Formulation and solid state characterization of carboxylic acid-based co-crystals of tinidazole: An approach to enhance solubility

Jyotsana R. Madan[1,A–F], Rishikesh H. Dagade[1,B–D,F], Rajendra Awasthi[2,A,C–F], Kamal Dua[3,A,C–F]

[1] Department of Pharmaceutics, Smt. Kashibai Navale College of Pharmacy, Savitribai Phule Pune University, India
[2] Amity Institute of Pharmacy, Amity University, Noida, India
[3] Discipline of Pharmacy, Graduate School of Health, University of Technology, Sydney, Australia

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

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Address for correspondence
Jyotsana R. Madan
E-mail: jyotsna.madan@sinhgad.edu

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Abstract

Background. Tinidazole (TNZ) is an anti-parasite drug used in the treatment of a variety of amebic and parasitic infections. It has low solubility in aqueous media and is categorized under Class II of the Biopharmaceutical Classification System.

Objectives. The aim of this research was to study the potential for enhancing the solubility of TNZ using carboxylic acid co-crystals.

Material and methods. The solubility of TNZ was determined individually using 6 carboxylic acids for forming co-crystals at a 1:1 stoichiometric ratio. Three carboxylic acids – namely tartaric acid (TA), oxalic acid (OA) and glutaric acid (GA) – resulted in the formation of co-crystals with enhanced solubility. An equilibrium solubility study of TNZ co-crystals at 1:1.5 and 1:2 stoichiometric ratios was also carried out. The co-crystals which developed were evaluated using X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC) to study the drug–co-crystal former interactions.

Results. The solubility of TNZ in distilled water was found to be 0.014 mg/mL. The highest enhancement ratio was obtained with TNZ and TA at a ratio of 1:1. Differential scanning calorimetry thermograms suggested that the drug and carboxylic acids had undergone interactions such as hydrogen bonding. The XRD and DSC results confirmed the formation of co-crystals.

Conclusions. It was concluded that the results of enhanced solubility of TNZ using co-crystals is a clear indication of the potential for co-crystals to be used in the future for other poorly water-soluble drugs, considering that co-crystals are a safe and cost-effective approach.

Key words: solubility, co-crystals, solvent evaporation

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Introduction

Pharmaceutical co-crystals are multi-component crystals based on hydrogen bonds without the transfer of hydrogen ions to form salts.[1] Co-crystal formation has recently gained attention in pharmaceutical applications. The ability to tailor the physicochemical properties of a substance via complexation is highly desirable in terms of dissolution rate, bioavailability, stability, and processing.[2–5] Co-crystals can also enhance the flowability, compressibility and hygroscopicity of drugs.[6] A co-crystal may be defined as a material which contains 2 or more discrete molecular entities in its crystal lattice.[7] In pharmaceutical terms, a co-crystal is a molecular complex of an active pharmaceutical ingredient and a second molecule, known as a co-crystal former, which typically requires complementary hydrogen bonding between the 2 components.[8] Co-crystallization may influence the pharmacokinetics of therapeutically active compounds, which may in turn influence their biopharmaceutical and bioavailability properties, including absorption.[9–11] The components in a co-crystal exist in a definite stoichiometric ratio, and are assembled via non-covalent interactions such as hydrogen bonds, ionic bonds, π–π, or van der Waals interactions rather than by ion pairing.[12]

Tinidazole [1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole] (TNZ) (Fig. 1) is an anti-parasite drug used against protozoan infections. It may also be used as part of a combination therapy for *Helicobacter pylori* eradication. It has low solubility in aqueous media and is categorized as Class II in the Biopharmaceutical Classification System.[13] This property makes the drug a suitable candidate for research investigating new salts with improved solubility.

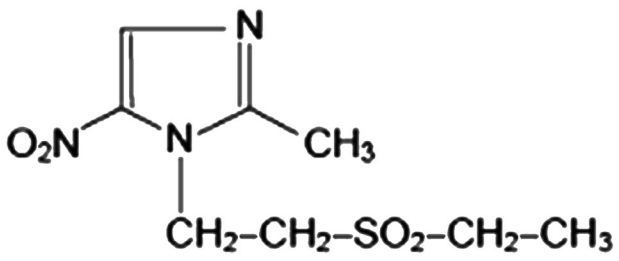

Fig. 1. Chemical structure of TNZ

The aim of this work was to explore the possibility of TNZ co-crystal formation with various carboxylic acids, with an emphasis on determining whether it can form co-crystals with multiple stoichiometries. A method based on solvent evaporation was used to determine the possibility of forming co-crystals from the 2 components.

