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EFFECT OF CERTAIN POLYMERS ON PHYSICOCHEMICAL PROPERTIES OF TENOXICAM.

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ABSTRACT

Tenoxicam is a widely used non-steroidal anti-inflammatory drug (NSAID). It is practically insoluble in water 14.1mg/ml, it is sparingly soluble in methylene chloride, very slightly soluble in ethanol and dissolves in solutions of acids and alkalis. The work in this study was performed in order to investigate the effect of certain polymers (Eudragit RL100, EudragitRS100 and methyl cellulose) in different drug to polymer ratios on the dissolution of tenoxicam in acidic as well as alkaline pH values. Solid dispersion technique was the technique of choice for preparing microbeads. FT-IR and X-ray diffraction were performed in order to investigate the interaction - if any- between the drug and the polymers.

KEYWORD: Tenoxicam, Eudragit RL100, Eudragit RS100, methyl cellulose, solid dispersion.

INTRODUCTION

Non -steroidal anti-inflammatory drugs (NSAIDS) are among the most commonly used drugs worldwide and their analgesic, anti-inflammatory and anti-pyretic therapeutic properties are thoroughly accepted. More than 30 million people use NSAIDs every day according to a study published in the American Gastroenterological Association (AGA) journal NSAIDs for 60% of the US over-the-counter analgesic market, however, NSAIDs are associated with a broad Spectrum of side effects, including gastrointestinal (GIT) and cardiovascular (CV), renal toxicity, increased blood pressure, and deterioration of congestive heart failure among others.[1]

The damage of gastric and duodenal mucosa caused by NSAIDs has been widely studied. These upper GIT side effects include troublesome symptoms with or without mucosal injury, asymptomatic mucosal lesions, and also serious complications, even death. About 30 to 50% of NSAID users have endoscopic lesions (such as subepithelial hemorrhages, erosions, and ulcerations), mainly located in gastric antrum and often without clinical manifestations. Generally, these lesions have no clinical significance and tend to reduce or even disappear with chronic use, probably because the mucosa is adapted to aggression.[2]

Tenoxicam is an oxicam derivative belonging to the "enol acid" group; it is a very effective NSAIDs drug. The molecule was synthesized in 1976 by Hromatka[3] and its pharmacology was investigated by Tanaka and coworkers in 1981.[4] The three basic therapeutic effects of NSAIDs drugs are analgesic, anti-inflammatory and antipyretic; these are attained by the blockage of cyclooxygenase, with a consequent decrease in prostaglandin biosynthesis. [5] There are two cyclooxygenases: COX-1 and COX-2. COX-2 synthesizes the prostaglandins, and is activated in inflammed tissues, induced by cytokines and endotoxins. COX-1 is responsible for the synthesis of prostaglandins in other tissues (stomach, kidney, blood vessels, thrombocytes, etc.) in the organism. Most NSAID compounds block both COX-1 and COX-2. The blockage of COX-2 results in anti-inflammatory, antipyretic and analgesic effects, while that of COX-1 is responsible for ulcerogenic side-effects.

Tenoxicam is recommended in several types of chronic arthritis, tendovaginitis and sprain, and to relieve postoperative pain, among other indications.[6-10] The half-life of tenoxicam is 72 hours, and it is therefore administered once daily. A daily dose of 20 mg is generally well tolerated. Fig. I shows chemical structure of tenoxicam.

The aim of work in this study was to investigate the effect of certain polymers namely Eudragit RL100, Eudragit RS100 and methyl cellulose on the release of tenoxicam Also the effect of the polymers on the physicochemical properties of the drug was investigated.

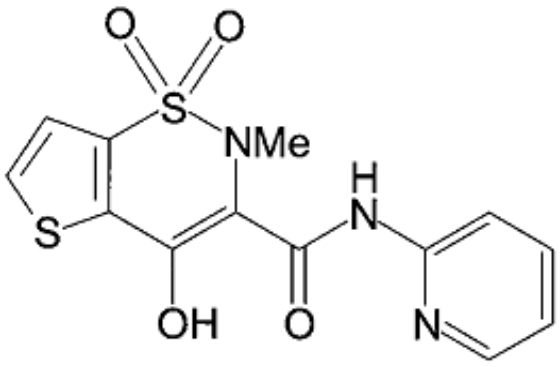

Fig. I chemical structure of tenoxicam

MATERIALS AND METHODS

Materials

Tenoxicam(GMBH, Germany) was a gift sample kindly supplied by EIPICO pharmaceutical industries, El-Asher, Egypt; Eudragit RL100 and Eudragit RS100 were purchased from RÖhm Pharma(Germany), methyl cellulose from Sigma- Aldrich Chemi(Germany), Potassium hydroxide scales (Reidel de Haein, Germany), Potassium dihydrogen phosphate (Reidel de Haein, Germany), Hydrochloric acid(SDS, France), Ethanol 99% from Sigma- Aldrich Chemi(Germany), Dichloromethane from Sigma- Aldrich Chemi(Germany), All the reagents and chemicals were analytical grades and were used as received.

