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TENOXICAM-KOLLICOAT IR® BINARY SYSTEMS: PHYSICOCHEMICAL AND BIOLOGICAL EVALUATION

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Abstract: Tenoxicam (TNX) binary systems in Kollicoat IR (KL) matrix were prepared in different drug : polymer ratios using kneading and spray-drying method. The prepared binary systems were characterized for drug dissolution rate, differential scanning calorimetry (DSC), IR spectroscopy and x-ray diffractometry. The results showed that the drug dissolution rate was remarkably enhanced by incorporating it in the KL matrix either by kneading or spray-drying, and the dissolution rate was increased by decreasing the drug weight ratio. The DSc and x-ray studies revealed the presence of TNX in less crystalline or amorphous state in its-KL binary systems. Moreover, the spray-dried TNX-KL system in 1 : 4 ratio, that exhibited the faster dissolution rate, was formulated in oral disintegrating tablets (ODTs). The data indicated that a fast disintegration and higher drug dissolution rate was achieved in case of the ODTs containing the spray-dried form compared to the ODTS containing untreated drug or the commercial tablet (Epicotil®). Also, the drug exhibited significantly ($p < 0.01$) faster onset of the anti-inflammatory analgesic activities in case of the ODTs containing the spray-dried form, that was superior to that observed with both the commercial tablet product and the ODTS containing untreated drug.

Keywords: tenoxicam, Kollicoat IR, spray-drying, kneading, oral disintegrating tablets

Tenoxicam (TNX) is a member of the non-steroidal anti-inflammatory drugs. It inhibits the biosynthesis of prostaglandins by inhibiting the cyclooxygenase pathway. It is also considered as an effective anti-inflammatory agent and has been used in the management of rheumatic and inflammatory diseases, including osteoarthritis (1). However, TNX is very slightly water soluble drug and, as with all poorly soluble drugs, its dissolution may be the rate determining step in the absorption process.

The enhancement of the dissolution rate and solubility of poorly soluble drugs is connected with the application of auxiliary substances or with new technological possibilities (2). Solid dispersions of drugs in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability, of a range of hydrophobic drugs (3). In such systems, drug undergoes particle size reduction and the consequent increase in the surface area results in the improved dissolution (4), break up the crystal lattice (5) or increasing drug wettability by surrounding hydrophilic carriers (4).

Among the techniques to prepare a solid dispersion, spray-drying has the ability to produce spherical and size controlled particles and simultaneously to improve the dissolution properties (6).

The dissolution rates of several drugs have been improved by spray-drying with hydrophilic polymers, including indomethacin (7), tolbutamide (8), carbamazepine (9), and ketoprofen (10).

Kollicoat IR is a poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG) (11). El-Badry et al. (12) showed that Kollicoat IR-omeprazole microparticles prepared using spray- and freeze-drying techniques revealed the transformation of omeprazole from crystalline to amorphous state with increasing its dissolution rate nine times in comparison to the rate of the physical mixture. Also, Janssens et al. (13) showed that itraconazole was dispersed on a molecular level in the Kollicoat IR microparticles prepared by spray-drying, and showed enhanced dissolution.

Due to the high melting point of Kollicoat IR (210^{o}C) and its poor solubility in the organic solvents, it will be difficult to prepare solid drug-Kollicoat dispersions in its matrix either by melting or solvent evaporation methods.

The present study aims at the preparation of TNX-KL binary systems either by spray-drying or

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kneading and the physicochemical characterization of such systems. In addition, oral disintegrating tablets of an improved TNX-KL binary system will be prepared and characterized in comparison with the untreated drug and the commercial tablet product.

EXPERIMENTAL

Materials

Tenoxicam was kindly supplied by Egyptian International Pharmaceutical Industries Co., EIPICo (Cairo, Egypt). Kollicoat IR (KL) was obtained from BASF (Ludwigshafen, Germany). Microcrystalline cellulose (Avicel PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Spray-dried mannitol (Mannogem™ EZ), used as a filler for the orally disintegrating tablets, was kindly supplied by SPI (Grand Haven, USA). Crospovidone (CPV) was kindely supplied by Riyadh Pharma (Riyadh, KSA). Magnesium stearate was purchased from Riedel-de Haën (Seelze, Germany). Epicotil® tablets (immediate release oblong scored film coated tablets, weighing 200 mg and containing 20 mg TNX), batch number 1108632, was produced by EIPICo (Cairo, Egypt). Carrageenin was purchased from Sigma Chemical Co. (USA). Other materials and solvents are of reagent or analytical grade, and they were used without further purification.

Methodology

Preparation of tenoxicam-Kollicoat IR binary systems

Since Kollicoat is insoluble in most organic solvents, it was not possible to prepared TNX solid dispersions with it using coevaporation method. Therefore, TNX-KL binary systems in different drug : polymer ratios (1 : 1, 1 : 2 and 1 : 4) were prepared either by spray-drying from aqueous solution or kneading methods.

Kneading method

TNX-KL physical mixture was kneaded with appropriate amounts of water (0.1 mL of distilled water for each gram of physical mixture) using a mortar and pestle for 10 min. The mass was dried (room temperature overnight), crushed, sieved and dried again in an oven (Heraeus, Germany) (40^{o}C for 24 h).