The spherical crystallization technique is a novel agglomeration method for liquid systems which was developed by Kawashima in the 1980s.[1] In this system, agglomeration and spheroidization can be carried out simultaneously during the crystallization process of a substance with a bridging liquid by means of stirring. In the beginning, the spherical crystallization technique was mainly used in direct tableting technology because crystallization and agglomeration could be carried out simultaneously in a single step. The resultant agglomerates exhibited dramatically improved flowability, packability and compressibility.[2,3] Later on, functional drug devices such as microspheres,[4] microcapsules,[5] microballoons,[6] and biodegradable nanospheres[7] were developed using the emulsion-solvent-diffusion method, one of the spherical crystallization techniques involving the introduction of a functional polymer into the system.

Material and methods

Material

The TNZ was received as a gift sample by Aarti Drugs Ltd., Mumbai, India. Tartaric acid (TA), oxalic acid (OA), glutaric acid (GA), citric acid, salicylic acid, malonic acid, magnesium stearate, talc, and lactose monohydrate were purchased from Research-Lab Fine Chem Industries, Mumbai, India. Sodium starch glycolate and microcrystalline cellulose were purchased from BASF India Ltd., Mumbai, India. Methanol was purchased from Thomas Baker Chemicals, Mumbai, India. All other reagents were of analytical grade.

Methods

Determination of solubility

The saturation solubility of TNZ was determined in distilled water. In brief, 100 mg of TNZ was added to the distilled water and kept in an incubator shaker (100 rpm) for 24 h at 37°C. After 24 h, the solution was centrifuged at 2000 rpm for 15 min and filtered through Whatman grade 41 filter paper. The supernatant was diluted with distilled water and its absorbance was measured at 318 nm using a UV spectrophotometer (model V-630; Shimadzu Corporation, Kyoto, Japan). The saturation solubility was then calculated.

Preliminary trials for the preparation of TNZ co-crystals

Based on the literature,[14–18] 6 carboxylic acids were initially selected for producing co-crystals of TNZ at a 1:1 stoichiometric ratio. In brief, a precisely weighed amount of TNZ and individual carboxylic acids (TA, OA, GA, malonic acid, salicylic acid, and citric acid) at a 1:1 stoichiometric ratio were dissolved in methanol and sonicated for 10 min in order to completely mix the ingredients. The resulting solution was poured onto a Petri plate and stored

to allow the solvent to completely evaporate at room temperature (25°C). Co-crystals of TNZ formed with 3 of the carboxylic acids (TA, OA and GA). No co-crystals were obtained from malonic acid, salicylic acid or citric acid. Based on these results, TA, OA and GA were selected for further study and were used to produce TNZ co-crystals at 1:1.5 and 1:2 stoichiometric ratios (Table 1).

Equilibrium solubility study of TNZ co-crystals (1:1, 1:1.5, and 1:2 stoichiometric ratios)

The solubility of TNZ in water from co-crystals formed with the 3 carboxylic acids remaining after screening (TA, OA and GA) was determined at room temperature using an incubator shaker (OS-02; Chromus Biotech, Bengaluru, India). Excess amounts of the TNZ co-crystals with the individual carboxylic acids at different ratios (Table 2) were added to 5 mL of distilled water and were shaken until a saturated solution was formed. The vials were shaken on a mechanical shaker for 24 h. The solution was then centrifuged at 2000 rpm for 10 min in an ultra-centrifuge and were filtered through Whatman grade 41 filter paper. Aliquots were suitably diluted with distilled water and methanol (1:1) and analyzed using a UV spectrophotometer (model V-630; Shimadzu Corporation) at 318 nm.

