycine. Tartaric acid. Wet co-grinding. Neurological deficits. Rapidly dissolving tablet

**Introduction**

Nimodipine is a 1,4-dihydropyridine-derivative. It was initially used to cure hypertension due to its calcium channel blocking effect\(^1\). It is highly lipophilic molecule with a log P of 4.05 (data from SciFinder database), therefore it has the capacity to cross blood-brain barrier\(^2\). The molecular weight of nimodipine is 418.4 and it has pKa value of 5.41. It has been recommended as a safe agent with a crucial place in pharmacotherapy due to its ability to reduce the seriousness of neurological deficits arising from vasospasm in subarachnoid hemorrhage patients\(^3\)-\(^5\).

Nimodipine belongs to Class II drug, according to BCS, with low solubility and high permeability through the gastro-intestinal tract. The limited solubility can lead to failing to get the needed plasma concentration for the desired pharmacological action\(^6\). It suffers low bioavailability (about 13-30 %) after oral administration due to extensive hepatic first pass metabolism\(^7\). Therefore, patients are advised to take two tablets (30 mg each) every 4 h. This is inconvenient, taken into consideration that most patients on nimodipine therapy are geriatrics.

To improve the geriatrics quality of life, there is a growing demand to formulate novel dosage form to fulfill the increased patients’ desire for convenience and improve compliance. Oral disintegration tablets (ODT), also known as fast disintegrating tablets (FDT), are one such approach to administer solid dosage form in a more convenient way. ODT have been profitably employed in therapy and are widely accepted especially by geriatrics, pediatrics and bedridden. ODT is put on the tongue, with no water, and disintegrate or dissolve immediately within few seconds liberating the drug. Importantly, ODT will provide a greater chance for direct buccal drug absorption into blood bypassing the pre-systemic hepatic metabolism, with expected improvement in drug bioavailability\(^8,9\). To achieve such benefits of ODT, drugs with low aqueous
solubility should be manipulated in a way to hasten the dissolution rate to ensure immediate dissolution after disintegration. Pharmaceutical co-crystal and salt formation showed promising potential for enhanced dissolution of slowly dissolving drugs.

Pharmaceutical cocrystals are neutral crystalline homogenous solids that comprise two different molecular and/or ionic agents at stoichiometric ratio\textsuperscript{10}. One of the two agents is the API and the other is the co-former and this interaction involves bond formation mostly hydrogen bonding\textsuperscript{11}. A co-crystal possesses different crystallinity compared with the pure components and shows different physicochemical characteristics. Cocrystals are given a lot of attention lately because the cocrystal can be tailored to have better physical properties than pure molecules. One of these properties is the dissolution rate of the API. Cocrystal approach was previously used to enhance the dissolution of many drugs\textsuperscript{12-14}. On the other hand, basic or acidic excipients can form salts with acidic or basic drugs, respectively. It was reported that if the difference in the pKa values between the drug and the co-former is higher than 2, this would favor proton transfer with successive ionization and potential salt formation\textsuperscript{15}. Salt formation was utilized in several research as formulation approach for modulating physicochemical properties of drug including drug dissolution\textsuperscript{16-18}.

Therefore, the objective of this study was to prepare orally disintegrating/dissolving tablets of nimodipine. To obtain maximum benefit, it was necessary to improve nimodipine dissolution first. Crystalline structure modification was adopted. This was achieved via co-grinding of nimodipine with potential co-crystals and/or salt forming excipients. Glycine (amino acid) and tartaric acid (organic acid) were selected for this purpose. Tartaric acid was stated to be a successful co-crystal co-former for fenofibrate with a potential of salt formation depending on the pKa difference\textsuperscript{19}. In addition to its health benefits, glycine was also inspected as a potential modifier for the crystalline structure with promising results being recorded with other drugs\textsuperscript{20}. The optimized co-ground formulations were used to prepare ODTs with optimum drug release.

\textbf{Materials and methods}

\textit{Materials}
Nimodipine was supplied as a gift sample by Future, Badr city, Egypt. Ethanol (99% ethyl alcohol), sodium lauryl sulfate (SLS) and tartaric acid were of pharmaceutical grade purchased from EL Nasr Pharmaceuticals Chemicals CO., Cairo, Egypt. Glycine was purchased from LOBA CHEMIE PVT. LTD, India. Croscarmellose sodium, crospovidone, magnesium stearate, mannitol and Avicel PH 102 were obtained from Sigma for Pharmaceutical Industries, Quesna, Egypt.

Spectrophotometric quantification of Nimodipine

The stock solution of nimodipine in ethanol was prepared at a concentration of 1 mg/ml. This was appropriately diluted with 0.5% w/v sodium lauryl sulfate solution in water to prepare a sequence of nimodipine concentrations (4, 6, 8, 10, 12, and 14 µg/ml). The absorbance of each concentration was recorded spectrophotometrically at 238 nm. The calibration curve was then constructed and validated regarding linearity, intra-day and inter-day precision (expressed as RSD%), accuracy, limit of detection (LOD) and limit of quantitation (LOQ)21.

