ISSN : 2249 - 8877 Volume 3 Issue 2

Trade Science Inc.

Research & Reviews On Polymer

Full Paper

RRPL, 3(2), 2012 [67-73]

Tiaprofenic acid-Eudragit sustained release solid dispersions

Mohamed A.Ibrahim[1, 2*], Sayed H.Auda[1], Ihab T.Abdel-Raheem[3]

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut, (EGYPT)

[2]Kayyali Chair for Pharmaceutical Industries, Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, (SAUDI ARABIA)

[3]Department of Pharmacology and Toxicology, Al-Azhar University, Assiut, (EGYPT)

E-mail: abbma71@yahoo.com

Received: 28th November, 2011 ; Accepted: 28th December, 2011

ABSTRACT

Tiaprofenic acid (TA) is a potent non-steroidal anti- inflammatory drug having a short half-life of 3 to 6 hours. Administration of TA conventional doses might prevail serious side effects, in addition to patient inconvenience. The study aim at preparing TA solid dispersions in the matrices of Eudragit RS 100 and RL 100 by coevaporation technique. The prepared solid dispersions were characterized for their physicochemical properties, the in vitro drug release as well as the analgesic activity using tail-flick method. The results obtained showed that dispersion of the drug in RS polymeric matrix resulted in a retarding action on the drug release, while the dispersion in RL polymer type slightly retarded drug release in higher polymeric weight ratios, due to the greater number of quaternary ammonium functions on RL surfaces. The IR and PXRD studies proved the homogeneous dispersion of TA in the polymer matrices. Moreover, The maximum analgesic activity of TA-Eud RS100 (1:3) coprecipitate was between 6.5 and 7 hours extended to 11 hours, while the maximum analgesic activity of untreated drug was between 1.5 and 2 h.

KEYWORDS

Tiaprofenic acid;
Eudragit;
Sustained release;
Coprecipitates;
Analgesic activity.

INTRODUCTION

The term solid dispersion is applied to those systems in which a drug is homogeneously distributed throughout a solid matrix. Dependent on matrix aqueous solubility, drug dissolution rate can be either decreased or enhanced. In terms of increasing drug solubility, the matrix material must be water soluble[1]. Solid dispersions prepared using water-insoluble carriers have been aimed at optimizing pharmacokinetics and reduce the gastrointestinal side effects of several drugs[2-4].

Tiaprofenic acid (TA) is an active agent having potent analgesic and anti- inflammatory effects having a short half-life of 3 to 6 hours[5]. Like other NSAIDs, the oral administration of conventional dosage forms of TA causes systemic side effects and gastric irritation[6]. Designing a sustained release formulation of TA will give the opportunity to reduce drug dosing amount and frequency and improve patient compliance.

In developing new drug delivery systems, many studies have been carried out to investigate the influence of Eudragit acrylic resins on the release of drugs

from matrices[7-10]. The nature of drugs and polymers, and their reciprocal interactions, significantly influence the drug release pattern[11, 12]. In particular, the incorporation and release of non-steroidal anti-inflammatory drugs (NSAIDs) from RS and RL polymers was shown to be strongly dependent on the acidic nature of these drugs, which allows chemical interactions, physical interactions, or both to occur with the ammonium group on the RS and RL backbone[13].

The objective of this work was to prepare and characterize TA coprecipitates in different Eudragit polymers via coevaporation technique. The effect of drug loading, polymer type and polymer blend on the *in vitro* release of the drug has been evaluated. The study was also aimed to study the mechanism of interaction between Eud RS and Eud RL polymers with TA using IR and X-ray spectroscopic techniques. Furthermore, the analgesic activity of TA sustained release copreciptate compared to untreated drug has been studied using an animal model.

MATERIALS

Tiaprofenic acid (TA) was kindly supplied by Aventis pharma Egypt (Cairo, Egypt), Eudragit® RS 100 and Eudragit® RS 100 were kindly supplied from Evonik Röhm Gmbh, Germany, Acetone and absolute ethanol (95%) were purchased from EL-Nasr Co., Abu-Zabal, Egypt, Other materials and solvents are of reagent or analytical grade, and they were used without further purification.