Spray-drying

Kollicoat solution was prepared by dissolving the polymer in distilled water in different concentrations (0.5, 1 and 2%) according to the selected TNX : Kollicoat ratios. To the polymeric solution, the weighed amount of TNX was added and dispersed. Thereafter, 1–2 mL of 30% ammonium hydroxide solution was added to raise the solution pH to about 8–9. The clear polymeric solution of TNX was then spray-dried using Büchi 190 mini spray drier (Büchi Labortechnik AG, Germany) with 0.5 mm nozzle. The drug-polymer solution was fed to the nozzle through a peristaltic pump in a spray flow rate of 5 mL/min. The solution was sprayed under the effect of compressed air force (air flow rate of 4 pound per square inch) with an aspiration rate of 100%. The sprayed droplets were dried to remove the solvent in drying chamber by the blown hot air (inlet air temperature of 150^{o}C and outlet air temperature of 80^{o}C). Finally, the resulting dried product was collected from vessel, weighed and stored in tightly closed amber glass containers pending further investigations.

Physical mixture

TNX-KL physical mixtures in different drug weight ratios were prepared by gentle mixing of the weighed amounts the drug and carrier in porcelain mortar.

Characterization of tenoxicam-Kollicoat IR binary systems

In vitro dissolution studies

The *in vitro* dissolution experiments from its KL binary systems and ODTs were performed using USP dissolution apparatus 2, paddle method, (Caleva Ltd., Model 85T), at 100 rpm using a continuous automated monitoring system. This system consists of an IBM computer PK8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cell spectrophotometer Model PU 8620, Epson FX 850 printer, and Watson-Marlow peristaltic pump using in each flask a 900 mL phosphate buffer, pH 6.8. The temperature was maintained at 37 ± 0.5^{o}C. Twenty milligrams TNX or equivalent amount was spread over the dissolution medium. At predetermined time intervals, absorbance was recorded automatically at 362 nm and the percentage of TNX dissolved was determined as a function of time in triplicates.

Dissolution efficiency (DE%) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (14). Also, the relative dissolution rate (RDR_{15}) data of the different samples were calculated by determining the amount

of TNX dissolved from a particular sample and normalizing for the amount of drug dissolved from pure drug sample over the same time interval (15 min).

In case of oral disintegrating tablets, the same previous conditions were adopted, but the dissolution experiments were carried out on six tablets.

Solubility studies

The aqueous solubility of TNX in its KL binary systems was investigated as follows: an excess amount of TNX or TNX-KL binary system was added to 10 mL of distilled water in a 50 mL glass stoppered bottle. The bottles were firmly closed and placed into the mechanical shaking water bath previously adjusted at 37 ± 0.1°C. After equilibration has been attained (24 h), one mL aliquot sample was withdrawn from each tested solution and diluted to an appropriate volume with distilled water. The absorbance was measured at 362 nm against a suitable blank similarly treated and the drug concentration was calculated

Scanning electron microscopy (SEM)

Morphological characteristics of certain TNX-KL spray-dried and kneaded systems compared to the individual components were observed by scanning electron microscopy (SEM). The samples were sputter-coated with a thin gold palladium layer under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Coated samples were then scanned and photomicrographs were taken with an SEM (Jeol JSM-1600, Japan).

Differential scanning calorimetry (DSC)

DSC scans were recorded for TNX-KL binary systems compared to that of the individual componenets in order to determine the extent of crystallinity of the drug in the presence of the studied polymers.

The samples (3–5 mg) were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25 to 250°C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N_2 was used as purging gas at rate of 30 mL/min.

Table 1. Composition of TNX ODTs formulation.

Ingredient	Weight (mg)
TNX (or spray-dried TNX-KL equivalent to 20 mg TNX)	20
Crosspovidone (CPV)	10
Spray-dried mannitol	50
Magnesium stearate	2
Avicel PH101	To 200 mg

X-ray diffraction analysis

The x-ray diffraction patterns of the powder samples were obtained using RIGAKU diffractometer (Japan), which was equipped with curved graphite crystal monochromator, automatic divergence slit and automatic controller PW/1710. The target used was CuKa radiation operating at 40 kV and 40 mA (λ_{ka} = 1.5418 Å). The diffraction patterns were achieved using continuous scan mode with $2\theta^o$ ranging from 4 to 60°.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of TNX, KL and their binary systems were recorded using FTIR Perkin Elmer spectrophotometer (Spectrum BX). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 600 cm^{-1}. The data were analyzed using Perkin Elmer software (Spectrum V5.3.1).

Preparation of TNX oral disintegrating tablets (ODTs) by direct compression method

TNX ODTs were prepared by direct compression method and the composition of the prepared ODTS containing TNX is listed in Table 1.

The corresponding amounts of TNX, avicel pH 101 and superdisintegrant (CPV) were accurately weighed and mixed using Turbula mixer (Erweka, S2Y, Heusenstamm, Germany) for 5 min. Thereafter, the corresponding amount of mannitol was accurately weighed, added to the mixture and mixed for further 5 min. Finally, the amount of magnesium stearate was mixed with the powder in the Turbula mixer for further 2 min. The powder was compressed into tablets weighing 200 mg using Korsh single punch machine with 9 mm flat punches (Erweka, EKO, Germany).

Evaluation of ODTs containing TNX

Weight variation

Twenty tablets were weighed individually (analytical balance, Shimadzu, EB-3200D, Kyoto, Japan) and the average tablet weight and standard deviation were calculated.

Thickness

Pre-weighed 10 tablets were tested for thickness using a micrometer (Mitutoyo M 110-25, Japan), the average thickness and standard deviation were calculated.

Hardness

Tablet hardness of 10 tablets of known weight and thickness was measured using a hardness tester (Pharma test GmbH, Hainburg, Germany). The average hardness and standard deviation were reported.