Apparatus

UV-visible recording spectrophotometer, SHIMADZU (UV-160A)(Japan);Balance (Citizen CX 220, U.S.A), Vortex mixer (Maxi mix 11, Thermolyne corporation, U.S.A.), pH meter(HANNA Instruments, Romania), Water Bath (KOWELL N4, Germany),Sonicator (BRASONIC ultrasonic cleaner U.S.A), Dissolution apparatus :USP(paddle type)(Copley, England), FTIR analyzer (Perkin Elmer model), Differential Thermal Analyzer (Mettler- Toledo star 822 e system, Switzerland), powder X-ray diffractometer GNR from spectra technology(Italy).

METHODS

Preparation of solid dispersion systems using different polymers

Solid dispersion systems were generally prepared by solvent evaporation methods. Solvent evaporation method was considered as one of the most convenient methods for preparation of solid dispersion.[11]

Three ratios of solid dispersions containing tenoxicam with Eudragit RL100, Eudrgit RS100 and methyl cellulose.(in ratios of 1:1, 1:2&1:3) drug to polymer were prepared. The method was achieved by dissolving the appropriate amount of the polymer in a mixture of ethanol 99% and dichloromethane in a ratio (1:1), with continuous stirring where ethanol :dichloromethane mixture was used as the solvent for the above three polymers. An amount of tenoxicam (20 mg) was accurately weighed and dissolved in a minimal amount of a mixture of ethanol to dichloromethan in a ratio (1:1) at 70°C. the calculated amount of the polymer was weighed and dissolved in the same solvent and added gradually to the drug with continuous stirring. Solvent was allowed to evaporate at room temperature till a dry film was obtained.

Determination of tenoxicam content

Percentage yield can be determined by calculating the initial weight of raw materials and the finally obtained weight of solid dispersion. Percentage yield can be calculated using the following formula.

$$percentage\ yield = \frac{practical\ yield}{Theoritical\ yield} \times 100$$

An amount of drug equivalent to 5mg drug in the solid dispersion tenoxicam was transferred to volumetric conical flask (25ml), completed with solvent (99% ethanol dichloromethane 1:1 ratio).

In a volumetric conical flask, half ml of stock solution was completed to 10 ml using the same solvent mixture, the absorbance of sample was measured using UV-visible spectrophotometer at 372 nm.

The drug content is calculated according to the following formula.[12][13]

$$Entrapment\ efficiency = \frac{Drug\ loading\ in\ the\ solid\ dispersion}{Theoritical\ drug\ loading} \times 100$$

Release studies of tenoxicam from its solid dispersion systems

Release studies of tenoxicam from its solid dispersion systems with different polymers (Eudragit RL100, Eudrgit RS100 and methyl cellulose) were conducted in 0.1N HCL pH(1.0) and Phosphate buffer pH(7.4). The experimental design of the in vitro release experiments of tenoxicam from its solid dispersion systems was shown in Table (1).

Table (1): Shows the experimental design of the in vitro release experiments of tenoxicam from its solid dispersion systems.

Formula	Drug to polymer ratio	Dissolution media	
Tenoxicam	Free drug	0.1N HCL pH(1.0)	Phosphate buffer pH(7.4)
Tenoxicam(20mg) with Eudragit RL 100	1:1 1:2 1:3	0.1N HCL pH(1.0)	Phosphate buffer pH(7.4)
Tenoxicam(20mg) with Eudragit RS 100	1:1 1:2 1:3	0.1N HCL pH(1.0)	Phosphate buffer pH(7.4)
Tenoxicam(20mg) with methyl cellulose	1:1 1:2 1:3	0.1N HCL pH(1.0)	Phosphate buffer pH(7.4)

Infrared spectroscopy (IR)

