Fast dissolving film nanocrystal (FDFN)

preparation as a new trend for solubility enhancement of poorly soluble class ii drug tenoxicam

Preparación de nanocristales de películas de disolución rápida (FDFN) como nueva tendencia para mejorar la solubilidad de tenoxicam, un fármaco de clase II poco soluble

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Resumen

Objetivo: Esta investigación tuvo como objetivo preparar, caracterizar y evaluar nanocristales de película de disolución rápida (FDFN) de tenoxicam (TNX) como un sistema innovador utilizando tres polímeros formadores de película diferentes, HPMC E 30, PVP K90 y PVA, para la optimización de la clase BCS. II solubilidad del fármaco, velocidad de disolución y biodisponibilidad. Métodos: Los nanocristales TNX se prepararon primero usando el método de nanoprecipitación ácido-base, que luego se formularon en quince FDF usando HPMC E 30, PVP K90 y PVA como formadores de película. A continuación, se evaluaron las películas en cuanto a apariencia, pH de la superficie, resistencia al plegado, espesor, variación de peso, TS, PE, tiempo de desintegración y duraciones de liberación de TNX. Resultados: Los nanocristales TNX se prepararon con éxito con propiedades físicas optimizadas, incluida la solubilidad debido a la reducción de tamaño. Seis formulaciones, F-1, F-2, F-6, F-8, F-11 y F-12, exhiben características FDF deseadas según lo indicado por técnicas de caracterización que incluyen desintegración rápida en menos de 30 segundos y disolución in vitro en dos minutos. Conclusión: Se prepararon con éxito seis formulaciones de TNX-FDFN con propiedades de película ideales y solubilidad de TNX mejorada y, por lo tanto, se pueden usar como una alternativa a la forma oral evitando así las limitaciones asociadas de irritación GI y mala solubilidad de TNX.

Palabras clave: *nanocristal de tenoxicam (TNX), nanocristal de película de rápida disolución (FDFN), escasa solubilidad.*

Abstract

Objective: This research targeted to prepare, characterize and evaluate fast dissolving film nanocrystals (FDFN) of tenoxicam (TNX) as an innovative system using three different film-former polymers, HPMC E 30, PVP K90 and PVA, for the optimization of BCS class II drug solubility, dissolution rate and bioavailability. **Methods:** TNX nanocrystals first prepared using acid-base nanoprecipitation method, which further formulated into fifteen FDF using HPMC E 30, PVP K90 and PVA as film-formers. Films were then evaluated for appearance, surface pH, folding endurance, thickness, weight variation, TS, PE, disintegration time and TNX release durations. **Results:** TNX nanocrystal were prepared successfully with optimized physical properties including solubility due size reduction. Six formulation, F-1, F-2, F-6, F-8, F-11 and F-12, exhibit desired FDF features as indicated by characterization techniques including fast disintegration in less than 30 seconds and *in vitro* dissolution within two minutes. **Conclusion:** Six TNX-FDFN formulations were prepared successfully with ideal film properties and improved TNX solubility and hence, can used as an alternative to the oral form thereby avoiding associated limitations of GI irritation and poor solubility of TNX.

Keywords: *Tenoxicam (TNX) nanocrystal, fast dissolving film nanocrystal (FDFN), poor solubility.*