Friability

Tablet friability was determined according to USP30-NF25. In brief, 20 tablets were weighed (W_1) and placed into the friabilator (Erweka, TA3R, Heusenstamm, Germany), which was rotated at 25 rpm for 4 min. The tablets were then reweighed after removal of fines (W_2), and the loss % was calculated by:

$$100 \times (W_1 - W_2)/W_1$$

***In vitro* disintegration**

In vitro disintegration test was assessed according to the USP30-NF25 requirements. One dosage unit was put in each of the six tubes of the basket (Electrolab, ED-21, Mumbai, India). The apparatus was operated, using phosphate buffer, pH 6.8, as the immersion fluid, which was maintained at 37 ± 0.5°C. Time for complete disintegration of each table, standard deviation and relative standard deviation were calculated.

In vivo studies

Anti-inflammatory activity

The anti-inflammatory activity of TNX ODTs compared to the commercial product (Epicotil®) was evaluated using carrageenin-induced paw edema model (15). All studies were in accordance with the Guidelines of Animal Ethical Committee of King Saud University and had its approval.

The experiment was conducted on 25 albino rats of both sex weighing 90–120 g fasted for 18 h with water available *ad libitum*. They were equally and randomly allocated in 4 groups (6 rats per group). The first group was the rats received ODTs containing untreated TNX; the second group received ODTs containing spray dried TNX-KL system (1 : 4); the third group received the commercial tablet product (Epicotil®) and the fourth group was considered as control.

The rats were anesthetized with urethane (0.5 mL, intraperitoneal) and 100 µL of 1% w/v carrageenin physiologic solution was injected subcutaneously into the treated area. One hour later, a definite weight of the tested tablet containing TNX dose (20 mg/kg) was dispersed in 5 mL of distilled water and immediately given to the rat by an esophageal tube.

Edema volume was measured using a plathysmometer, at suitable time intervals (0.5, 1, 2, 3, 4 and 5 h).

The anti-inflammatory activity (% response) was calculated according to the following equation (16):

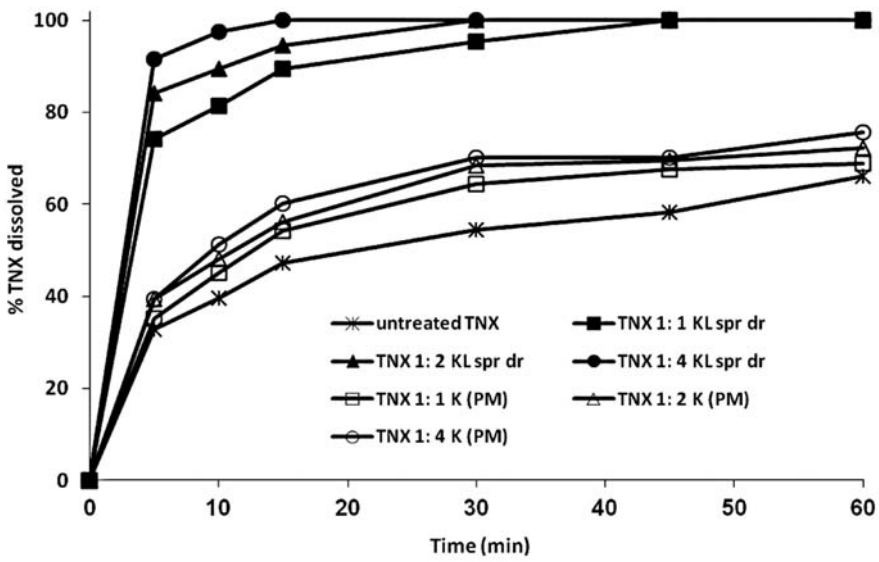

Figure 1. Dissolution profiles of TNX-KL spray-dried (spr dr) systems compared to the corresponding physical mixtures (PM)

Table 2. Dissolution efficiency percentages after 15 min ($DE\%_{15}$), relative dissolution rate after 15 min (RDR_{15}) and aqueous solubility of TNX from its-KL binary systems.

System	$DE\%_{15}$	RDR_{15}	Solubility* (mg/mL)
TNX	31.97	-	0.087
TNX-KL spray dried (1 : 1)	66.82	2.06	0.733
TNX-KL spray dried (1 : 2)	73.65	2.18	0.754
TNX-KL spray dried (1 : 4)	79.67	2.30	1.109
TNX-KL Kneaded mixture (1 : 1)	52.51	1.94	0.717
TNX-KL Kneaded mixture (1 : 2)	63.54	1.96	0.88
TNX-KL Kneaded mixture (1 : 4)	66.54	2.20	0.950
TNX-KL Physical mixture (1 : 1)	35.84	1.25	0.102
TNX-KL Physical mixture (1 : 2)	38.60	1.30	0.109
TNX-KL Physical mixture (1 : 4)	40.27	1.41	0.145

*Determined at 37°C

$$\% \text{ Response} = \frac{C - T}{C} \times 100$$

where C = the volume of right paw minus volume of left paw for control rat and T = volume of right paw minus volume of left paw for treated rat.

Hot-plate analgesic test

The analgesic test of the drug ODTs was evaluated using hot-plate method in mice. Mice were divided into 4 groups (6 mice/group). The first group was the mice received ODTs containing untreated tenoxicam; the second group received ODTs containing spray dried TNX-KL system (1 : 4); the third group received the commercial tablet product (Epicotil®) and the fourth group was considered as control. The temperature of the hot-plate metal surface was kept constant at 54 ± 1.0°C. A specific weight of each tablet formulation containing the required drug dose for mice (20 mg/kg) was dispersed in 2 mL of distilled water and administered immediately *via* an esophageal tube. The time taken by the animals to lick the fore or hind paw or jump out of the place was taken as the reaction time. Latency to the licking paws or jumping from plate was recorded by a stop watch before and after treatment. A latency period of 30 s was defined as complete analgesia cut off time to prevent damage to mice (17).

Statistical analysis

The data from each treatment group were analyzed using an analysis of variance test to determine the p-value for different variables. The Fisher's least significant difference test was used to determine significant differences between two variables.