Characterization of TNZ co-crystals

Differential scanning calorimetry (DSC)

To investigate the effect of temperature, thermograms of TNZ, TA, OA and GA, as well as of co-crystals of TNZ and the 3 carboxylic acids were recorded using a differential scanning calorimeter (DSC 4000 System; Perkin Elmer, Waltham, USA). An empty aluminum pan was used as a reference. The DSC measurements were taken at a heating rate of 10°C/min from 30°C to 300°C.[19,20]

Table 2. Formulation of TNZ tablets prepared by the direct-compression method (formulation T1)

Ingredients	Quantity [mg]
Co-crystal equivalent of 300 mg of tinidazole with tartaric acid (1:1)	482
Microcrystalline cellulose	60
Sodium starch glycolate	12
Magnesium stearate	8
Talc	8
Lactose	150

X-ray powder diffraction analysis

The physical state of pure TNZ and TNZ in co-crystals was examined using an X-ray diffraction analyzer (Philips 1710 powder X-ray diffractometer; Koninklijke Philips N.V., Amsterdam, the Netherlands). The X-ray diffraction patterns were recorded using Cu *Kα* radiations (θ = 1.54059 Å), a current of 30 mA, and a voltage of 40 kV. The samples were analyzed over a 2θ range of 10–80.[21–23]

In vitro dissolution study

The drug dissolution rates from different co-crystals were determined and compared to that of pure TNZ. The dissolution study was performed using a United States Pharmacopeia (USP) type-II apparatus (model TDT-08L; Electrolab India, Mumbai, India). The dissolution medium (900 mL of distilled water) was maintained at a temperature of 37 ±0.5°C in the dissolution vessel. The co-crystal equivalent of 300 mg of TNZ was placed into the dissolution vessel and the paddle was rotated at 50 rpm. Aliquots were withdrawn at 15 min intervals for 90 min. Those samples were filtered and analyzed using a UV spectrophotometer (model V-630; Shimadzu Corporation) at 318 nm. The dissolution study was conducted in triplicate.[19,20]

Table 1. Results of solubility studies for TNZ–carboxylic acid co-crystals

Drug	Carboxylic acid	Quantity of drug [mg]	Quantity of carboxylic acid [mg]	Solubility [mg/mL]*	Solubility enhancement ratio
1:1 stoichiometric ratio					
TNZ	tartaric acid	200	121.39	0.1540 ±0.002	11.00
TNZ	oxalic acid	200	72.81	0.0700 ±0.001	5.00
TNZ	glutaric acid	200	106.85	0.0784 ±0.001	5.60
1:1.5 stoichiometric ratio					
TNZ	tartaric acid	200	182.08	0.0995 ±0.002	7.10
TNZ	oxalic acid	200	109.22	0.1445 ±0.003	10.32
TNZ	glutaric acid	200	160.28	0.1183 ±0.002	8.45
1:2 stoichiometric ratio					
TNZ	tartaric acid	200	242.78	0.0995 ±0.001	1.12
TNZ	oxalic acid	200	145.62	0.1445 ±0.002	3.41
TNZ	glutaric acid	200	213.70	0.0160 ±0.001	1.18

* Data is presented as mean ± standard deviation (SD) (n = 3).

Production of TNZ tablets by the direct-compression method

Tablets of co-crystal equivalents of 300 mg of TNZ and TA (1:1) were prepared using the direct-compression method according to the formula given in Table 2. All of the ingredients were passed separately through a 60-mesh sieve. Co-crystals and microcrystalline cellulose were mixed by adding small amounts of each several times and blending them to obtain a uniform mixture and kept aside. The ingredients were then weighed and mixed in geometrical order and the tablets were compressed with a Rimek Compression Machine using the 8-millimeter flat round punch. The resulting tablets were evaluated and the pre-compression and post-compression parameters were compared.

In vitro drug release study

The in vitro drug release from the resulting tablets was studied using a USP type-II apparatus (USP XXIII Dissolution Test Apparatus; Electrolab India, Mumbai, India) at 100 rpm using 900 mL of distilled water as a release medium. The temperature of the medium was maintained at 37 ±0.5°C. Aliquots were withdrawn at 30-minute intervals for 180 min, then filtered and analyzed at 318 nm using a UV spectrophotometer (model V-630; Shimadzu Corporation). The drug concentration was determined from the standard calibration curve. The release profile of a commercially available TNZ tablet (300 mg of TNZ – Tiniba 300 tablet; Zydus Cadila, Ahmadabad, India) was compared with that of the tablets produced.

Results and discussion

Some of the acids (TA, OA and GA) provided satisfactory results in terms of safety for acceptance in therapy (Fig. 2). Hydrogen bonds occur between the nitrogen and sulfonyl oxygen of TNZ and the hydrogen of the hydroxyl group of TA. When it comes to OA and GA, the formation of hydrogen bonds between these atoms may not be favorable. The 2 carbon atoms separating the carboxyl groups (-COOH) from the hydrogen-bond donor hydroxyl groups in TA may be optimally suited to form such hydrogen bonds, whereas the 3 carbon atoms separating the carboxyl groups (-COOH) in GA – or 0 carbon atoms in the case of OA – may be less favorable than TA. The stronger ability of TA to form hydrogen bonds with TNZ may be responsible for the enhanced solubility of these co-crystals.