METHODS

Preparation of TA-Eudragit coprecipitates

Co-evaporation technique was employed to prepare coprecipitates of TA with Eudragit RL 100 and Eudragit RS 100. Different drug: polymer weight ratios (1:1, 1:3 and 1:5) were used to prepare TA coprecipitates with the Eudragit polymers. Briefly, the weighed amounts of TA (0.5 g) and Eudragit RS or RL (0.5–2.5 g) were dissolved in 50 ml of a mixture of absolute ethanol: acetone (1: 1). The solution was stirred at room temperature for 20 minutes, and the solvent was then removed under vacuum in a rotary evaporator, at a maximum temperature of 40°C. Solid residue was dried in a desiccator for 24 h at room temperature, pulverized and sieved (Sieve shaker, Rx-86-1, Cole-Parmer Instrument Co., USA). Powder samples below 420 μm (40 mesh) were stored in closed containers away from the light and humidity until use.

Preparation of the physical mixtures

Samples having the same composition of the coprecipitates were prepared by simply mixing the triturated powdered drug and the tested Eudragit polymer in a porcelain mortar. The mixtures were then sieved, and the particles below 420 μm were collected and stored in capped amber-glass containers until use.

Determination of drug content

About 10 mg of each solid dispersion were dissolved in 5 ml of a mixture of absolute ethanol: acetone (1:1). Tiaprofenic acid was determined spectrophotometrically (Double beam Spectrophotometer UV. 1601, Shimadzu Co., Japan) at 325 nm. The mean of at least three determinations was calculated. The polymers did not interfere with the absorbance of the drug.

In vitro release studies

The drug dissolution experiments on TA-Eudragit systems or individual components were carried out by the rotating paddle method (Dissolution test apparatus, SR11 6 Flask, Hanson Co., USA). The in vitro release experiment were performed in triplicate at 37°C and the dissolution media was 500 mL of phosphate buffer saline (PBS, pH 7.4).

The powder was spread over the surface of the dissolution liquid. At pre-set intervals, samples of 5 ml were withdrawn through a pipette and filtered. The sample was diluted to a suitable volume with the buffer solution and the absorbance was measured at 316.5 nm. Equal volume of fresh dissolution medium, prewarmed at 37°C, was replaced into the dissolution medium so as to keep the volume of the dissolution medium constant.

IR-Spectroscopy

IR spectra of certain TA-Eudragit coprecipitates and the corresponding physical mixtures as well as the individual components were determined at a range 4000-400 cm^{-1} using KBr disk method (IR-Spectrophotometer, IR-476, Shimadzu Co., Japan). The

samples were ground, mixed thoroughly with KBr and compressed at a pressure of 6 ton/cm^2 using Shimadzu SSp-10A IR compression machine.

Powder X-Ray diffraction (PXRD)

The X-ray diffractograms were obtained using Jeol XR Diffractometer (Jeol, Tokyo, Japan). The radiation source was a copper (λ=1.54184 Å) high-intensity x-ray tube operated at 35 KV and a current of 15 mA. The diffraction patterns were achieved using continuous scan mode with 2θ values ranging from 4-100 at a rate of 4 degrees/minute.

Analgesic activity (Tail-flick analgesic test)

The analgesic activity of TA-Eud RS 100 (1:3) coprecipitate of an expected sustained release action was compared to that of untreated TA using Tail-flick method as described by[14]. Briefly, a rat (Wister albino) weighing about 200 gm was fixed on a tail-flick analgesimeter with a portion of the tail, 10 cm from its tip, exposed to heat from a projector lamp. The temperature from the projector was kept constant with the aid of digital thermometer for careful monitoring of the temperature near the animal tail. A single control switch simultaneously activated the light and a timer. The timer stops automatically when the exposed rat's tail flicks. The time interval between switching on the light and flick of the tail was recorded. A 30 s cut-off time was used to avoid thermal injury. The sustained release TA coprecipitate (TA-Eud RS 100 1:3) was suspended in distilled water containing 0.5% w/v carboxymethyl cellulose then administered orally at a dose of (15mg/kg)[15]. Untreated TA was dissolved in distilled water containing 0.5% w/v carboxymethyl cellulose and given orally at the same dose to another rat. Tail-flick test was started at 0 time after administration of oral TA, and the test was done every 30 min for 11.5 h (690 min). Control group was administered the same volume of distilled water.