A qualitative IR investigation has been performed for plain tenoxicam, tenoxicam with Eudragit RL100 (1:1) solid dispersion system, tenoxicam with Eudrgit RS100(1:1) and methyl cellulose in drug to polymer ratios of(1:1). Samples of 2-3 mg were ground and mixed with potassium bromide (IR grade),compressed into disks in the compressor unit under vaccum at a pressure of 10 ton/cm^2 and scanned from 4000cm^{-1} to 400 cm^{-1} with an empty pellet holder acting as reference using FTIR analyzer (Perkin Elmer model). FT-IR studies were carried out to check for any interaction between the drug and the polymer. Chemical integrity of the drug was determined by comparing the IR spectra of the drug, drug: polymer solid dispersion system.

Differential Thermal Analysis (DTA)

The physical state of the drug in the solid dispersion was analyzed by Differential Thermal Analyzer (Mettler-Toledo star 822 e system,Switzerland). The thermogram of the samples were obtained at a scanning rate of 15 °C /min conducted over a temperature range of 25-220 °C, respectively.

Powder X-ray diffraction analysis (XRD)

Powder X- ray patterns were recorded using a powder X-ray diffractometer (Brakeraxs model D8 Advance) under the following condition :target Cu ; filter Ni ; voltage 40 kv ; current 40 A ; receiving slit 0.05 inches. The scanning range was 3-60°C at a wavelength of 1.54°A.

Release conditions

Release of the drug from the solid dispersion system was done by using USP II apparatus (paddle type). The dissolution media was 0.1N HCL (pH 1.0) as well as phosphate buffer (pH 7.4). Temperature of the dissolution media was kept at 37°C ±1°C and the paddle agitation was 50 r.p.m.5ml samples were withdrawn at different intervals. The withdrawn samples were replaced by the same volume of the fresh media to keep sink conditions.

Statistical analysis

ANOVA test was used to compare the percentages released of the drug measured during in vitro release studies in 0.1N HCL, pH (1.0) or phosphate buffer as well as pH (7.4).

RESULTS AND DISCUSSION

Characterization of solid dispersion systems

Tenoxicam content determination

Tenoxicam content in different solid dispersion formulations was found to range from 90% and 114.38%. Table (2) summarises tenoxicam content in the different solid dispersion formulations.

It is clear that the percentage yield of different solid dispersion formulations varied from 90% to 114.38%, it is evident that drug to polymer ratio did not play any rule in the entrapment efficiency of the drug. This in contrast to the results obtained by Trivedi et al.[14] who reported that by increasing the polymer ratio in aceclofenac microsphere formulations from 1:1 to 1:5 was followed by increasing the drug entrapment efficiency and this is in contrast to Pongpaibul et al.[15] who showed that drug dissolution rate could be decreased with increased polymer concentration in indomethacin microsphere formulations.

Table 2: Tenoxicam content in different solid dispersion formulations.

Polymer used	Drug: polymer ratio	Tenoxicam content (%)
Eudragit RL100	1:1	106.41±1.1
	1:2	101.44±2.5
	1:3	95.43±3
Eudrgit RS100	1:1	97.72±1.5
	1:2	94.42±0.5
	1:3	90±0.5
methyl cellulose	1:1	106.66±0.2
	1:2	114.38±0.5
	1:3	107.71±0.5

(Mean ±SD, n=3)

Infrared spectral analysis

Infrared studies (Fig. 2) reveals that there is no appearance of new peaks and disappearance of existing peaks, which indicated that there is no interaction between the drug and the polymers used.

IR spectrum of tenoxicam (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) (Fig. 2- 4(A).

IR spectrum of Eudragit RL100(RL100) has a broad band characteristic of hydroxyl groups (O – H stretch vibration) in the range of 3.476 – 2.358 cm^{-1}, characteristic bands of methyl and methylene (C H stretch vibration) at 2.976 cm^{-1} and 2.895 cm^{-1}, and a strong band due to carbonyl groups (C – O stretch vibration) at 1.733 cm^{-1} and two bands due to ester linkages (C – O stretch vibration) at 1.368 and 166 cm^{-1} (Fig. 2 (B). The interaction of (RL100) and the pure drug (TL) are given (Fig. 2(C).

IR spectrum of Eudragit RS 100(RS100) has a broad band characteristic of groups carbonyl (C=O) at 1723 cm^{-1}, and ester linkages (C-O stretch vibration) at 1149 cm^{-1} (Fig. 3 (B). The interaction of (RS100) and the pure drug (TS) are given (Fig. 3(C).