Introduction

Tenoxicam (TNX) is a potent member of non-steroidal anti-inflammatory drugs (NSAIDs) that belongs to oxicam group, it is used in the treatment of rheumatoid arthritis, osteoarthritis, and other disorders associated with inflammation and pain, in addition to antipyretic effect[1]. As many other NSAIDs, TNX cause gastrointestinal (GI) tract adverse effects after oral administration, such as bleeding, due to its interference with peripheral biosynthesis of prostaglandins mediated by the non-selective inhibition of cyclooxygenase-2 enzyme[2]. Therefore, TNX formulation for alternative routes of administration than oral appears to be of interest to circumvent such GIT harmful effects. TNX fits to class II of Biopharmaceutical Classification System (BCS) with low solubility and high permeability, and therefore demonstrate dissolution limited absorption[3]. It is a weakly acidic drug with pH-dependent solubility, which limit its absorption in the upper GIT due to low solubility in acidic stomach. Additionally, the poor lipophilicity of drug lead to its slow and limited distribution. All these factors contribute to the slow onset TNX with more 2-3 hours to reach plasma therapeutic level and T_{max} (time required to attain maximum concentration) of 5-6 hours[4,5]. This slow onset of TNX limit its application for mild cases of pain and analgesia, and make it less suitable for more acute conditions, such as exacerbation of rheumatic arthritis. Furthermore, TNX as a potent NSAID, chronic use for prolonged period enhance the risk of gastrointestinal perforation and/or ulceration, or even bleeding. Therefore, improving TNX solubility is expected to enhance its absorption through GIT with the reduction of residence time in acidic stomach and thereby decreasing potential GIT side effects. Despite of the availability of marketed intramuscular injection of TNX, it is not recommended for chronic use due to the potential of local irritation and should be switched to oral tablet for relative prolonged use[1,6].

Several approaches are available for enhancing the solubility and dissolution of poorly soluble drugs, among which alteration in drug formulation or dosage form utilized, particle size reduction and thereby enhancing the effective surface area available for dissolution[7], and by lattice structure alteration from crystalline to more soluble amorphous arrangement of drug molecules[8]. Fast oral dissolving or orodispersible drug delivery systems approve their effectiveness over conventional oral dosage forms (such as tablet, capsules, etc.) due to rapid disintegration and dissolution within the mouth cavity by saliva without the need of water drinking or chewing[9]. Additionally, and most importantly, these dosage forms alleviate GIT adverse reactions triggered by the passage of irritating drugs, in particular NSAIDs. Fast dissolving films (FDFs), as a form of fast dissolving dosage, allow rapid dissolution of formulation within a minute in oral cavity with localized (oral conditions) or systemic (absorbed rapidly by sublingual mucosa) effects[10]. Such FDF provide quick onset by the rapid absorption through the rich blood capillary sublingual area with consistent plasma levels or bioavailability[11]. In addition to the active drug ingredient, FDFs consist mainly from two components, film forming polymer and plasticizers that are critical to obtain the desired flexibility of the film, as it control the mechanical properties like tensile strength and percent elongation of the prepared film[12].

Particle size reduction to a nano-scale can further optimize drug dissolution and absorption using several techniques including nanocrystal preparation. Nanocrystals are nano-sized crystals of drug molecules; such crystals offer simple, low cost and efficient method for improving drug solubility and bioavailability[13]. Generally, two chief methods involved in nanocrystal preparation by either top-down process that involve the mechanical breakage of big drug particles using simple mechanical millers or homogenizers, or bottom-up method utilized by precipitation of drug molecules to assembled up nano-sized crystals induced by the use of anti-solvent. Alternatively, a combination of two methods used when necessary. Better particle size distribution manifested when using bottom up process with minor labor necessity than that afforded in top-down method, yet caution is required in this method to avoid potential toxicity of organic solvent residues after nanocrystal preparation[14,15]. Regarding the chemical nature of TNX used in this study, which is a weak acid, and its corresponding pH-dependent solubility, it is reasonable to prepare TNX nanocrystals via nanoprecipitation method with acid-base neutralization.

The selection of appropriate stabilizing agent (S.A) or stabilizer is critical, as it plays a key role in particle size lessening and stability of nanocrystals. These agents adsorbed to the surface of newly formed particles to decrease their interfacial tension and surround the hydrophobic particles as condensed hydrophilic layer providing steric hindrance to particle-particle attraction (steric stabilization)[15,16].

This research targeted to prepare, characterize and evaluate fast dissolving film nanocrystals (FDFN) of tenoxicam (TNX) as an innovative system using three different film-former polymers, HPMC E 30, PVP K90 and PVA, for the optimization of BCS class II drug solubility, dissolution rate and bioavailability. This improvement in pharmaceutical properties tend to fasten the pharmacologic effect of TNX due to faster absorption directly via sublingual capillary bed. First, nanocrystals of TNX prepared via acid-base nanoprecipitation technique. Afterward, the prepared nanocrystals further formulated as a fast dissolving film nanocrystals (FDFN) of TNX.