Preparation of co-grinded mixtures

Nimodipine was subjected to grinding with either glycine or tartaric acid at different molar ratios as illustrated in Table 1. Mixing was augmented by ethanol (wet co-grinding). The process was adopted from published work with slight modification14. The calculated amount of nimodipine and glycine or tartaric acid were mixed in a mortar and ethanol was added drop wise till the development of a soft paste. The paste was exposed to continuous grinding until evaporation of ethanol and the formation of a dry powder. The process of paste formation and grinding until dryness was repeated five times at the end of which the product was left overnight at ambient temperature (25 °C) to ensure complete evaporation of any residual solvent before packaging in an air-tight container until required. Pure glycine, tartaric acid and drug were treated similarly. The later was used as positive control.

Solid state characterization

Fourier–transform infrared spectroscopy (FTIR)

The FTIR spectra of nimodipine (processed and unprocessed), glycine and tartaric acid (processed and unprocessed) and their co-ground products were collected
using KBr diffuse reflectance mode. The test powders were mixed with a spectroscopic grade of KBr prior to compression to flat disks employing hydraulic press. The disks were scanned from 4000 to 400 cm\(^{-1}\) using FTIR spectrophotometer (Bruker Tensor 27, Ettlingen, Germany). Data analysis was performed using Opus IR, FTIR spectroscopy software, Ettlingen, Germany. The spectrophotometer is supported with a DLaTGS detector.

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

The X-ray diffraction pattern of the drug (processed and unprocessed), excipients (processed and unprocessed), and their co-grinded mixtures were recorded using PAN analytical X-Ray diffractometer (model X’Pert PRO, Netherlands). The equipment is supplied with secondary monochromator, CuK\(\alpha\) radiation (\(\lambda = 1.542 \text{ Å}\)) operated at 45 kV and current of 35 mA. Data gathering is enabled using X’Celerator detector. Incessant scan mode using 2theta scan axis was conducted at ambient temperature with scanning range of 3 to 65° and scanning step size of 0.02°.

**Differential scanning calorimetry (DSC)**

Thermal analysis of the drug, glycine, tartaric acid, and the prepared formulations was performed using a Differential Scanning Calorimeter (DSC) (Perkin Elmer DSC 6 module, Waltham, MA). This equipment can measure the melting transition and enthalpy with uncertainty values of 1 and 3% respectively. Amount equivalent to approximately 2-3 mg of each test sample were loaded into aluminum pans before crimping the lids. The thermal behavior of all samples was investigated at a temperature range of 30-400 °C with a heating rate of 10 °C per minute under a continuous flow of dry nitrogen (20 ml/min). The data gathering and analysis were performed using Pyris software.

**Dissolution studies**

The dissolution rate of the prepared formulations and unprocessed 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 study was done in 900 ml water containing 0.5 % w/v sodium lauryl sulfate, this media is as recommended by the FDA. The dissolution vessels maintained at 37±1 °C with stirring rate of 50 rpm. Samples equivalent to 30 mg of nimodipine from each
powder formulation were introduced into the dissolution vessels which were previously equilibrated to the mentioned working conditions. Aliquots (5ml) were collected periodically for 60 min. The dissolution medium was replenished with new medium after each sample to maintain a constant volume. The collected samples were subjected to immediate filtration using a 0.45 µm Millipore filter before nimodipine quantitation by UV spectrophotometric method at 238 nm. The dissolution studies were performed in triplicates. The dissolution profiles were created by plotting the cumulative amount released as a function of time. These profiles were used to calculate the dissolution parameters that included the amount of drug released after 5min (Q5), total amount released at the end of the experiment and the dissolution efficiency (DE). The later was determined according to Khan, by computing the area under the dissolution curve at time (t) expressed as a percentage of the area of the rectangle supposing 100 % dissolution within similar time\(^2\). The dissolution parameters were employed for comparing formulations. Further comparison was performed using the similarity factor test. Employing the following equation:

\[
F_2=50\times\log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-\frac{1}{2}}\right\} \times 100
\]

Where \(F_2\) is the similarity factor, \(n\) is the number of data points, \(Rt\) is amount dissolved of the reference (%) at time \(t\), and \(Tt\) is amount of the test dissolved (%) at the same time\(^2\). \(F_2\) values more than 50 reflects similarity of the two dissolution profiles.

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

The formulations showed highest enhancement in drug dissolution rate, NG 1:1 and NT 1:3, were used to prepare ODT. The Master formula of the prepared tablets are presented in Table 2. An amount equivalent to 30 mg drug from NG 1:1 or NT 1:3 was geometrically mixed using mortar and pestle with other additives: Avicel as filler, granular mannitol as sweetening agent, croscarmellose and crospovidone as supers- disintegrants.