RESULTS AND DISCUSSION

Characterization of TNX-KL binary systems

In vitro dissolution

Figure 1 shows the dissolution profiles of TNX-KL spray-dried systems in different drug :

polymer ratios (1 : 1, 1 : 2 and 1 : 4) compared to the corresponding physical mixtures as well as the untreated drug. It is clearly evident that TNX showed slow dissolution rate, in which only 47% of the amount was dissolved after 15 min, and has a dissolution efficiency value DE% of 31.97% after 15 min (Table 2). The incorporation of TNX in the matrix of KL during spray-drying resulted in a pronounced enhancement of drug dissolution rate by increasing the polymer weight ratio and a complete drug release was recorded for 1 : 4 ratio after 10 min. The calculated data of DE% after 15 min for the spray-dried systems 1 : 1, 1 : 2 and 1 : 4 were 66.82, 73.65 and 79.67%, respectively. Also, the drug RDR values after 15 min were 2.06, 2.18 and 2.3, respectively. Comparatively, concerning TNX-KL kneaded mixtures, the enhancement of TNX dissolution rate was slightly less than that obtained in case of spray-dried systems (Fig. 2). The recorded DE% after 15 min were 52.51, 63.54 and 66.54% for 1 : 1, 1 : 2 and 1 : 4 kneaded systems, respectively, and the RDR values were 1.94, 1.96 and 2.20, respectively (Table 2). Fouad et al. (18) showed that the increased dissolution rate of celecoxib in spray-dried mixtures of KL IR and other excipients was due to improving the wettability of the drug particles, by significantly reducing the drug particle size during the formation of the SD, or by the inherently higher dissolution rate of the soluble component of the SD introducing the less-soluble component as finely divided particles into the dissolution medium. Other investigators support these finding (19–21).

The dissolution rate of TNX from its KL physical mixture using the same drug : polymer ratios were slightly enhanced compared to the noticeable increase in the dissolution rate when dispersed in KL matrix by spray-drying or kneading. This might be due to the hydrophilic nature of KL in the physical mixtures.

The solubility of untreated TNX in water was calculated to be 0.087 mg/mL, while its solubility in spray-dried systems was enhanced noticeably by increasing the polymer weight ratio (Table 2). For example, the drug solubility in case of TNX-KL 1 : 4 spray-dried form was 1.09 mg/mL, while it was 0.73 and 0.75 mg/mL in case of 1 : 1 and 1 : 2 ratios. In addition, the solubility improvement of TNX was more pronounced in case of spray-dried binary systems than in case of kneaded ones. Moreover, very slight improvements were recorded for the solubility of TNX in its KL physical mixtures.

Scanning electron microscopy (SEM)

Scanning electron micrographs of TNX, KL, spray dried TNX-KL (1 : 4) mixture and kneaded TNX-KL (1 : 4) mixture are displayed in Figure 3. TNX showed regularly shaped crystals, while KL particles appear highly spherical. The SEM images of spray dried TNX-KL (1 : 4) revealed the presence of very small spheres with regular shapes with no evidence of TNX crystalline shapes. The spherical shapes of the spray-dried TNX-KL with small particle sizes might be one of the factors that are responsible for enhancing drug dissolution and solubility by providing large surface area in addition to surrounding drug particles by the hydrophilic KL particles. However, the kneaded TNX-KL (1 : 4) system appeared as irregular aggregates with large sizes. These data are in accordance with the *in vitro* dissolution data, which proved that spray-dried TNX-KL

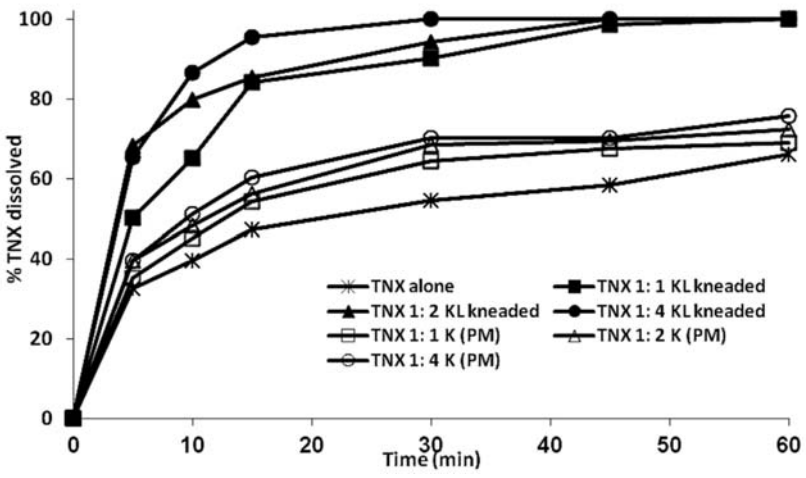

Figure 2. Dissolution profiles of TNX-KL kneaded mixtures compared to the corresponding physical mixtures (PM)