Materials and Methods

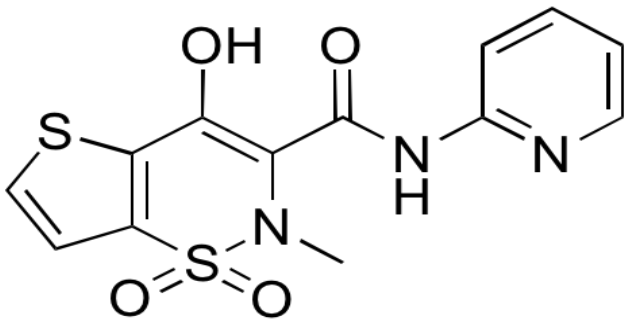
Tenoxicam (TNX) was obtained as a gift from The Middle East Pharmaceutical Manufacturing Company Ltd. The polymers HPMC E30, Polyvinyl polyvidone (PVP K30); polyvinyl alcohol (PVA) obtained from Zhejiang CP Chemical CO., LTD, China. The plasticizers Polyethylene Glycol (PEG 400), Propylene Glycol (PG), glycerol, and Cremophor EL were obtained from Sigma Aldrich, USA. Citric acid and Acesulfame-K gotten from Thomas baker, CO., India.

Methods

Preparation of TNX nanocrystals

Tenoxicam (TNX) is a weak acidic drug (figure 1) that can precipitated after treatment with a basic solution, and hence TNX nanocrystals can be prepared using acid-base nanoprecipitation technique. A mixture consisting 2:1 ratio of 0.6 g TNX / Cremophor-EL (as stabilizing agent) was placed in 20 mL of 0.1 M NaOH aqueous solution with magnetic stirring. Subsequently, 2 mL of 1 M HCl aqueous solution was added rapidly under continuous vigorous stirring to get uniform particle size distribution using magnetic stirrer (C-MAG HS 4, Germany) at 1500 rpm for 10 min to obtain the precipitated TNX as uniformly distribution nanocrystals[17,18].

Fig. 1. Chemical structure of tenoxicam (TNX)



Preparation of TNX-FDFN

Fifteen formulations (F-1 to F-15) of TNX-FDFN were prepared using solvent-casting method by selecting three different film-forming polymers, HPMC E30, PVP K90 and PVA, with three different plasticizers, PEG 400, PG and glycerol respectively. Other excipients used in film formulation include citric acid as saliva stimulant and flavourant, and acesulfame-K as a second-generation calorie-free artificial sweetener. While Cremophor-El work as a surfactant or solubilizing agent to ensure self-emulsifying and disintegration of the film within seconds, and menthol as flavourant [19].

Preparation of HPMC E30 / FDFN of TNX

First, the polymeric solution was prepared by soaking the specified weight of HPMC E30 in 15 mL of distilled water with continuous stirring and then kept aside for 1 h to remove all trapped air bubbles. Afterward the plasticizer PEG 400 was added in rapid drop-wise manner with stirring to form homogenous solution. The other excipients were dissolved in 6 mL water, added to polymeric solution, and stirred for 1 h; menthol was priory solubilized in a very small quantity of ethanol. After that, a specific amount of TNX nanocrystals was mixed gently with the polymeric solution under constant stirring to obtain a homogenous dispersion. Which eventually sonicated for 2 min and casted into 9-cm diameter glass petri-dish to obtain a thin film (63.62 cm^2 area) and dried in oven at 50 ˚C for 24 h, afterward the final thin film was removed carefully and cut into 2 X 2 cm^2 square pieces of film each containing 20 mg of TNX. Table 1 summarize the formulations prepared using HPMC E 30 polymer as the film former [20, 21].