FT-IR spectrum of methyl cellulose (MC) showed a typical peak at OH stretching vibration peak at 3413 $cm^{-1}$and C–H stretching vibration peaks at 2902 and 2835 cm^{-1} C–O carbonyl stretching peak was observed at 1647 cm^{-1} and ring stretching was observed at 948 cm^{-1} (Fig. 4 (B) . The interaction of methyl cellulose and the pure drug (MC) are given (Fig. 4(C).

IR studies (Fig. 2C, 3C, 4C) show no interaction between drug and excipients. However, addition peak were absorbed in solid dispersions which could be due to the presence of polymers and indicated that there was no chemical interaction between tenoxicam and other excipients. The spectra showed no incompatibility between the polymers and tenoxicam drug The spectra of the polymers and the pure drug are given (Fig.(2- 4).

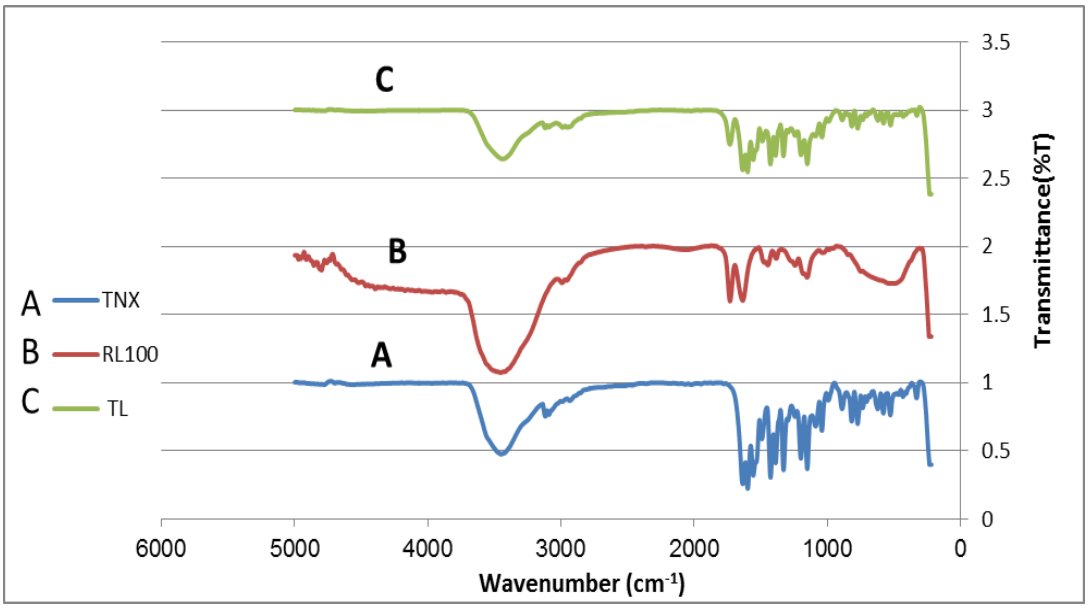

Fig 2: IR spectrum of TNX (A), RL 100(B), their solid dispersion formulation TL (C).

TL=The interaction of (RL100) and the pure drug.