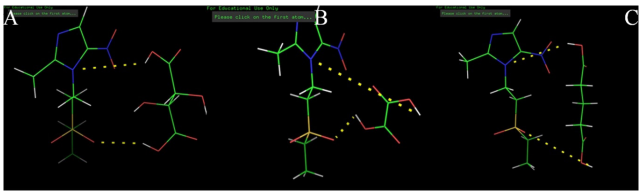

Fig. 2. The probable hydrogen bond formation between TNZ and tartaric acid (A), TNZ and oxalic acid (B), and TNZ and glutaric acid (C)

Equilibrium solubility studies of the co-crystals

The solubility of TNZ in distilled water was found to be 0.014 mg/mL. Co-crystals of TNZ and tartaric acid demonstrated maximum solubility at a stoichiometric ratio of 1:1, while OA and GA co-crystals performed best at a ratio of 1:1.5. The solubility enhancement ratios of the above combinations were 11.00 (TNZ:TA, 1:1), 10.32 (TNZ:OA, 1:1.5), and 8.45 (TNZ:GA, 1:1.5), respectively (Table 1).

Differential scanning calorimetry analysis

As the physical state of a drug influences its release kinetics, differential scanning calorimetry (DSC) was conducted for the pure drug, for carboxylic acids and for the co-crystals in order to determine the physical state of drug – i.e., amorphous or crystalline – before and after the production of co-crystals. The results of the DSC study are presented in Fig. 3. The DSC spectrum of TNZ showed a sharp endothermic peak at 128°C, indicating its melting point (126–129°C). In the DSC thermogram of the co-crystals with enhanced solubility (TNZ:TA, 1:1, TNZ:OA, 1:1.5 and TNZ:GA, 1:1.5), the endothermic peaks of both the drug and the carboxylic acids (TA, OA and GA) were visible, but not very intense and slightly shifted from their original positions, indicating that the TNZ and the carboxylic acids had undergone interactions such as hydrogen bonding.

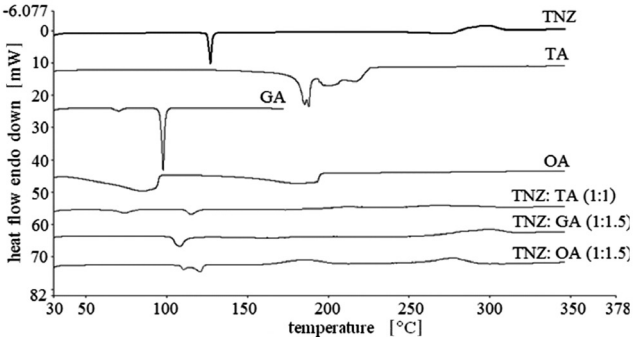

Fig. 3. Differential scanning calorimetry analysis (DSC) of TNZ and co-crystals

X-ray powder diffraction analysis

X-ray diffraction was used to evaluate the physical state of TNZ and the drug within the co-crystals produced. The X-ray diffractograms of TNZ, the carboxylic acids and the co-crystals are presented in Fig. 4. Tinidazole displayed characteristic, intense peaks at 2θ of 10.62, 15.24, 17.84, 18.18, 18.84, 21.23, 22.42, 23.87, 27.20, 27.63, 28.28, 29.57, 31.28, 33.15, 35.26, 36.26, 37.26, 38.26, 31.21, 34.24, and 39.46, indicating its crystalline nature.