Preparation of PVP K90 / FDFN of TNX

The same steps used in HPMC E30 / FDFN preparation was followed for the preparation of TNX-PVP K90 / FDFN with using PVP K90 as the film-forming polymer, and PG as the plasticizer as shown in table 2 [22].

Preparation of PVA / FDFN of TNX

Table 3 present the components used in the preparation of film, in which the assigned amount of PVA polymer was dissolved in 15 mL of hot water at 80 ˚C with under magnetic stirring until a clear solution was attained and then left for 1 h to get rid any trapped air bubbles. Afterward, a second aqueous solution containing glycerol (as plasticizer) and other film components was blended with polymeric solution under magnetic stirring to form a homogenous solution above which TNX nanocrystals added. The stirring continued for 2 h and then sonicated for 2 min and then poured into 9-cm diameter glass petri-dish and dried in oven at 60 ˚C for 24 h, afterward a thin film was removed carefully and cut into 2 X 2 cm^2 square pieces of film each containing 20 mg of TNX[23].

Table 1. Formulation of TNX-FDFN using HPMC E30 (F-1 to F-5)

F-code	TNX Nanocrystal (mg)	HPMC E30 (mg)	PEG 400 (mL)	Cremophor-EL (mL)	Citric acid (mg)	Menthol (mg)	Acesulfame-K (mg)	Water
F-1	320	400	0.5	1	25	20	40	Q.S
F-2	320	500	0.75	1.15	25	20	40	Q.S
F-3	320	650	1	1.25	25	20	40	Q.S
F-4	320	800	1.25	1.5	25	20	40	Q.S
F-5	320	1000	1.5	2	25	20	40	Q.S

Table 2. Formulation of TNX-FDFN using PVP K90 (F-6 to F-10)

F-code	TNX Nanocrystal (mg)	PVP K90 (mg)	PG (mL)	Cremophor-EL (mL)	Citric acid (mg)	Menthol (mg)	Acesulfame-K (mg)	Water
F-6	320	400	0.25	1	25	20	40	Q.S
F-7	320	500	0.3	1.15	25	20	40	Q.S
F-8	320	650	0.5	1.25	25	20	40	Q.S
F-9	320	800	0.75	1.5	25	20	40	Q.S
F-10	320	1000	1	2	25	20	40	Q.S

Table 3. Formulation of TNX-FDFN using PVA (F-11 to F-15)								
F-code	TNX Nanocrystal (mg)	PVA (mL)	Glycerol (mL)	Cremophor-EL (mL)	Citric acid (mg)	Menthol (mg)	Acesulfame-K (mg)	Water
F-11	320	400	0.2	1	25	20	40	Q.S
F-12	320	500	0.4	1.15	25	20	40	Q.S
F-13	320	650	0.6	1.25	25	20	40	Q.S
F-14	320	800	0.8	1.5	25	20	40	Q.S
F-15	320	1000	1	2	25	20	40	Q.S

Evaluation of TNX-FDFN

Physical properties

(a) Film appearance

Visual observation was made to check the physical nature of the prepared film, such as surface smoothness and imperfections, color, uniformity, air bubbles and transparency.

(b) Surface pH

The surface pH measuring performed using digital viscometer (TIII-02303, Singapore) to investigate potential local side effect due *in vitro* pH variation of the film after dissolving within the mouth, as acidic or alkaline pH may result in buccal mucosa irritation[24]. Each tested TNX-FDFN was placed separately in petri dish and moisten with 0.5 mL distilled water and left for 30 sec, afterward the electrode of digital pH-meter bring into contact to the surface of formulation and the reading is recorded when equilibrium is attained after 1 min[25]. The test was made three times and the mean result was dependent.

(c) Weight variation

Digital analytical balance device (JM-974, USA) of high-accuracy was used, in which ten films (2 cm X 2 cm) were selected randomly from each test TNX-FDFN formulation and the average weight was determined with calculating standard deviation (SD) from mean value of three readings[26].

(d) Folding endurance

This test performed to investigate the capacity of each prepared TNX-FDFN to withstand rupture upon folding and hence indicate film fragility. It is done by folding each film (2 cm X 2 cm) repeatedly at the same site until it broke, which represent folding endurance value. Alternatively 300 times folding without breakage indicate good film properties[27].