This process employed a rotary press tablet machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India) using 12 mm rounded punch with flat surface. The compression 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, USP 2000. The weight uniformity test was conducted by estimating the mean weight of 20 tablets selected randomly before comparing the weight of each tablet to this mean value. According to tablet weight of 245 mg, the allowed percentage deviation was ±7.5%. The tablets conform to the specification if no more than two tablets are outside the limit and none differs by more than twice that limit.

Content uniformity test was conducted to ensure consistent quantity of drug in all tablets. The procedure involved random selection of 10 tablets. Each tablet was ground then dispersed in ethanol to solubilize the drug with the aid of sonicator. The clear supernatant was properly diluted before quantification of nimodipine using the UV spectrophotometer. The tablets pass the test if the drug content of at least nine tablets was in the range of 85–115% of the labeled amount of nimodipine. The 10th 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 oral disintegrating tablets 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 taken for complete disintegration of each tablet was recorded.

Though the compression force during compression was adjusted to obtain tablets with hardness ranging from 5-6 Kp, the mechanical property was further confirmed by conducting tablet hardness test. The test was conducted on 10 tablets using Erweka hardness tester.

Nimodipine in vitro release from the prepared ODT was evaluated using the same conditions described for the tested powdered formulation, where tablets were loaded in the dissolution vessels as an alternative to the powdered formulations (see above).

Wetting time

This test was specially designed for ODT and is related to the hydrophilicity of tablet, that is a pre-request for tablet disintegration. A filter paper was sited in a medium
size petri dish. Distilled water (6 ml) was poured over the filter paper. Allura red powder was sprinkled over the tablet surface. The tablets were then carefully placed on the wet filter paper. The wetting time was calculated as the time consumed till the appearance of red color on the tablet surface. The test was conducted on four tablets for each batch and the average wetting time was calculated.

**Results and Discussion**

**Spectrophotometric quantification of Nimodipine**

Nimodipine quantification in the dissolution samples was performed utilizing UV spectrophotometry. The constructed calibration curve was linear within the tested concentration range from 4 to 12 µg/ml. The equation of this calibration curve was \( Y = 0.0732 (\pm 0.0021) \times 0.0097 (\pm 0.014) \). The calculated RSD values were in the range of 1.3 to 3.9 % and 1.8 to 3.5 % for the intraday and interday data, respectively, indicating the precision of the assay method. The lower limit of nimodipine detection was calculated to be 0.639 µg/ml and that of quantitation was computed to be 1.9 µg/ml.

**Characterization of the prepared formulations**

**Fourier Transform Infrared Spectroscopy (FTIR)**

In order to assess the possibility of interaction between nimodipine and the utilized co-formers (tartaric acid and glycine), FTIR was performed for drug, wet grinded nimodipine WGN (positive control), wet grinded glycine WGG, tartaric acid, wet grinded tartaric acid WGT and their formulations. The recorded FTIR spectra are shown in Figure 1 and 2. The spectrum of unprocessed nimodipine revealed the characteristic pattern of the drug indicating the presence of its key functional groups (Figure 1 a). These included NH group of aliphatic secondary amine which appeared as NH stretching vibration at 3299 cm\(^{-1}\) with its bending vibrations at 1647 cm\(^{-1}\). The peak that was recorded at 3099 cm\(^{-1}\) can be accredited to C-H stretching of benzene ring with that recorded at 2821 cm\(^{-1}\) can be attributed to C-H symmetric stretching of methylene group. In addition, stretching vibration for carbonyl group of the ester moiety appeared at 1696 cm\(^{-1}\). The aromatic C=C stretching vibration was noticed as absorption bands at values of 1621 cm\(^{-1}\), 1523.7 cm\(^{-1}\) and 1496 cm\(^{-1}\). For symmetric and asymmetric stretching vibration of NO\(_2\) group, characteristic absorption bands were seen at 1305
and 1461 cm\(^{-1}\). Similar spectral pattern was reported previously for nimodipine by other investigators\(^2\). Processing of nimodipine alone in the same way at which the formulations were treated (positive control) didn’t change its FTIR spectrum (Figure 1 a).

The recorded spectrum of glycine revealed absorption peaks at high wave number values (2794-3431 cm\(^{-1}\) and 2170-2607 cm\(^{-1}\)) which can be accredited to the presence of NH\(^{+3}\) and CH\(_2\) groups (Figure 1 a). The peaks that were noticed around 1498 cm\(^{-1}\) and 1335 cm\(^{-1}\) can be assigned for symmetric stretching mode of COO\(^-\) group and CH\(_2\) wagging vibrations, respectively. The peak at 929 cm\(^{-1}\) is due to the bending vibration of C–H group. The C–N stretching vibrations were recorded as absorption band at 1043 cm\(^{-1}\) and C–C stretching vibrations were seen at 889 cm\(^{-1}\). The absorption bands that were noticed at 504 cm\(^{-1}\), 607 cm\(^{-1}\) and 686 cm\(^{-1}\) indicated the existence of carboxylate group. The presence of carboxylate group stretching vibrations in addition to NH\(^{+3}\) absorption bands reflect the presence of glycine molecule as zwitterionic. Similar peak assignments were reported by other investigators\(^2\). WGG showed slight change in the spectral pattern compared with the unprocessed one. This can be accredited to intramolecular hydrogen bond formation during its processing with ethanol.