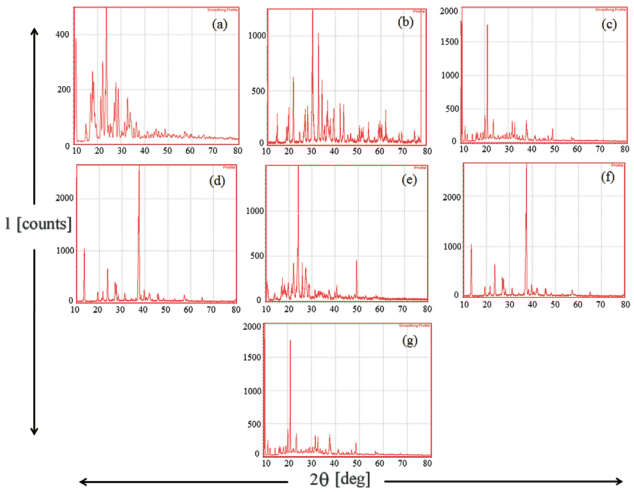

Fig. 4. X-ray powrder diffraction (XRPD) spectra of (a) TNZ, (b) tartaric acid, (c) TNZ + tartaric acid (1:1), (d) glutaric acid, (e) TNZ + glutaric acid (1:1.5), (f) oxalic acid, and (g) TNZ + oxalic acid (1:1:1.5)

In the co-crystals prepared with TA, peaks of a reduced intensity were visible at 2θ of 11.39, 13.92, 15.84, 17.93, 18.17, 19.42, 20.34, 21.14, 23.42, 32.34, 33.17, and 37.52, indicating that the drug is partly dissolved within the formed matrix and partly in an amorphous form distributed throughout the system.

The co-crystals with GA showed peaks at 2θ of 10.62, 13.94, 17.24, 18.44, 19.14, 22.22, 24.24, 26.42, 25.13, 29.31, 37.41, 41.16, and 49.46, while the co-crystals with OA demonstrated peaks at 2θ of 10.12, 11.95, 12.87, 14.24, 16.14, 17.24, 18.24, 19.57, 20.11, 21.22, 23.24, 29.42, 30.23, 31.37, 32.21, 37.86, and 49.34. Overall, the decrease in the number and intensity of peaks indicates that the drug is partly dissolved within the formed matrix and partly in a crystalline form distributed throughout the system; this confirms the formation and existence of co-crystals.

Dissolution profile of TNZ and TNZ co-crystals at different stoichiometric ratios

The dissolution profiles of TNZ and co-crystals of TNZ with different carboxylic acids and at different stoichiometric ratios are presented in Fig. 5–7. From the equilibrium solubility studies and dissolution studies, it was determined that a 1:1 stoichiometric ratio is best for TNZ + TA co-crystals. A 1:1.5 stoichiometric ratio was found to be best for TNZ + OA and TNZ + GA co-crystals. The analysis indicates that TNZ + TA (1:1 stoichiometric ratio) performed the best of all the ratios, and was therefore selected for the production of tablets.

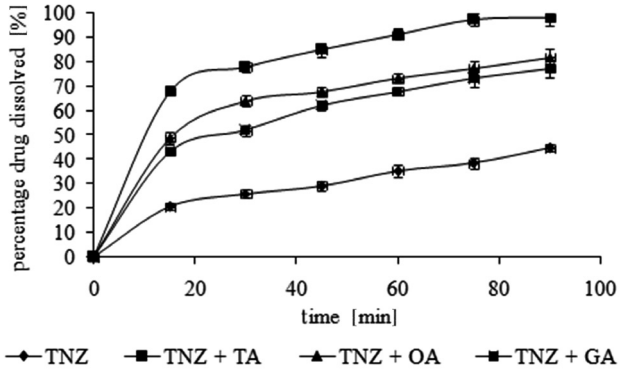

Fig. 5. Dissolution profile of TNZ and TNZ co-crystals (1:1 ratio) in distilled water at 37°C ±0.5°C (data presented as mean ±SD, n = 3)

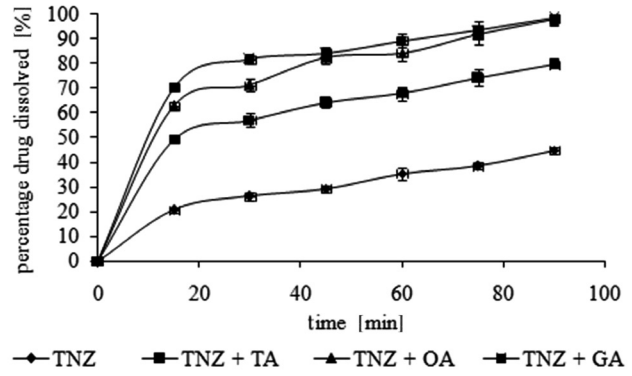

Fig. 6. Dissolution profile of TNZ and TNZ co-crystals (1:1.5 ratio) in distilled water at 37°C ±0.5°C (data presented as mean ±SD, n = 3)