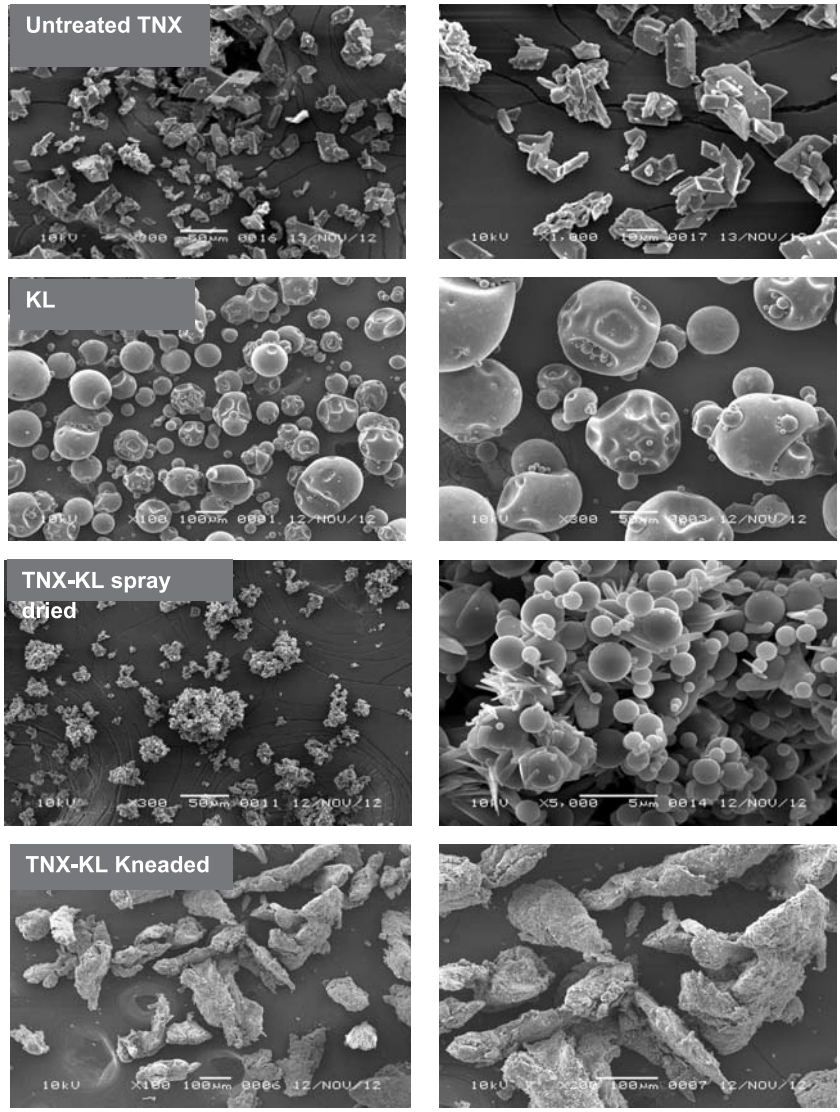

Figure 3. Scanning electron micrographs of TNX-KL spray dried and kneaded systems in drug : polymer ratio 1 : 4 compared to the individual components

improved both drug dissolution rate and aqueous solubility in comparison to the corresponding kneaded form.

The pronounced change of the particles shape in spray-dried mixture may indicate the presence of a new solid phase (22, 23).

Differential scanning calorimetry

Figures 4A and B show the DSC scans of TNX-KL kneaded systems and TNX-KL spray-dried systems in different drug weight ratios compared to the individual components. The DSC curves of TNX show an endothermic peak at 215.9°C with a thaw point at 214°C and heat of fusion, DH, of –47.88 joule/g at a scanning rate of 10°C/min. This endothermic peak ends with an exothermic peak at 220°C, which may be due to the decomposition of the drug when reaching its melting point as reported (24). Kollicoat IR exhibits a broad endotherm at 213.14°C with a thaw point of 207.5°C.

The DSC scans of TNX-KL spray-dried systems (in drug : polymer ratios of 1 : 1, 1 : 2 and 1 : 4), compared to the drug and polymer scans, are displayed in Figure 4A. The drug endothermic peak completely disappeared in all tested TNX-KL spray-dried mixtures, and only the polymer peak was observed at 200°C. This might be due to the solubility in the melted polymer (25). In addition, the drug exothermic peak was shifted to lower temperatures

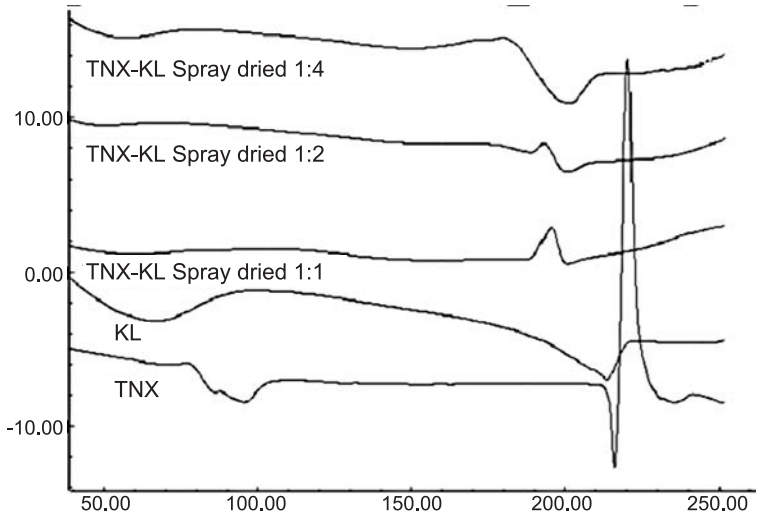

Figure 4A. DSC thermograms of TNX-KL spray-dried systems in different drug : polymer ratios compared to the individual components

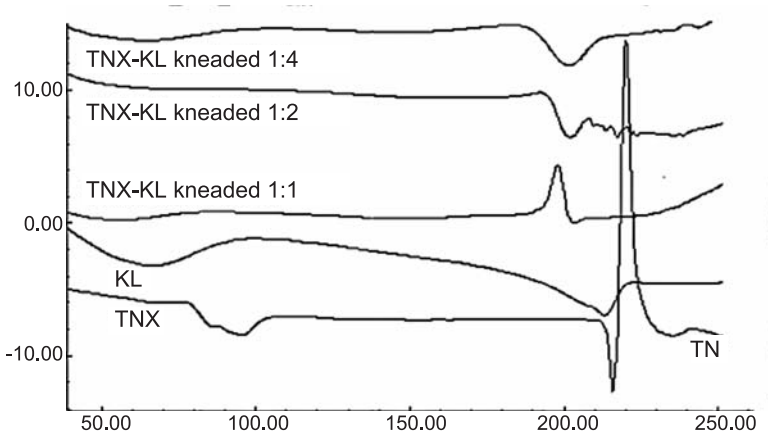

Figure 4B. DSC thermograms of TNX-KL kneaded systems in different drug : polymer ratios compared to the individual components