FTIR spectrum of unprocessed tartaric acid revealed the absorption peaks that are characteristic for tartaric acid (Figure 2 a). This was appeared as bi-forked peak with its apex at 3414 cm\(^{-1}\) indicating the existence of hydroxyl groups. Carbonyl group stretching vibration was recorded as strong band at 1742 cm\(^{-1}\). The absorption bands that were observed at 1454 and 1400 cm\(^{-1}\) can be assigned for C–O–C bending vibrations and that were recorded at 1288 and 1276 cm\(^{-1}\) being assigned for C–O stretching vibrations. The recorded FTIR spectrum for tartaric acid correlates with the previously reported spectrum\(^9\). Processed form of tartaric acid (WGT) kept on the same spectral pattern as the unprocessed form. However, the difference in intensity of the absorption bands of WGT and tartaric acid is attributed to the difference in relative proportion of the acid to that of potassium bromide during sample preparation.

Simultaneous wet co-grinding of nimodipine with glycine at different molar ratios resulted in spectral pattern that represent the summation of both components (Figure 1 b). This was confirmed from the presence of the main characteristic
absorption bands in the spectra of the prepared formulations. This behavior may indicate no chemical interaction with nimodipine. Similar data were reported previously and were taken as indication on the absence of chemical interaction\textsuperscript{21, 27}. The spectra of the product of co-grinded nimodipine with tartaric acid showed changes from the spectrum of individual component (Figure 2 b). Absorption band for amino group of nimodipine shifted to lower wave number compared with its original position. Upon increasing the concentration of tartaric acid, the peak disappeared. This could suggest interaction between tartaric acid and nimodipine.

**Differential scanning calorimetry (DSC)**

Nimodipine, glycine, tartaric acid, their wet ground forms and the prepared formulations at different molar ratios were characterized using differential scanning calorimeter. The recorded thermograms are shown in Figures 3 and 4 with the calculated thermodynamic parameters including onset, endset, transition midpoint (T\textsubscript{m}) and enthalpy being presented in Table 3.

For pure untreated nimodipine, the thermogram showed a sharp melting endotherm at T\textsubscript{m} value of 128.5 °C with an onset of 124.9 °C and endset of 133.2 °C which confirms nimodipine crystallinity. A broad endothermic peak was detected at 337 °C and can be owed to drug decomposition (Figure 3). The same thermal behavior of nimodipine was reported by other researchers\textsuperscript{21}. Nimodipine that was treated using ethanol in the same way (WGN) at which the formulations were treated showed a shift in the position of the main melting transition to appear at 119.1 °C (Figure 3 and Table 3). This change can be attributed to polymorphic transition of nimodipine after recrystallization from ethanol. However, this requires verification using X-ray diffraction. Two distinct polymorphs have been identified for nimodipine and showed significant difference in the melting transition\textsuperscript{28}.

The thermogram of untreated glycine revealed an endothermic peak at T\textsubscript{m} value of 258 °C indicating its melting and this matches with the previously published thermal behavior for glycine\textsuperscript{26}. Processing of glycine alone (WGG) didn’t change its thermal behavior significantly with the recorded onset being 251.21 °C, endset of 274.35 °C and T\textsubscript{m} of 260.27 °C (Figure 3 and Table 3).

Co-grinding of nimodipine with glycine in presence of ethanol at different molar ratios resulted in thermograms in which the main melting transition for nimodipine underwent noticeable alterations in the position and shape of the endotherm
which broadened with increased proportions of glycine. These changes were associated with significant increase in the enthalpy of the first transition endotherm (Figure 3 and Table 3). These manifestations suggest possible development of new crystalline structure. These results contradict with the recorded FTIR data that indicate absence of chemical interaction between glycine and nimodipine.

Regarding tartaric acid, an asymmetric endothermic peak which was characterized by sharp apex with a recorded Tm of 216.5 °C. The peak was broad at higher temperature and can be credited to melting and decomposition of tartaric acid (Figure 4 and Table 3). Similar thermal pattern was published previously for tartaric acid⁹.

Recrystallization of tartaric acid from its ethanolic solution (WGT) resulted in non-significant alteration in the position of the main endothermic peak to be recorded at an onset of 209.94 °C, endset of 226.5 °C and Tm value of 217.83 °C (Figure 4 and Table 3).