RESULTS AND DISCUSSION

In vitro release studies

To study the impaction of Eudragit type and weight ratio with TA on the release characteristics of the drug from TA - Eudragit coprecipitates, different drug: polymer ratios were prepared for each polymer. The release profile from such coprecipitates in PBS (pH 7.4)

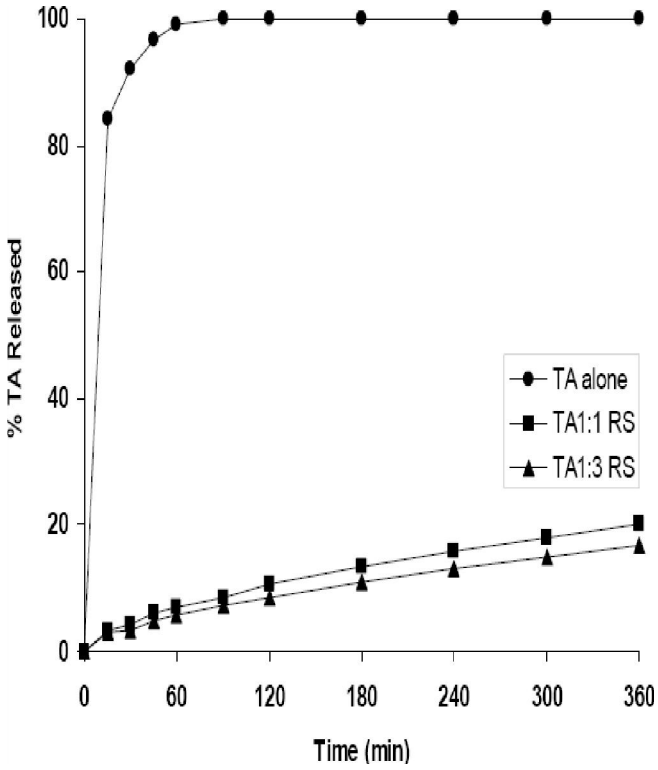

Figure 1 : In vitro release pattern of TA from Eud RS 100 coprecipitates in PBS (pH 7.4) at 37 ^{0}C.

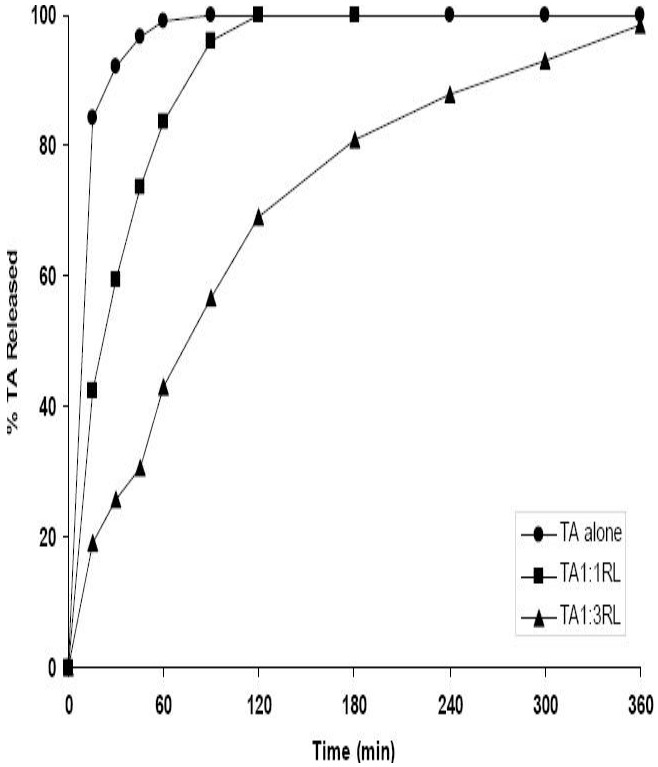

Figure 2 : In vitro release pattern of TA from Eud RL 100 coprecipitates in PBS (pH 7.4) at 37 ^{0}C.

is plotted in Figure 1 and 2. Untreated TA exhibited a faster release rate in which 85% of the drug released after 15 minutes, and the drug exhibited a 96% release after 45 minutes. However, dispersion of TA in the matrices of Eudragit RS 100 showed a strong retarding action on the release rate of the drug, Figure 1. The drug showed 20.12% and 16.72 % release from TA1: 1RS 100 and TA1: 3RS 100 coprecipitates, respectively, after 360 minutes.