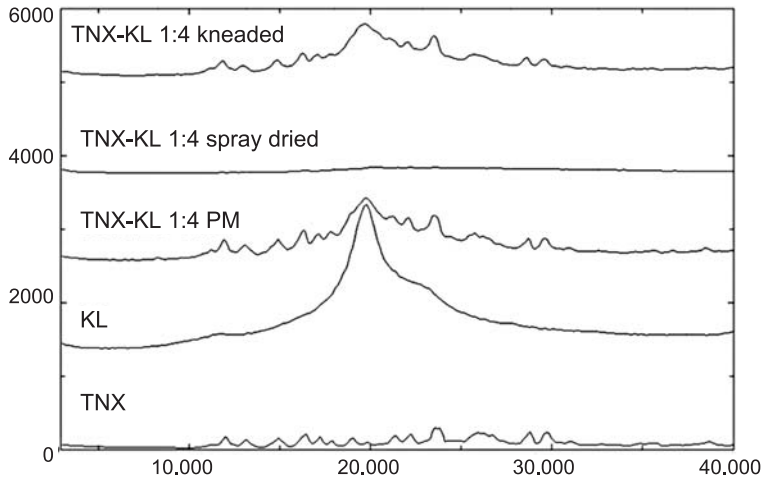

Figure 5. X-ray powder diffraction pattern of TNX-KL spray-dried and kneaded systems in drug : polymer ratio 1 : 4 compared to the corresponding physical mixture (PM) and individual components

Table 3. Physical properties of TNX ODTs (mean ± SD) compared to the commercial product (Epicotil® tablets).

Tablet formulation	Weight (mg)	Disintegration time (s)	TNX Content (mg)	Hardness (Kp)	Friability (%)	T_{50} (s)
ODT containing untreated TNX	205 ± 5.34	148 ± 5.91	19.82 ± 0.89	6.45 ± 0.25	0.84 ± 0.19	89.70
ODT containing spray dried TNX-KL (1 : 4)	207 ± 6.45	23 ± 1.34	20.12 ± 0.76	5.98 ± 0.45	0.86 ± 0.21	35.73
Epicotil®	200	155 ± 8.49	20.14 ± 0.84	–	–	120

(the peak was shifted to 199.4 and 192.9°C in case of spray-dried 1 : 1 and 1 : 2 systems, respectively). However, this exothermic peak was no more seen in the spray dried system at a drug : polymer ratio 1 : 4. Similar results were obtained in case of TNX-KL kneaded mixtures (Fig. 4B). The drug endothermic peak disappeared and the polymer endotherm has been detected in all tested drug : polymer ratios. Also, the exothermic decomposition peak of TNX was shifted to lower temperatures in case of 1 : 1 and 1 : 2 ratios (201°C), and disappeared completely by increasing polymer weight ratio 1 : 4. The characteristic endothermic peak of TNX in its-polymer spray-dried or kneaded mixtures was almost disappeared or reduced in intensity, shifted to lower temperatures and lost its sharpened distinct appearance. The obtained data, in combination with x-ray and scanning electron micrograph findings, confirm the presence of TNX in an amorphous form in these mixtures (26). El Badry et al. (12) found that total drug amorphization of omeprazole was induced in its Kollicoat IR® spray-dried form and these results confirmed that the drug was no longer present in crystalline form and it was changed to amorphous state.

The disappearance of TNX exothermic peak in its-Kollicoat systems (either spray-dried or kneaded) might indicate increased drug stability after kneading or spray-drying (12).

X-ray powder diffraction

To get further evidence on the solid state changes, x-ray diffraction spectra were carried out on TNX, TNX-KL binary systems (1 : 4 weight ratio of drug : polymer) compared to the individual components. The presence of numerous distinct peaks in the x-ray diffraction spectrum of TNX indicates that the drug is present as a crystalline material with characteristic diffraction peaks appearing at diffraction angles of 2q at 12Å, 14.9Å, 16.5Å, 23.8Å, 28.8Å and 29.7Å (Fig. 5). The diffraction peaks of KL could be assigned to the two polymers of which Kollicoat IR is composed: polyvinyl alcohol (PVA) and polyethylene glycol (PEG). Indeed, a reflection at 19.7° 2θ due to the presence of crystalline PVA domains and two reflections, 19° (hidden) and 22.9° 2θ, due to the presence of crystalline PEG domains were observed after extrusion (27). The x-ray diffraction spectra of either TNX-KL physical mixture or kneaded mixture did not show any sign of change in the intensity of the drug characteristic diffraction peaks and each of them is seen as a combined effects of TNX and KL diffraction peaks. However, the diffraction spectrum of spray-dried TNX-KL mixture showed a complete disappearance of both the drug and polymer diffraction peaks indicating the loss of their crystallinity. This finding is in accordance with the data obtained by Janssens et al. (13), who showed that the data obtained from x-ray diffraction studies of itraconazole-Kollicoat IR spray-dried solid dispersions suggested that the crystallinity of itraconazole was washed out in the solid dispersions.

FTIR spectroscopy

Figure 6 demonstrates FTIR spectra of the untreated TNX, KL and TNX-KL binary systems in a drug : polymer ratio of 1 : 4.