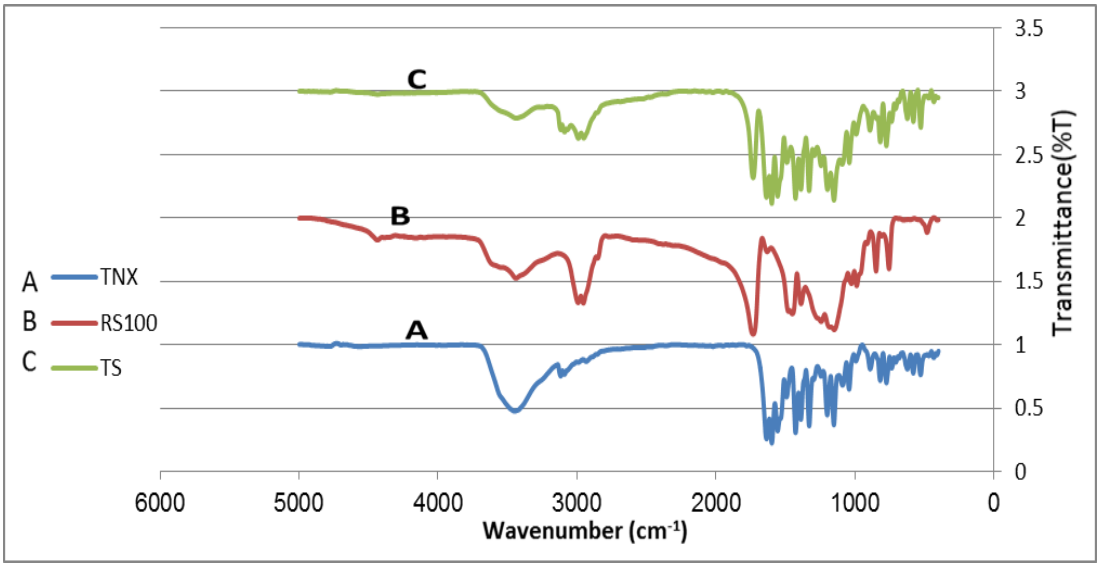

Fig. 3 IR spectrum of TNX (A), RS 100(B), their solid dispersion formulation TS (C)

TS= The interaction of (RS100) and the pure drug.

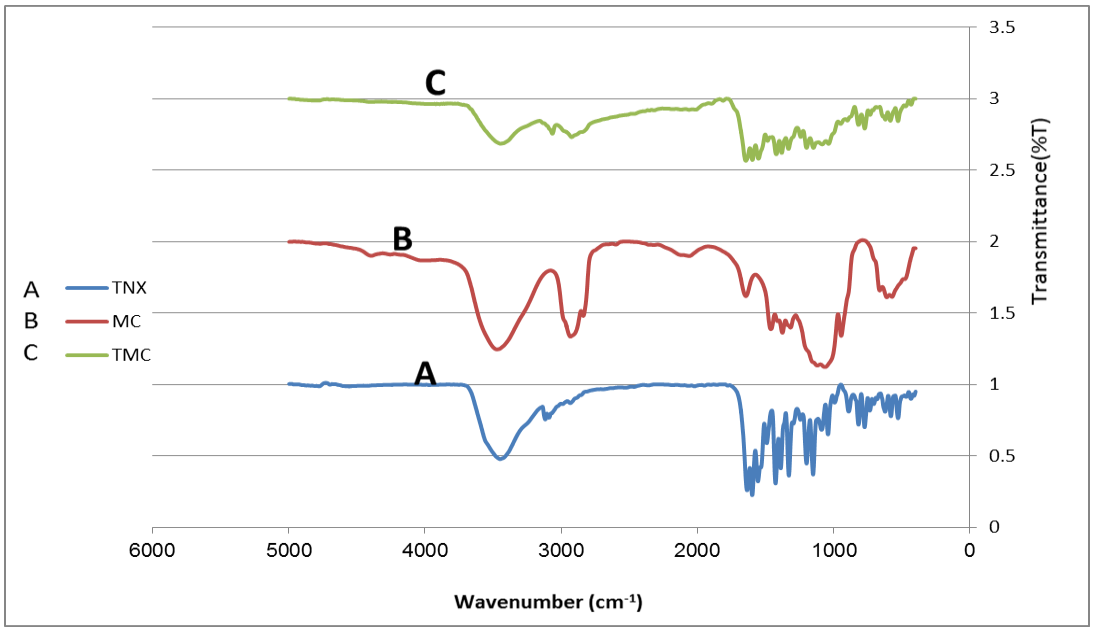

Fig. 4 IR spectrum of TNX (A), MC (B), their solid dispersion formulation TMC (C)

TMC=The interaction of (MC) and the pure drug.

X-ray diffractometry(XRD)

In order to confirm the physical state of the drug in the solid dispersion systems, powder X-ray diffraction studies of the pure drug(TNX), and drug in the solid dispersion systems were carried out, (TL) tenoxicam to Eudragit RL100 (1:1) drug to polymer ratio, (TL2) tenoxicam to Eudragit RL100 (1:2) drug to polymer ratio, (TL3) tenoxicam to Eudragit RL100 (1:3) drug to polymer ratio, (TS) tenoxicam to Eudragit RS100 (1:1) drug to polymer ratio, (TS2) tenoxicam to Eudragit RS100 (1:2) drug to polymer ratio, (TS3) tenoxicam to Eudragit RS100 (1:3) drug to polymer ratio, (MC) tenoxicam to methyl cellulose (1:1) drug to polymer ratio, (MC2) tenoxicam to methyl cellulose (1:2) drug to polymer ratio and (MC3) tenoxicam to methyl cellulose (1:3) drug to polymer ratio.[16]

X-ray diffractograms of the samples showed that the drug is present in another lattice structure with higher dissolution results and rates and higher diffusion results were observed for those products for which the presumably amorphous part of the polymers was more extensive.