In contrast, the dispersion of TA in the matrices of Eudragit RL 100 resulted in different retarding action on the drug release. The drug exhibited 100% release rate from its 1:1Eeudragit RL coprecipitate after 120 minutes, while TA1: 3 Eudragit RL coprecipitate release 98.59% of the loaded drug after 360 minutes with a graduate release along the experiment time, Figure 2.

The dispersion of the drug in the polymer matrices strongly influenced its dissolution rate, which appeared slower and more gradual than that of the pure drugs, while increasing the polymer ratios. RL coevaporates usually displayed higher dissolution rates compared to those observed in case of RS ones. This might be because of the greater quaternary ammonium group content in the 2 materials. RS polymer is only slightly permeable to water; hence, drug release is relatively retarded with respect to the freely permeable RL[11, 16]. Ibrahim et al[12] prepared ketrolac tromethamine solid dispersions in the matrices of eudragits RL 100 and RS 100. They found that the in vitro release results indicated that the dispersions made of pure Eud RS exhibited a slower release when compared to those prepared using RS/RL blends. They arrtibuted these findings Eudragit RL has higher water permeability than Eudragit RS due to the higher quaternary ammonium content of RL type.

Other TA coprecipitates were prepared by dispersing the drug in two blends of Eud RS 100-Eudragit RL, namely 1: 2 and 2: 1. Blending RL: RS result in improving the drug release in comparison to pure Eudragit RS 100 dispersions. TA showed 53.75% and 62.35 % released from RS: RL 1: 2 and 2: 1 coprecipitaes, respectively, at the end of release experiment, Figure 3. Howevr, on comparing the drug release from these two systems, the difference is said to be insignificant.

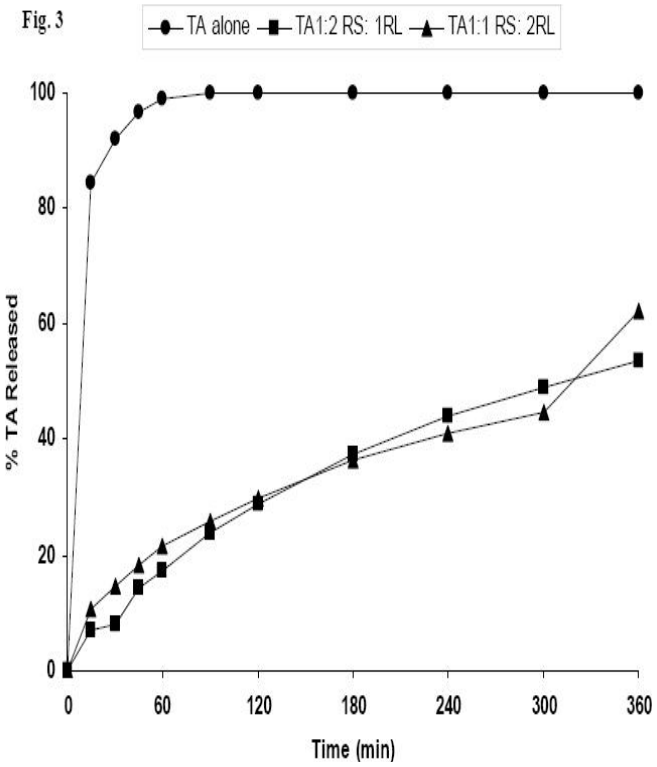

Figure 3 : In vitro release pattern of TA from coprecipitates prepared from different Eudragit RS/RL blends in PBS (pH 7.4) at 37 ^{0}C.

Kinetic assessment of the in vitro release of TA from the prepared Coprecipitates

In order to determine the release model which best describes the pattern of drug release, the *in vitro* release data were fitted to zero order, and diffusion controlled release mechanisms according to the simplified Higuchi model[17].