Grinding of nimodipine and tartaric acid in presence of ethanol produced thermal pattern depending on the composition of the mixture. The most important change was the disappearance of the thermal events of drug decomposition. This suggests transformation of the drug into new species whose decomposition events took place in temperature range outside that of the DSC studies. Interestingly, the mixture containing nimodipine with tartaric acid at molar ratio of 1:0.5 showed a thermogram in which the endothermic peak of tartaric acid disappeared. This endothermic peak started to show up again in mixture containing 1:1 molar ratio. This behavior supports possible development of new crystalline species in which 1:0.5 molar ratio of nimodipine with tartaric acid provided the optimum composition for this transformation. A broad endothermic peak at Tm value of approximately 88 °C was noticed in all tested formulations due to the evaporation of bonded liquid. The proposed crystalline changes may be attributed to possible salt formation between nimodipine (pKa =5.41) and tartaric acid (pKa =2.72). The difference in pKa values of nimodipine and tartaric acid supports this possibility²⁹,³⁰.

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

Powder x-ray diffractometry was employed to investigate the crystalline behavior of nimodipine, WGN, glycine, WGG, tartaric acid, WGT and their formulations. The recorded diffractograms are shown in Figure 5 and 6.
Nimodipine diffractogram shows the main diffraction peaks that are characteristic for nimodipine, proving its crystallinity. These peaks were recorded at 6.3°, 12.95°, 17.4°, 20.37°, 23.9°, 24.8°, 26.4° and 33.3°. This diffractogram is identical to that reported by other authors²¹. Processing of nimodipine using ethanol (positive control) produced diffraction pattern showing no significant changes compared with untreated nimodipine indicating absence of any change in drug crystallinity (Figure 5). This finding contradicts the recorded assumption made on the base of DSC studies and eliminates the existence of polymorphic transition after recrystallization form ethanol.

For pure unprocessed glycine, the recorded diffractogram contained numerous diffraction peak at 23.9, 25.1, 28.3, 33.5, 35.2, 36.5, 38.4, 39.2, 42.01, 42.61, 44.63, 63.3°. This indicates its crystalline nature. After wet processing with ethanol this, pattern changed drastically producing new diffraction peaks. This behavior can be attributed to polymorphic transition of glycine after processing with ethanol. This behavior was recorded previously for glycine³¹.

Wet co-processing of nimodipine with glycine at various molar ratios produced crystalline products with modulated diffraction patterns compared with the individual diffractogram of the processed components of the mixtures (Figure 5). The changes were manifested by the appearance of new diffraction peaks which were recorded at 12.05, 16.03, 19.57, 20.85 and 27.07° associated with these changes the integral peaks of the drug and glycine were disappeared or distorted (Figure 5). These data correlate with the DSC results which suggests development of new crystalline product. Along with development of the crystalline product, the recorded diffraction peaks showed significant reduction in the intensity suggesting size reduction after co-processing³².

The recorded diffractogram for tartaric acid can be taken as evident for its crystallinity owing to the presence of the main diffraction peaks of tartaric acid (Figure 6). These peaks were recorded at 2 Theta of 10.0, 14.2, 18.7, 19.6, 21.7, 22.6, 26.7, 26.6, 29.9, 32.6, 34.2, 36.0, 37.9, 39.7, 42.51 and 44.0°. This crystalline nature was proven in many researches and was retained after processing with ethanol but with slight reduction in peak intensity⁹.

Co-grinding of nimodipine with tartaric acid at different molar ratios in presence of ethanol produced completely different diffraction pattern compared to that of pure wet ground nimodipine or tartaric acid (Figure 6). This was confirmed from the
existence of new diffraction peaks which were not recorded in the individual components at 2 theta values of 10.35, 12, 15, 19.6, 20.74, 25.45, 27.1, 31.36, 37.54 and 38°. The newly recorded diffraction pattern coincides with the obtained data from DSC and indicates possibility of new species formation which is likely to be salt. Alteration in X-ray diffraction pattern was considered previously as an evident for salt formation\textsuperscript{33}. However, salt formation requires future confirmatory investigations using SCXRD.

\textit{Scanning electron microscopy}

The morphology and size of nimodipine crystals, WGN, WGG, WGT and the optimum product (with the highest dissolution rate) of wet co-grinding were monitored via scanning electron microscopy. The recorded photomicrographs are shown in Figure 7. Pure nimodipine appeared as irregular shape crystals but mostly elongated with non-uniform size. Similar photomicrographs were reported previously for nimodipine\textsuperscript{34}. Wet grinding of nimodipine in absence of glycine and tartaric acid reduced the particle size compared to the unprocessed crystals with the crystals preserving their shape with some aggregations. Regarding wet grinded excipients, glycine crystals appeared elongated with polyhedron morphology. For tartaric acid, the crystals were of wide variation in size with mixed oblong and flack shapes (Figure 7 c-d).

Wet co-grinding of nimodipine with glycine and tartaric acid produced crystalline product with altered morphology. The photomicrograph of nimodipine with tartaric acid revealed new crystal morphology that differ from the individual components (Figure 7e). The aggregates of nimodipine disappeared with the appearance of almost round crystals. This could suggest possible interaction and formation of new species. This new species could be the salt form of the drug as suggested by DSC and X-ray diffraction data. In case of co-processed drug with glycine, new morphological features were recorded supporting the development of new crystalline species in which the crystal shape of both nimodipine and glycine were not preserved (Figure 7 f). These results support the instrumental analysis data.