As may be seen in Fig. (5-7) tenoxicam had a crystalline structure while Eudragit RL100, Eudragit RS100 and methyl cellulose had an amorphous structure, their products exhibit lower peak intensity, and this intensity almost reduced upon dilution with the polymers.

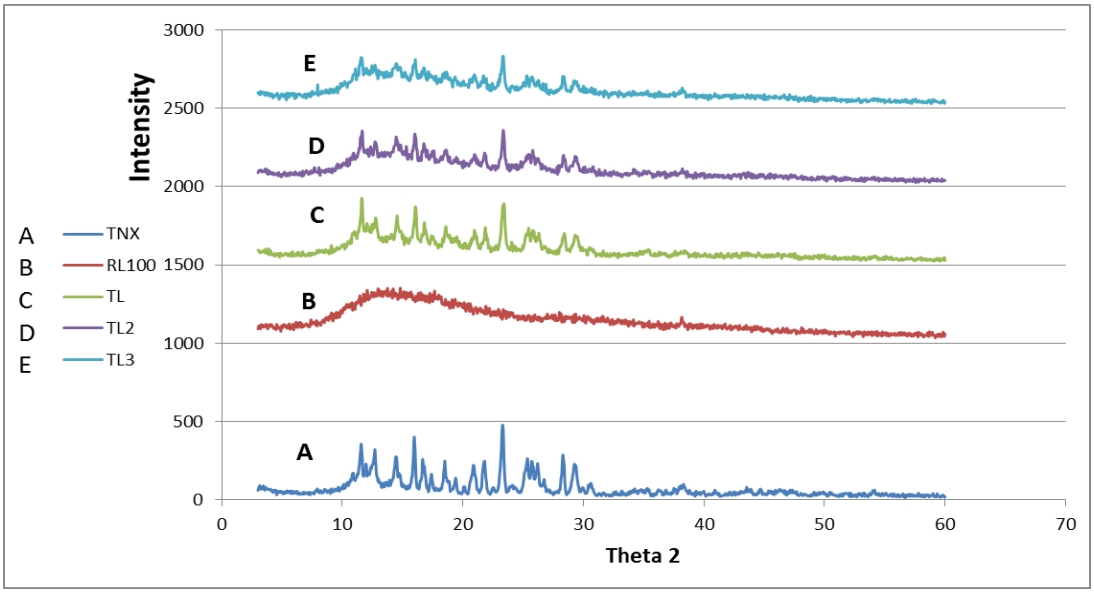

Fig. 5 X- ray diffraction of TNX (A), RL100(B),their solid dispersion 1:1(C),1:2(D),1:3(E).