The preference of a certain mechanism was based on the root mean square of the residuals (RSS) for the parameters studied, where the lowest RSS is preferred

TABLE 1 : Kinetic modeling of TA release from different solid dispersions

Formula	Zero order model		Higuchi diffusion model		
	r	RSS	r	RSS	n-value
TA alone	-	-	-	-	-
TA 1: 1 Eud RS	0.979	1.37	0.997	0.54	0.576
TA 1: 3 Eud RS	0.980	1.12	0.997	0.47	0.578
TA 1: 1 Eud RL	0.928	14.35	0.998	2.69	0.466
TA 1: 3 Eud RL	0.933	12.67	0.989	5.32	0.554
TA 1: 2 Eud RS: 1RL	0.977	4.13	0.993	2.32	0.696
TA 1: 1 Eud RS: 2RL	0.968	4.64	0.983	3.38	0.517

for the selection of mechanism of release[18], TABLE 1. Successive evidence of the relative validity of diffusion and zero order models obtained by analyzing the data using the following equation of[19, 20].

$$Mt/M8 = K.t^n$$

Where Mt/M8 is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the drug transport mechanism. When n = 0.43, Fickian diffusion is observed and the release rate is dependent on t, while 0.43 < n < 1.0 indicates anomalous (non-Fickian) transport and when n = 1, the release is zero-order. The recorded values of n were found to be located in the range 0.466-0.696, which indicates the anomalous (non-Fickian) transport.

Physicochemical characterization of solid dispersions

The physical changes of KT dispersed in the matrices of Eudragit polymer as coevaporate was studied using IR spectroscopy and x-ray diffraction techniques. The corresponding physical mixtures were tested as a reference.

IR Spectroscopy

In order to characterize possible interactions between the drug and the polymeric carriers in the solid state, infrared spectra were recorded for TA-Eud RS and TA-Eud RL systems as well. Figure 4-1 (A-D) demonstrates IR spectra of the untreated TA, Eud RS 100, TA-Eud RS 100 coprecipitate (1:3 weight ratio of drug: polymer) and the corresponding physical mixture. Two bands were observed at 3440 cm^{-1} (broad) and 1722cm^{-1} (sharp) which are corresponding to O-H and C=O stretching vibrations of TA, Figure 4-1 A. The characteristic TA C=O band at 1722cm^{-1} could not be further detected in the IR spectrum of coprecipitate, Figure 4-1 C, but are still present in the IR spectrum of the corresponding physical mixture, Figure 4-1 D. The disappearance of TA absorption bands in the IR spectrum of the coprecipitate is in accordance with data revealed in the x-ray studies that proved the homogeneous dispersion of TA in Eud RS 100 matrix. This finding is in accordance to that observed by[21] who found that the fourier transform infrared spectroscopy, differential scanning calorimetry and powder x-ray

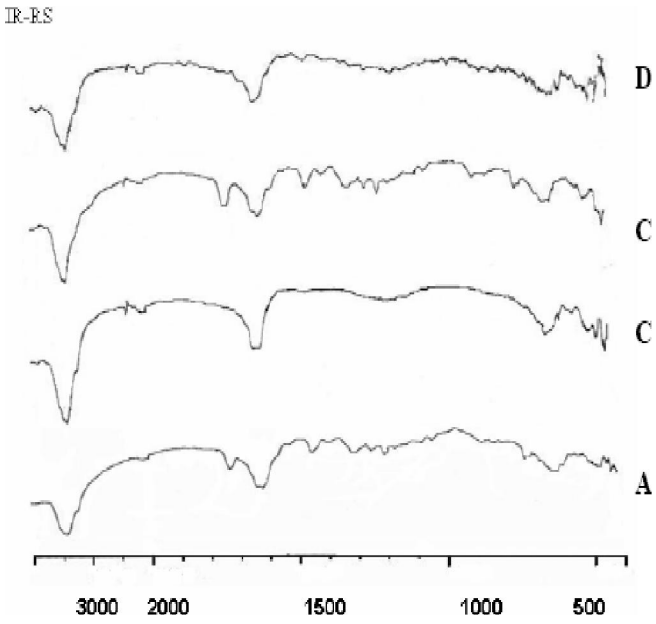

Figure 4-1 : The IR spectra of (A) TA; (B) Eud RS 100; (C) TA: Eud RS 100 1:3 physical mixture and (D): Eud RS 100 1:3 coprecipitae.