\textit{Dissolution studies}

Nimodipine dissolution rate was monitored from pure unprocessed drug, processed form (WGN) and the prepared wet co-ground formulations with either glycine or tartaric acid to evaluate the impact of co-grinding process on drug dissolution.
rate. The obtained dissolution profiles are presented in Figure 8. The recorded dissolution profiles were utilized to compute the dissolution parameters including the overall dissolution efficiency (DE%) and Q5 which is the quantity of drug dissolved in the first five minutes with these data being presented in Table 1. The dissolution profile for pure nimodipine revealed slow dissolution for the drug with 17.7 % of the loaded dose dissolved in the first five minutes and 58.4 % of the dose dissolved within one hour. This slow dissolution rate was confirmed from the DE value which was calculated to be 40.3 %. The recrystallized form of nimodipine WGN (positive control) didn’t show significant increase in drug dissolution rate with only 25.1 % dissolved in the first five minutes and calculated DE value of 48.5 % (Figure 8a and Table 1).

Wet co-grinding of nimodipine with glycine resulted in marked increase in nimodipine dissolution rate with the recorded Q5 values were 50.7 %, 51.1 % and 57.1 % for the preparations comprising the drug and glycine at molar ratios of 1:1, 1:2 and 1:3 respectively. The DE values were calculated to be 68.6 %, 68.2 % and 71.3 % for the same formulations, respectively. This enhancement in drug dissolution can be accredited to the modification in the crystalline structure of nimodipine that was detected by the adopted instrumental analysis techniques. The results of DSC and X-ray diffraction proposed formation of new crystalline species, most properly co-crystals. This new species showed better dissolution pattern compared to the parent raw drug. Particle size reduction, as reflected by X-ray spectra and SEM, with subsequent increase in the surface area can be taken as another contributing factor. To compare between the dissolution profiles of unprocessed nimodipine and the tested formulations, the in vitro dissolution similarity factor (f2) test was performed. The test revealed dissimilarity between the dissolution rate of pure drug (unprocessed or recrystallized) and the tested formulations confirming the superiority of the prepared formulations. This dissolution pattern was the same for all formulations regardless the ratio of glycine with the calculated f2 value ranged from 23–32 %. Similarity factor test revealed that the formulation containing nimodipine and glycine at different molar ratio had similar dissolution rate.

With respect to nimodipine and tartaric acid, the tested formulations showed significant increase in the dissolution rate compared with pure nimodipine or its recrystallized form. This enhancement was manifested as an increase in Q5 values which were recorded to be 38.9 %, 35.7 %, 41.2 %, 59.2 % and 59.6 % for formulations...
comprising nimodipine and tartaric acid at molar ratios of 0.5:1, 1:1, 1:2, 1:3 and 1:4, respectively. Besides, the dissolution efficiency values were similarly increased (Figure 8b, Table 1). This enhanced dissolution rate can be attributed to the formation of new species, most probably salt form, with higher drug dissolution as suggested from instrumental characterization techniques. The employed similarity factor test confirmed the superiority of the tested formulations compared with unprocessed nimodipine or the recrystallized nimodipine with the f2 value ranging from 16–42 %. Similarity factor test indicated that the formulations comprising nimodipine with tartaric acid at 1:3 and 1:4 molar ratio were similar and had higher dissolution rate compared with the formulations containing nimodipine and tartaric acid at 0.5:1, 1:1, 1:2 molar.

Characterization of oral dispersible tablets

The developed formulations showed the highest dissolution rate were utilized to prepare oral dispersible/disintegrating tablets. The prepared tablets were subjected to quality control tests with the results being presented in Table 2. The two tablet batches were of uniform weight (deviation from the average weight was less than 1 % and uniform drug content (96.8–107 %). The average hardness of the prepared tablets was 5.52 ± 0.3 and 5.6 ± 0.5 kp for NG and NT tablets, respectively. Disintegration time was measured to be 29 and 32 second for NG and NT tablets, respectively. This fast disintegration can be credited to the high level of superdisintegrants incorporated into these formulations. The time for disintegration of ODTs is generally accepted to be <1 minute, with actual disintegration time of 5 to 30 seconds when patient administer the tablet.

Regarding wetting time test, which is especially designed for ODT, NG and NT tablets showed 20 and 23 second, respectively. These values coincide with the disintegration time. Such short wetting and disintegration times are desirable for ODT and indicates good tablet porosity. These data are expected for the developed tablets which contains super-disintegrants at optimum concentration.

To elucidate the effect of excipient and tablet compression on nimodipine dissolution rate, the dissolution test was performed for the prepared tablets and compared with the same formulation (NG 1:1 and NT 1:3) before being incorporated into tablets. The obtained dissolution profiles are shown in Figure 8 (a and b), with the calculated dissolution parameters in Table 2. The dissolution data showed that 51.7 %
and 51.4 % of the labeled amount dissolved in the first five minutes with the calculated dissolution efficiency value being 76 % and 73 % for NG tablets and NT tablets, respectively. These data are similar to that recorded for the formulations before tableting indicating no effect of compression force or tablet excipient on the dissolution behavior.