(e) Thickness measurement

Film-thickness determination can explore the uniformity or accuracy of TNX dose distribution through each prepared TNX-FDFN that was measured using screw gauge micrometer (Digital Vernier caliper, Germany) at five diverse locations in the film, the four corners and the center. The test performed three times and the mean thickness value was taken with SD calculation[28].

(f) Tensile strength (TS) and Percent elongation (PE)

These two parameters refer to the mechanical property of each prepared film hardness and toughness. This test achieved by placing a 2 × 2 cm (4 cm^2) film between two clamps of Instron 5500 Universal Testing Instrument detained 2cm apart, then each film was pulled by the upper clamp at a rate of 50 mm/min by the clamp till break. The force and elongation at breakage recorded[29].

Tensile strength (TS) refer to the highest stress applied at one site on the film and cause its breakage and it is calculated using equation below (equation 1), in which the force required to break film (average of three measurements) divided by the cross-sectional area of the application site on the film[30].

TS = Force applied / cross-sectional area of application site (mm^2) (equation 1)

While PE refer to the measurement of film flexibility after application of a stress. In which the ability of each tested film to spread or elongate under the influence of stress is compared to the original length. Its value calculated using the equation below[31]:

Percent elongation = (Length increment / original length) X 100% (equation 2)

2. Content uniformity

The tested film of 2 X 2 cm (4-cm^2 area) was homogenized in 100 ml of simulated salivary fluid (phosphate buffer pH value 6.8) for 30 min under magnetic stirring at 37°C, the obtained solution was then diluted to a suitable concentration and TNX content was quantified using UV-Visible spectrophotometer (Shimadzu, Japan) at 360 nm. The average content value from three readings was dependent[32].

3. *In vitro* disintegration test

The time required by TNX-FDFN for *in vitro* disintegration was detected by placing each film with dimension 2 X 2 cm separately in 10 mL phosphate buffer solution pH 6.8 (within a glass petri dish that was stirred at constant time-intervals of 10 sec. Afterward the mean value from three tests was recorded.

4. *In vitro* dissolution study

The dissolution profile of TNX from each prepared TNX-FDFN was carried out with USP paddle apparatus (Type II), in which each 2 X 2 cm film was soaked in 300 mL phosphate buffer pH 6.8 to simulate salivary fluid under continuous stirring at 100 rpm and temperature kept at 37°C ± 0.5. Samples then withdrawn every 10 sec time-interval for TNX quantification at 360 nm and replaced with fresh medium. The experiment was achieved in trial[33].

Results

Evaluation of TNX-FDFN

Physical properties

(a) Film appearance

Visually, all prepared TNX-FDFN reveal transparent, smooth, air free (no bubbles) or imperfection protrude on tested films surfaces. The films were easily removed from petri-dish without rupturing or cracking as a thin of uniform thickness circular slide with smooth edges on contact.

(b) Surface pH

Referring normal pH range of salivary fluid, which lies between 6.2 and 7.6[34], all TNX-FDFN formulations demonstrate pH values lies within this range (6.36±0.11 to 6.98±0.14) as displayed in table 4, indicating safe application in the mouth without irritation.

(c) Weight variation

The average weight was taken for ten 4-cm^2 TNX-FDFN films from each formulation and results summarized in table 4, which reveal approximate values of average weight. This variation could be attributed to the weight differences in polymers imparted for film formation in each formulation.

(d) Folding endurance

The values were summarized in table 4 and reveal variable brittleness or flexibility of the prepared TNX films due diversity in physical nature and density of different film-forming polymers utilized in their fabrication. Formulations 5, 7, 10 and 14 rupture with folding endurance value of less than 300. The applied plasticizer as well as the addition of surfactant Cremophor EL play significant role in such conferred flexibility, as Cremophor EL aid in the enhancing of TNX solubility and dispersibility within polymer film in each formulation and hence, uniformly distributed without site localization or bulk formation that may affect the mechanical strength of the film in TNX-free areas[35].