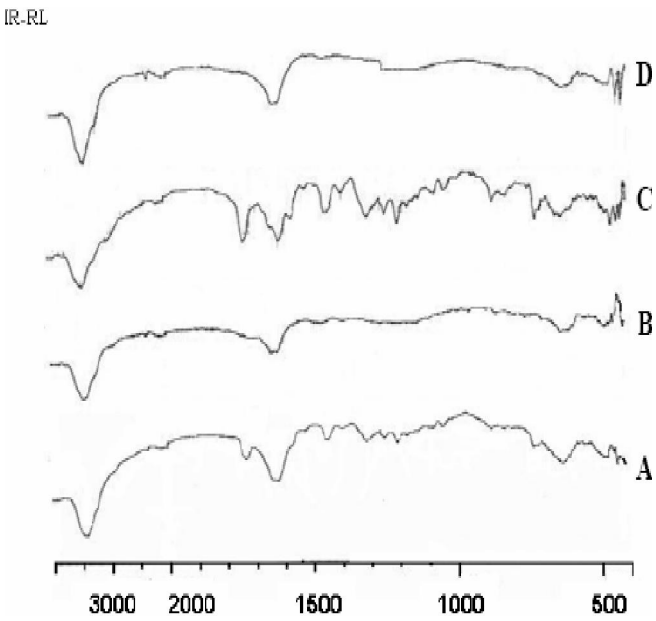

Figure 4-2 : The IR spectra of (A) TA; (B) Eud RL 100; (C) TA: Eud RL 100 1:3 physical mixture and (D): Eud RL 100 1:3 coprecipitae.

diffractometry confirmed that the diclofenac sodium was reduced to molecular or microcrystalline form in the hydrophobic polymeric matrices, which could be responsible for the controlled drug release from its Eudragit RS and RL solid dispersions.

Powder X-Ray diffraction (PXRD)

To get further evidence on the solid state changes,

the powder XRD patterns of TA binary (1: 3) systems with Eudragit RS 100 and Eudragit RL 100 are shown in Figure 5-1 and 5-2, respectively.

PXRD analysis of pure RS polymer is typical of amorphous materials, Figure 5-1 B. The presence of numerous distinct peaks in the x-ray diffraction spectrum of TA indicates that the drug is present as a crystalline material with characteristic diffraction peaks appearing at diffraction angels of 2θ at 15.52A°, 17.53A°, 21.85A°, 22.38A° and 23.93A° with relative intensities of 75, 40, 44, 100 and 90 respectively, Figure 5-1& 5-2.

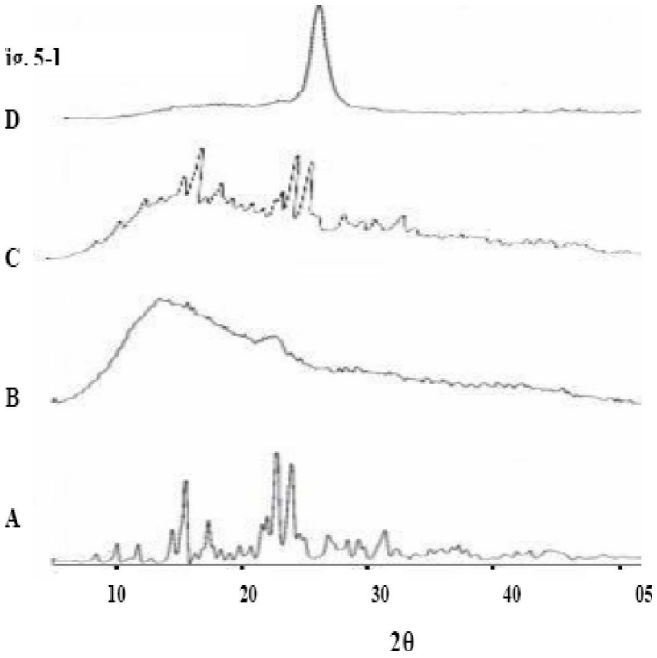

Figure 5-1 : Powder x-ray diffraction spectra of (A) TA; (B) Eud RS 100; (C) TA: Eud RS 100 1:3 physical mixture and (D): Eud RS 100 1:3 coprecipitae.