The spectrum (A) of the drug shows that it is identical with the reported data (24). According to these data, TNX showed a characteristic broad band at 3447 cm^{-1}, which is assigned for the O-H stretching vibration and two bands at 3155 and 3090 cm^{-1}, which are due to the N-H stretching and aromatic C-H vibrations. In addition, a strong band was observed at 1636 cm^{-1}, which was attributed to the amide carbonyl stretching band (C=O). The FTIR spectrum of KL showed a characteristic band at 3421 cm^{-1}, which is assigned for OH stretching.

The FTIR spectra of TNX-KL of both physical mixture and kneaded mixture did not show any change (in terms of the position or intensity) of

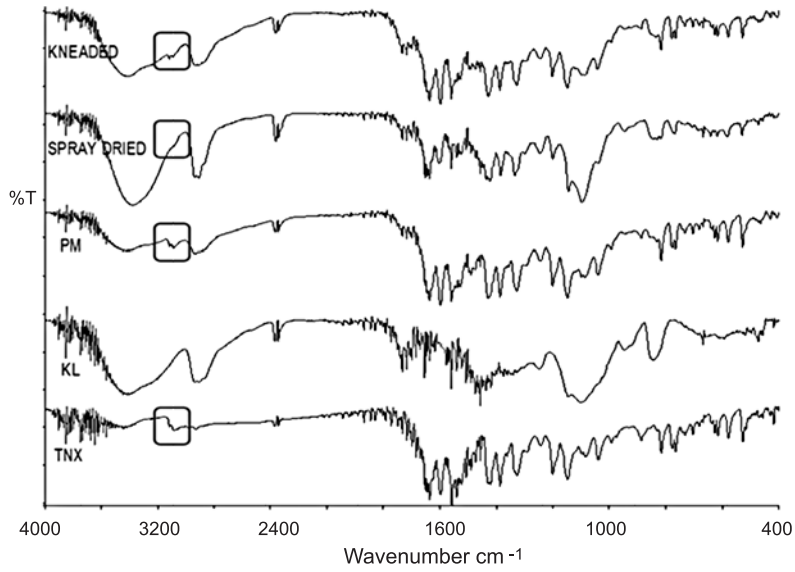

Figure 6. IR spectra of TNX-KL spray-dried and kneaded systems in drug : polymer ratio 1 : 4 compared to the corresponding physical mixture (PM) and the individual components

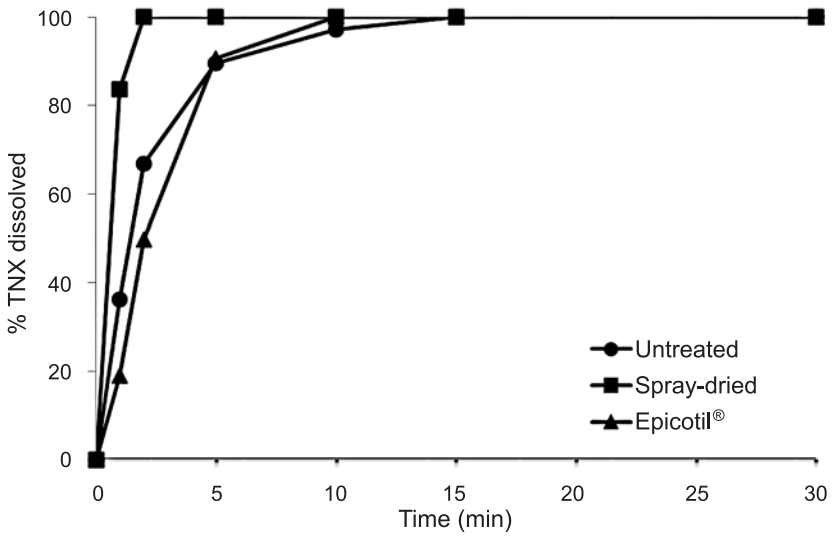

Figure 7. Dissolution profiles of TNX from ODTs formulations compared to the commercial product

either the drug or the polymer characteristic bands. In contrast, the analysis of spray-dried TNX-KL spectrum exhibited complete disappearance of the drug NH stretching band. Additionally, the N-H and O-H stretching bands of TNX and O-H stretching band of KL were all combined as a broad one and shifted to a lower frequency 3368 cm^{-1}. This might suggest the interaction of TNX and KL in the spray-dried mixture.

TNX oral disintegrating tablets

Tablet evaluation

The oral disintegrating tablets containing 20 mg TNX were successfully prepared using direct

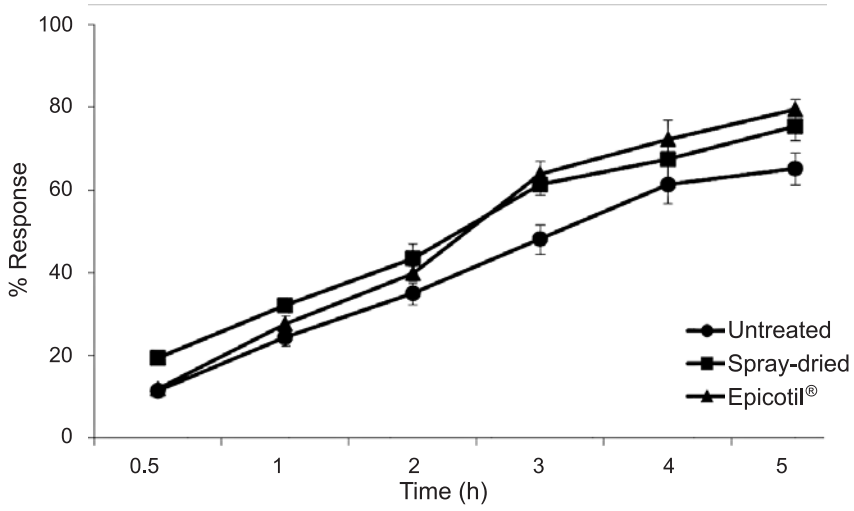

Figure 8. The % anti-inflammatory response of TNX from ODTs formulations compared to the commercial product