(e) Thickness measurement

Average thickness values measured for the prepared TNX-FDFN found to range from 61.78 μm ± 1.3 to 96.1 μm ± 2 (table 4) indicating acceptable thickness of all formulations with homogenous drug distribution throughout the film and uniform thickness[36]. This variation in the thickness among formulations could related to the type and amount of different polymers used in each formulation.

(f) Tensile strength (TS) and Percent elongation (PE)

The measured values of both parameters were displayed in table 4 as indicators of both, TNX-FDFN strength and elasticity, in which high TS and PE values refer to soft and tough film leading to satisfying flexibility to elongate and enough toughness to withstand the applies stress [37]. While low values indicate, weak and soft film formation[38]. The obtained values explore differences apparently between polymers used as film-formers due to diverse physical and mechanical properties. It was noted that TS and PE values increase with the increase in polymer concentration, despite of concurrent increase in plasticizer concentration. As a rule, ideal film should display moderate TS and high PE for best outcomes after film application concerning flexibility, mechanical strength and user comfort in use[39].

Content uniformity

The amount of TNX in all tested FDFN films located within acceptable range (85% - 115%) between 92.35% ± 1.8 to 102.63% ± 2.2 indicating successful formulation using different polymers as film-formers with uniform TNX distribution and correct dose presentation within each 4 cm^2 film.

***In vitro* disintegration test**

TNX-FDFN disintegration was evaluated for all fifteen formulations and results ranged from 18.5 sec ±1 to 56.7 sec ±3.9 indicating significant (p<0.05) wide variation among formulations in disintegration duration, such differences could attributed to several factors including type of polymer used for film preparation, amount of polymer used, percent and type of plasticizer, thickness of final film [40, 41]. Accordingly, formulations with higher polymer concentration shown slower disintegration time, while the opposite is correct. Additionally, HPMC E 30 is more viscus than PVA and PVP K90 when dispersed in water due to gelling tendency and therefore when used in high concentration may delay film disintegration and TNX release.

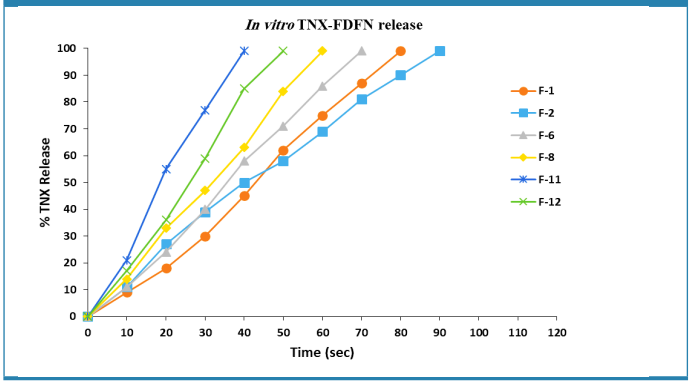
Table 4. Physiochemical characterization techniques results of TNX-FDFN formulations