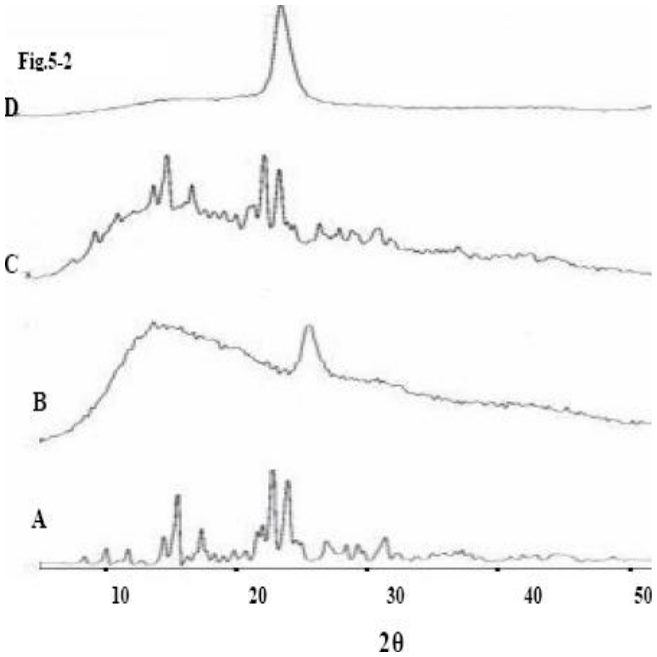

Figure 5-2 : Powder x-ray diffraction spectra of (A) TA; (B) Eud RL 100; (C) TA: Eud RL 100 1:3 physical mixture and (D): Eud RL 100 1:3 coprecipitae.

The spectrum of TA-Eud RS100 (1:3) solid dispersion (Figure 5-1: D) showed a complete disappearance of the drug diffraction peaks, with an exception of the diffraction peak at 23.93A°, which still appear unchanged. Similarly, TA-Eud RL100 (1:3) solid dispersion (Figure 5-2: D) exhibited the same previous x-ray diffraction profile. The corresponding physical mixtures displayed a higher degree of crystallinity in their PXRD spectra, but always lower than the theoretical amount of dispersed drug (Figure 5-1 C& 5-2 C). The recorded relative intensities of the characteristic diffraction peaks in case of TA-Eud RS100 (1:3) physical mixture are 65, 48, 44, 62 and 59, whereas those recorded in case of TA-Eud RL100 (1:3) physical mixture were found to be 58, 49, 40, 57 and 52. The disappearance of the most TA crystalline peaks in the drug-Eudragit coprecipitates suggests that TA undergone a microcrystallization in the Eudragit matrix when the drug concentration overcomes its solubility in the polymer[11].

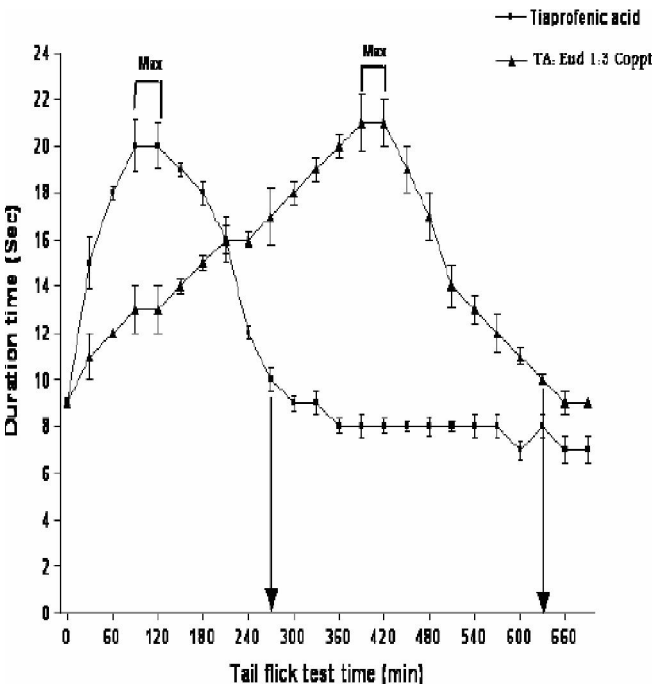

Figure 6 : Tail-flick analgesic test of TA-Eud RS 100 1:3 coprecipitate compared to untreated TA.