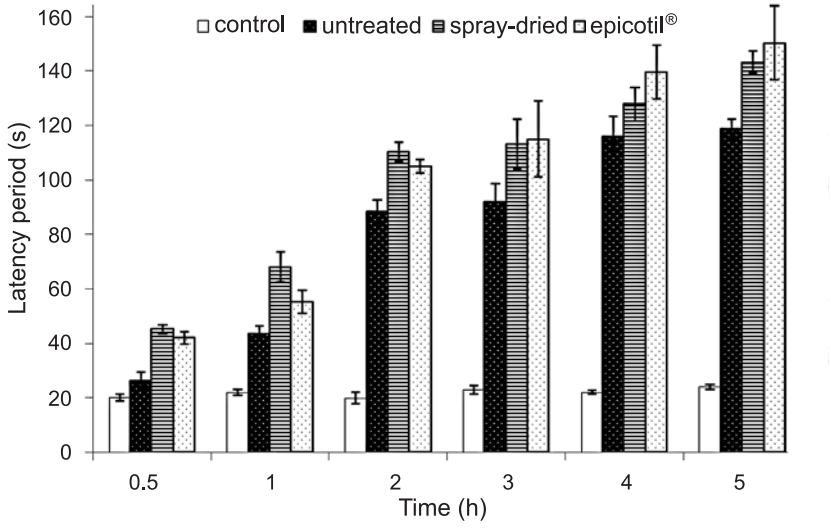

Figure 9. The analgesic activity (represented by latency period in seconds) of TNX from ODTs formulations compared to the commercial product

compression method. The manufactured ODTs were evaluated for their physical properties (weight variation, hardness, friability and drug content), and the obtained data are displayed in Table 3. The weight of the manufactured ODTs containing untreated drug was 205 ± 5.35 mg, while ODTs containing spray-dried drug have a weight of 207 ± 6.45 mg. Moreover, the tablets exhibited acceptable friability that is less than 1% in all ODTs formulations, in addition to acceptable hardness.

In vitro disintegration

The prepared oral disintegrating tablets formulation containing TNX were investigated for their *in vitro* disintegration and compared to the commercial tablet product. Tablets containing spray-dried TNX-KL system (1 : 4) showed fast and complete disintegration within 23 s, while in case of ODTs containing untreated drug, 148 s were required for complete disintegration (Table 3). In addition, the commercial product (Epicotil® tablets) disintegrated completely within 155 s.

In vitro dissolution

The *in vitro* dissolution of TNX from its ODTs containing 20 mg drug was compared to ODTs containing TNX-KL (1 : 4) spray-dried mixture equivalent to 20 mg of drug. Crosspovidone was used as a superdisintegrant in a concentration of 5%. The prepared ODTs were compared to the commercial product (Epicotil® tablets) in terms of dissolution and disintegration (Fig. 7 and Table 3). Untreated TNX showed 36% release within the first minute, and the T_{50} value was attained within 90 s, while ODTs containing spray dried TNX showed 83% release within the first minute and a complete release after 2 min, with a T_{50} value of 37 s. These data are in complying with the ODTs previous data, in which ODTs containing spray-dried drug exhibited faster disintegration. On the other hand, Epicotil® tablets showed slow dissolution rate within the first 2 min due to disintegration of the coating film. Thereafter, rapid dissolution was observed, in which complete drug dissolution was achieved after 10 min, with a calculated T_{50} value of 120 s.

Biological evaluation

Anti-inflammatory activity of TNX ODTs

Oral disintegrating tablets containing untreated TNX and TNX-KL spray-dried system was evaluated for their anti-inflammatory activity using carrageenin-induced paw edema and the data are displayed in Figure 8. Higher % response (i.e., % response of paw swelling) was observed in case of ODTs containing spray-dried TNX-KL system within the first 3 h, which was significantly ($p < 0.01$) higher than that recorded with either ODTs containing untreated drug or the commercial product. This finding is in accordance with the fast dissolution and disintegration of the tablets containing spray-dried TNX-KL system. Then, the calculated % response observed for the commercial product increased, but there was no significant difference between the % responses observed compared to that observed in case of OTDs containing spray-dried drug. During the whole studying period, OTDs containing untreated TNX showed significantly lower % responses compared to the commercial tablets or the ODTs containing spray-dried drug.

Hot-plate analgesic test

Figure 9 shows the analgesic effect of TNX formulation represented by the latency period in seconds. All tested TNX showed longer latency periods, which were significantly different from the control group ($p < 0.01$). During the first 2 h, the analgesic activity of ODTs containing spray-dried TNX-KL system was significantly ($p < 0.01$) superior to that of recorded with the untreated drug containing ODTs as well as the commercial product. Thereafter, the analgesic activity of the spray-dried TNX-KL containing ODTs and of the commercial tablet are insignificantly different, however, both are significantly different from the control group and untreated drug containing ODTs. It is worthy to refer that the analgesic activity of TNX in its all formulations persisted for 5 h (study period), which might be due to the long half-life of the drug (28).

CONCLUSION

The incorporation of TNX in the matrix of Kollicoat IR could be utilized in improving drug dissolution rate in addition to stabilizing it against exothermic decomposition. Moreover, the spray-dried TNX-KL binary system (1 : 4) showed faster dissolution rate when incorporated in ODTs and also was superior to the commercial product in enhancing both anti-inflammatory and analgesic activities.

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