**Conclusion**

Co-grinding of nimodipine with either glycine or tartaric acid improved dissolution rate relative to unprocessed drug. The mechanism of such enhancement differs according to the excipient used. Instrumental characterization suggested salt formation between the basic drug and the organic acid. Size reduction and formation of new crystalline species was proposed for glycine. The optimized formulation for each excipient was successively formulated into oral dispersible tablets suitable for administration by geriatrics with expected improve in drug bioavailability due to pregastric absorption.

**Conflict of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

**Author's contributions**

Houyda E. Abd-Elrahman: Investigation, Data curation, Visualization and writing original draft. Ebtesam A Essa: Conceptualization, Methodology, Visualization, Supervision, Reviewing and Editing. Gamal M. El Maghraby: Data Curation, Visualization, Reviewing and Editing. Mona F. Arafa: Methodology, Data Curation, Visualization, Writing, Reviewing and Editing.

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Figure 1: FTIR spectra of (a) pure unprocessed nimodipine, wet ground nimodipine, glycine and wet ground glycine and (b) the tested formulations. Formulation details are presented in Table 1.

Figure 2: FTIR spectra of (a) pure unprocessed nimodipine, wet ground nimodipine, tartaric acid and wet ground tartaric acid and (b) the tested formulations. Formulation details are presented in Table 1.
Figure 3: DSC thermograms of (a) pure unprocessed nimodipine, wet ground nimodipine and tested formulations and, (b) glycine and wet ground glycine. Formulation details are presented in Table 1.

Figure 4: DSC thermograms of (a) pure unprocessed nimodipine, wet ground nimodipine and tested formulations and, (b) tartaric acid and wet ground tartaric acid. Formulation details are presented in Table 1.
Figure 5: X-ray diffraction pattern of (a) pure unprocessed nimodipine, wet ground nimodipine and tested formulations and (b) glycine and wet ground glycine. Formulation details are presented in Table 1.

Figure 6: X-ray diffraction pattern of pure unprocessed nimodipine, wet ground nimodipine and tested formulations and (b) tartaric acid and wet ground tartaric acid. Formulation details are presented in Table 1.
Figure 7: Scanning electron micrographs of (a) nimodipine, (b) wet ground nimodipine, (c) wet ground tartaric acid, (d) wet ground glycine, (e) NT (1:3) and (f) NG (1:1). Formulation details are presented in Table 1.

Figure 8: The dissolution profile of pure unprocessed nimodipine, wet ground nimodipine, tested formulations and NG (1:1) tablet (a) and NT (1:3) tablet (b). Formulation details are presented in Table 1.
Table 1: Compositions of different formulations of nimodipine (N) prepared using either glycine (G) or tartaric acid (T), 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.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Nimodipine</th>
<th>Glycine</th>
<th>Tartaric acid</th>
<th>Q5</th>
<th>DE(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprocessed drug</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>17.77</td>
<td>40.33</td>
</tr>
<tr>
<td>Wet ground</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>25.1</td>
<td>48.55</td>
</tr>
<tr>
<td>NG1:1</td>
<td>1 (418.4)</td>
<td>1 (75.07)</td>
<td>-</td>
<td>50.77</td>
<td>68.6</td>
</tr>
<tr>
<td>NG 1:2</td>
<td>1 (418.4)</td>
<td>2 (150.14)</td>
<td>-</td>
<td>51.13</td>
<td>68.2</td>
</tr>
<tr>
<td>NG 1:3</td>
<td>1 (418.4)</td>
<td>3 (225.2)</td>
<td>-</td>
<td>57.17</td>
<td>71.3</td>
</tr>
<tr>
<td>NT 1:0.5</td>
<td>1 (418.4)</td>
<td>-</td>
<td>0.5 (75.04)</td>
<td>38.91</td>
<td>61.57</td>
</tr>
<tr>
<td>NT 1:1</td>
<td>1 (418.4)</td>
<td>-</td>
<td>1 (150.09)</td>
<td>35.69</td>
<td>56.66</td>
</tr>
<tr>
<td>NT 1:2</td>
<td>1 (418.4)</td>
<td>-</td>
<td>2 (300.18)</td>
<td>41.25</td>
<td>63.76</td>
</tr>
<tr>
<td>NT 1:3</td>
<td>1 (418.4)</td>
<td>-</td>
<td>3 (450.27)</td>
<td>59.64</td>
<td>74.64</td>
</tr>
<tr>
<td>NT 1:4</td>
<td>1 (418.4)</td>
<td>-</td>
<td>4 (600.36)</td>
<td>59.64</td>
<td>74.75</td>
</tr>
</tbody>
</table>