Tail-flick analgesic test of Tiaprofenic acid Solid dispersion preparations

From the rat tail-flick test (Figure 6), the sustained release TA-Eud RS 100 1:3 coprecipitate showed a more prolonged analgesic effects compared to that of untreated drug powder. The duration of action was extended from (4.5 hours = 270 min) in case of untreated drug to (10.5 hours =630 min) in case of the solid dispersion form of Tiaprofenic acid. It could be observed from the Figure that the maximum analgesic activity TA-Eud RS 100 1:3 coprecipitate was found to range between 6.5 and 7 hours while the maximum analgesic activity of untreated drug was between 1.5 and 2 hours after its administration.

CONCLUSION

This study shows that it is feasible to control TA release from Eudragit solid dispersions depending in the polymer nature and the drug concentration in the coprecipitates as well. In addition, the drug-polymer interaction may play an important role in controlling the drug release from such coprecipitates. Also, TA-Eud RS100 coprecipitate exhibited a prolonged analgesic activity indicating that formulation of TA in a sustained released form is beneficial not only in reducing dose frequency but also in minimizing the severity of TA adverse reactions.

REFERENCES

[1] E.Shefter; Techniques of Solubilization of Drugs, S.H.Yalkowsky (Ed.), Dekker, New York, **171**, **(1985)**.

[2] A.A.Karnachi, R.A.De Hon, M.A.Khan; Drug Dev.Ind.Pharm., **21**, 1473-1485 **(1995)**.

[3] M.G.Vachon, J.D.Nairon ; Eur.J.Pharm.Biopharm., **45**, 9-12 **(1998)**.

[4] H.Yuasa, T.Ozeki, Y.Kanaya, K.Oishi, T.Oyake; Chem.Pharm.Bull., **39**, 465-467 **(1991)**.

[5] N.M.Davies ; Clin.Pharmacokinet., **31**, 331-47 **(1996)**.

[6] Martindale; The Complete Drug Reference (33rd Edition), The Pharmaceutical Press, London, **88**, **(2002)**.

[7] S.Benita, A.Hoffman, M.Donbrow; J.Pharm.Pharmacol., **37**, 391-395 **(1985)**.

[8] D.B.Beten, A.J.Moes; Int.J.Pharm., **103**, 243-251 **(1994)**.

[9] M.R.Jenquin, J.W.McGinity; Int.J.Pharm., **10**, 23-34 **(1994)**.

[10] S.Y.Lin, C.L.Cheng, R.IPerng; Eur.J.Pharm.Sci., **1**, 313-322 **(1994)**.

[11] R.Pignatello, M.Ferro, G.Puglisi; AAPS Pharm.Sci.Tech., **3**, 1-11 **(2002)**.

[12] M.A.Ibrahim, M.A.Amin, G.Fetih, A.Abou Ela; STP Pharma.Pratiques, **20**, 189-200 **(2010)**.

[13] G.Heun, N.Lambov, R.Groning; Pharm.Acta.Helv., **73**, 57-62 **(1998)**.

[14] S.C.Shin, J.W.Lee, K.H.Yang, C.H.Lee; Int.J.Pharm., **260**, 77-81 **(2003)**.

[15] K.U.Weithmann, V.Schlotte, V.Jeske, D.Seiffge, A.Laber, B.Haase, R.Schleyerbach; Inflam.Res., **46**, 246-252 **(1997)**.

[16] M.P.Oth, A.J.Moes; Int.J.Pharm., **55**, 157-164 **(1989)**.

[17] T.Higuchi; J.Pharm.Sci., **52**, 1145-49 **(1963)**.

[18] G.M.Mahrous, M.A.Ibrahim, M.El-Badry, F.K.Al-Anazi ; J.Drug Del.Sci.Tech., **20**, 119-125 **(2010)**.

[19] R.W.Korsmeyer, N.A.Peppas ; In: T.J.Roseman, S.Z.Mansdorf (Eds.), Dekker, New York, 77-101 **(1983)**.

[20] P.L.Ritger, N.A.Peppas; J.Control.Release, **5**, 37-42 **(1987)**.

[21] H.N.Shivakumar, B.G.Desai, G.Deshmukh ; Ind.J.Pharm.Sci., **70**, 22-30 **(2008)**.