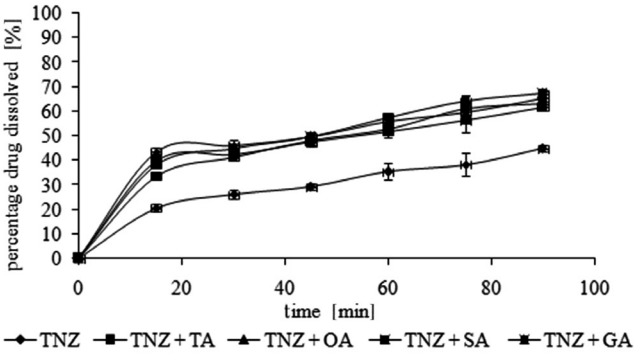

Fig. 7. Dissolution profile of TNZ and co-crystals of TNZ (1:2 ratio) in distilled water at 37°C ±0.5°C (data presented as mean ±SD, n = 3)

Evaluation of tablets

Pre-compression parameters

The small differences in the values of bulk density and tapped density illustrate the free-flowing nature of powder blend. Hausner's ratio was found to be 1.132, which indicates that the powder blend is free-flowing (Table 3). The value of compressibility index (15–16) and the angle of repose (30–31°) indicate good flowability, so the power blend can be used to directly manufacture directly compressed tablets.

Table 3. Results of pre-compression powder blend (formulation T1); the data is presented as mean ± standard deviation (SD) (n = 3)

Bulk density [gm/cm³]	Tapped density [gm/cm³]	Hausner ratio	Compressibility index [%]	Angle of repose [°]
0.845 ±0.04	0.926 ±0.08	1.132 ±0.06	16.30 ±1.26	31.00 ±1.45

Post-compression parameters

The post-compression parameters of the tablets containing TNZ–carboxylic acid co-crystals (formulation T1) are as follows: the hardness of the tablets was 2.0 ±0.14 kg/cm^2, their friability was 0.61 ±0.01%, the drug content was 97 ±0.82%, and the disintegration time was 120 ±5 s (Table 4). All of the post-compression parameters were within the acceptable ranges.

Table 4. Results of TNZ tablets (formulation T1); the data is presented as mean ± standard deviation (SD) (n = 3)

Hardness [kg/cm^2]	Friability [%]	Drug content [%]	In vitro disintegration time [s]
2.00 ±0.14	0.61 ±0.01	97.00 ±0.82	120 ±5

In vitro release studies

Figure 8 presents a graph comparing the percentage of cumulative TNZ release over time for the tablets produced in this study vs a commercially available formulation. The results indicate that after 2 h, the cumulative percentage release of formulation T1 was greater (74.23%) than that of the tablets available on the market (48.42%).

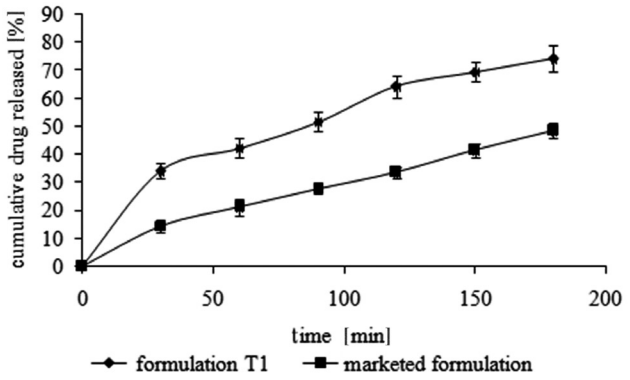

Fig. 8. Comparison of release profile of prepared tablet with marketed tablet in distilled water at 37°C ±0.5°C (data presented as mean ±SD, n = 3)

Conclusions

Our study has clearly revealed that the application of carboxylic acid co-crystals is an effective and safe approach to increasing the dissolution rate of poorly water-soluble drugs. We have demonstrated the utility of carboxylic acid co-crystals using a practically insoluble drug, TNZ, which is a clear indication of their potential application in various other poorly water-soluble drugs.

ORCID iDs

Jyotsana R. Madan https://orcid.org/0000-0001-6663-1890
Rishikesh H. Dagade https://orcid.org/0000-0001-6071-373X
Rajendra Awasthi https://orcid.org/0000-0002-1286-1874
Kamal Dua https://orcid.org/0000-0002-7507-1159

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