- Positive control is the wet ground drug.
- Values between brackets represent the weight ratios in milligrams (mg).
Table 2: The master formula for the preparation of nimodipine oral disintegrating tablets, together with in vitro dissolution parameters.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Glycine tablets</th>
<th>Tartaric acid tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG 1:1</td>
<td>35.38</td>
<td>_</td>
</tr>
<tr>
<td>NT 1:3</td>
<td>_</td>
<td>62.29</td>
</tr>
<tr>
<td>Avicel</td>
<td>100.62</td>
<td>73.71</td>
</tr>
<tr>
<td>Mannitol</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Tartaric acid sodium</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total tablet weight (mg)</td>
<td>245</td>
<td>245</td>
</tr>
<tr>
<td>Q5</td>
<td>51.7 (3)</td>
<td>51.4 (1.4)</td>
</tr>
<tr>
<td>Q60</td>
<td>90.5 (1.2)</td>
<td>85.4 (1.7)</td>
</tr>
<tr>
<td>Dissolution efficiency (%DE)</td>
<td>76 (0.6)</td>
<td>73.3 (1.7)</td>
</tr>
</tbody>
</table>

- This weight of NG 1:1 and NT 1:3 formulation is equivalent to the dose of the drug (30mg).
- Q5 and Q60 are the percentage drug released after 5 and 60 minutes, respectively.
Table 3: The calculated parameters for the main endothermic peaks of the pure nimodipine (processed (WGN) and unprocessed), glycine (processed (WGG) and unprocessed), tartaric acid (processed (WGT) and unprocessed) and the prepared formulations.

<table>
<thead>
<tr>
<th></th>
<th>Onset (°C)</th>
<th>Endset (°C)</th>
<th>T_m (°C)</th>
<th>Enthalpy J/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure nimodipine</td>
<td>124.9</td>
<td>133.2</td>
<td>128.5</td>
<td>43.9</td>
</tr>
<tr>
<td>WGN</td>
<td>114.6</td>
<td>124.4</td>
<td>119.1</td>
<td>90.5</td>
</tr>
<tr>
<td>Glycine</td>
<td>247.2</td>
<td>272.9</td>
<td>258.2</td>
<td>231.4</td>
</tr>
<tr>
<td>WGG</td>
<td>251.2</td>
<td>274.3</td>
<td>260.2</td>
<td>750.9</td>
</tr>
<tr>
<td>NG 1:1 1st peak 2nd peak</td>
<td>113.9</td>
<td>125.9</td>
<td>119.3</td>
<td>63.04</td>
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<tr>
<td></td>
<td>251.8</td>
<td>264.1</td>
<td>258.1</td>
<td>588.3</td>
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<tr>
<td>NG 1:2 1st peak 2nd peak</td>
<td>113.7</td>
<td>124.8</td>
<td>118.6</td>
<td>79.29</td>
</tr>
<tr>
<td></td>
<td>249.9</td>
<td>263.1</td>
<td>256.4</td>
<td>856.5</td>
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<tr>
<td>NG 1: 3 1st peak 2nd peak</td>
<td>111.2</td>
<td>129.2</td>
<td>120.1</td>
<td>103.4</td>
</tr>
<tr>
<td></td>
<td>230.9</td>
<td>260.2</td>
<td>248.8</td>
<td>983.4</td>
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<tr>
<td>Tartaric acid</td>
<td>211.7</td>
<td>228.7</td>
<td>216.5</td>
<td>362.5</td>
</tr>
<tr>
<td>WGT</td>
<td>209.9</td>
<td>226.7</td>
<td>217.8</td>
<td>777.1</td>
</tr>
<tr>
<td>NT 1:0.5 1st peak 2nd peak</td>
<td>113.5</td>
<td>122.5</td>
<td>117.2</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>195.8</td>
<td>205.2</td>
<td>201.0</td>
<td>7.1</td>
</tr>
<tr>
<td>NT 1:1 1st peak 2nd peak</td>
<td>114.6</td>
<td>123.3</td>
<td>118.5</td>
<td>7.86</td>
</tr>
<tr>
<td></td>
<td>194.7</td>
<td>207.6</td>
<td>202.1</td>
<td>209.3</td>
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<tr>
<td>NT 1:2 1st peak 2nd peak</td>
<td>113.2</td>
<td>128.4</td>
<td>119.5</td>
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</tr>
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<td>194.3</td>
<td>215.1</td>
<td>204.4</td>
<td>343.7</td>
</tr>
<tr>
<td>NT 1:3 1st peak 2nd peak</td>
<td>112.6</td>
<td>128.2</td>
<td>119.1</td>
<td>57.41</td>
</tr>
<tr>
<td></td>
<td>200.2</td>
<td>214.0</td>
<td>204.8</td>
<td>393.2</td>
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<tr>
<td>NT 1:4 1st peak 2nd peak</td>
<td>111.4</td>
<td>127.8</td>
<td>118.4</td>
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<td></td>
<td>198.0</td>
<td>219.4</td>
<td>206.4</td>
<td>581.7</td>
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