F-code	Surface pH	Weight variation %	Folding endurance	Thickness (µm)	TS (MPa)	PE%	TNX content %	Disintegration time (sec)
F-1	6.54 ± 0.23	100.26 % ± 0.33	>300	63.7 ± 2.3	13.32 ± 1.68	3.24 ± 0.41	100.04 % ± 1.4	22 ± 1.3
F-2	6.36 ± 0.11	101 % ± 0.67	>300	68.3 ± 1.9	15.11 ± 0.88	3.55 ± 0.39	98.58 % ± 2.1	23.3 ± 1.7
F-3	6.41 ± 0.15	100.87 % ± 0.21	>300	72.17 ± 1.7	17.53 ± 2.1	3.63 ± 0.56	94.07 % ± 0.5	33.2 ± 2.3
F-4	6.89 ± 0.21	102.03 % ± 0.93	>300	69.84 ± 1.1	17.15 ± 1.7	3.8 ± 0.67	101 % ± 1.1	43.5 ± 1.2
F-5	6.77 ± 0.1	100.05 % ± 0.74	< 300	86.29 ± 2.6	19.32 ± 1.4	3.96 ± 0.44	97.33 % ± 1.7	56.7 ± 3.9
F-6	6.98 ± 0.14	101.04 % ± 0.45	>300	68.45 ± 2.2	20.56 ± 0.42	5.66 ± 1.1	99.52 % ± 2	21.6 ± 1.1
F-7	6.71 ± 0.12	100.29 % ± 0.16	< 300	77.19 ± 2	22.92 ± 1.7	5.78 ± 0.72	92.35 % ± 1.8	39.2 ± 2
F-8	6.55 ± 0.24	99.86 % ± 1.12	>300	84.87 ± 1.8	24.45 ± 2	5.96 ± 0.87	96.88 % ± 1	27.3 ± 3.6
F-9	6.77 ± 0.26	100.04 % ± 0.43	>300	89.43 ± 1.5	21.55 ± 1.8	6.31 ± 1.2	99.87 % ± 0.7	45.8 ± 3
F-10	6.42 ± 0.13	101.87 % ± 0.58	< 300	96.1 ± 2	25.71 ± 2.1	6.46 ± 0.73	100.12 % ± 1.6	51.5 ± 2.9
F-11	6.39 ± 0.19	100.36 % ± 1.02	>300	61.78 ± 1.3	11.82 ± 0.66	2.12 ± 0.32	102.63 % ± 2.2	18.5 ± 1
F-12	6.84 ± 0.1	100.11 % ± 0.37	>300	65.3 ± 0.8	12.48 ± 0.84	2.3 ± 0.59	99.99 % ± 1.2	22.4 ± 1.5
F-13	6.66 ± 0.14	98.93 % ± 1.29	>300	75.18 ± 2.4	14.28 ± 1.1	2.44 ± 0.89	94.85 % ± 1.9	32.8 ± 2.1
F-14	6.81 ± 0.23	100.48 % ± 0.91	< 300	81.19 ± 1.7	14.93 ± 0.91	2.71 ± 1.1	102.4 % ± 0.1	45.3 ± 3.3
F-15	6.78 ± 0.16	99.93 % ± 1.18	>300	94.2 ± 2.7	16.78 ± 2.1	3.02 ± 0.94	97.19 % ± 2.9	50.6 ± 4.1

In vitro dissolution study

Among fifteen TNX-FDFN formulations, six formulas selected for *in vitro* dissolution study including F-1, F-2, F-6, F-8, F-11 and F-12. These formulations exhibit desired disintegration time of less than 30 sec as guided in FDA, in addition to acceptable physical and mechanical properties according to the results of characterization techniques (table 4). Dissolution profiles of all tested films demonstrate almost complete (99%) TNX release from TNX-FDFN within first two minutes in accordance with the fast disintegration of prepared formulations of less than 30 seconds[42]. Additionally, the nano-sized crystals of TNX and possible lattice transformation into more soluble amorphous form with enhanced area to volume ration that cause enable larger contact area between TNX particles within each film with dissolution medium of simulated salivary fluid pH 6.8[43,44]. From all these outcomes, it can be concluded that all six tested films approve efficient and successful TNX-FDFN formulation. The type and nature of polymer used in film preparation significantly ($p < 0.05$) affect TNX dissolution and release, as noticed in figure 2 that faster release from F-11 and F-12 constructed from PVA polymer.

Fig. 2. In vitro TNX release profiles from FDFN formulations F-1, 2, 6, 8, 11 and 12 in simulated salivary fluid pH 6.8 dissolution medium.



Conclusion

The goal of preparation TNX-FDFN was successfully attained as indicated by physiochemical characterization processes. TNX-nanocrystals were prepared efficiently with optimized drug solubility. Six formulations including F-1, F-2, F-6, F-8, F-11 and F-12 demonstrate optimum physiochemical properties for application as a FDF with ideal disintegration time and *in vitro* TNX release, and therefore successful preparation of TNX-FDFN.

Conflict of interest

No conflict present by authors regarding this work.

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