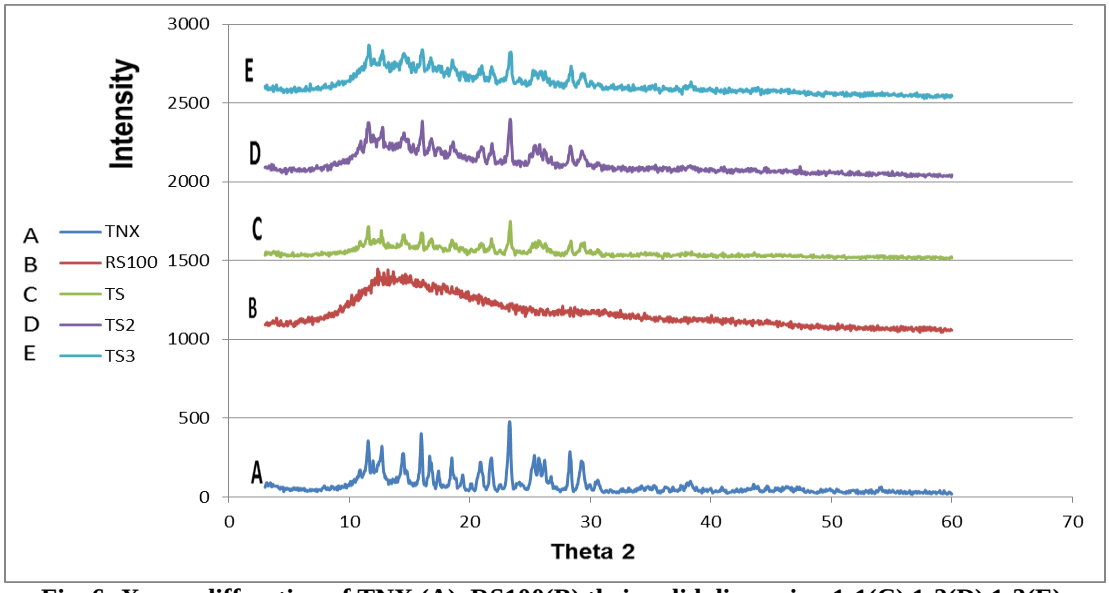

Fig. 6: X- ray diffraction of TNX (A), RS100(B),their solid dispersion 1:1(C),1:2(D),1:3(E).

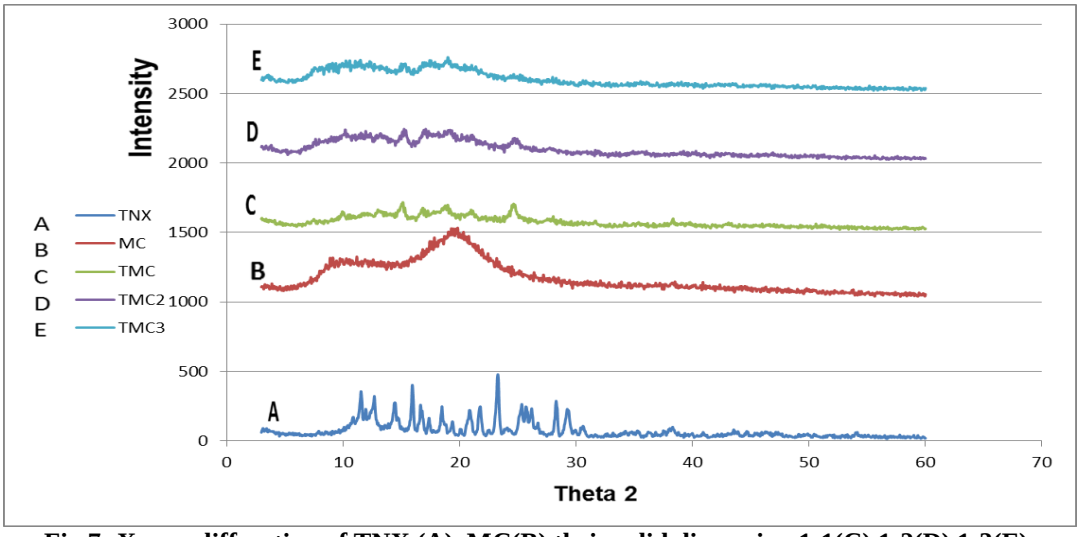

Fig 7: X- ray diffraction of TNX (A), MC(B),their solid dispersion 1:1(C),1:2(D),1:3(E).

Differential Thermal Analysis (DTA):
To confirm the interaction between the drug and polymers used if any, Differential Thermal Analysis was carried out for the same samples tested by FTIR technique.

(TL) tenoxicam to Eudragit RL100 (1:1) drug to polymer ratio, (TL2) tenoxicam to Eudragit RL100 (1:2) drug to polymer ratio, (TL3) tenoxicam to Eudragit RL100 (1:3) drug to polymer ratio, (TS) tenoxicam to Eudragit RS100 (1:1) drug to polymer ratio, (TS2) tenoxicam to Eudragit RS100 (1:2) drug to polymer ratio, (TS3) tenoxicam to Eudragit RS100 (1:3) drug to polymer ratio, (MC) tenoxicam to methyl cellulose (1:1) drug to polymer ratio, (MC2) tenoxicam to methyl cellulose (1:2) drug to polymer ratio and (MC3) tenoxicam to methyl cellulose (1:3) drug to polymer ratio.

DTA showed a sharp endothermic peak for tenoxicam around 220ºC which decomposed immediately, no change can be seen in the DTA curve polymers at this temperature range.

The absence of the endothermic peak at 220 ºC in DTA of the drug in the solid dispersion systems suggests that the drug exists in an amorphous or disordered crystalline phase as a molecular dispersion in polymeric matrix as seen in(Fig. 8-10).[17]

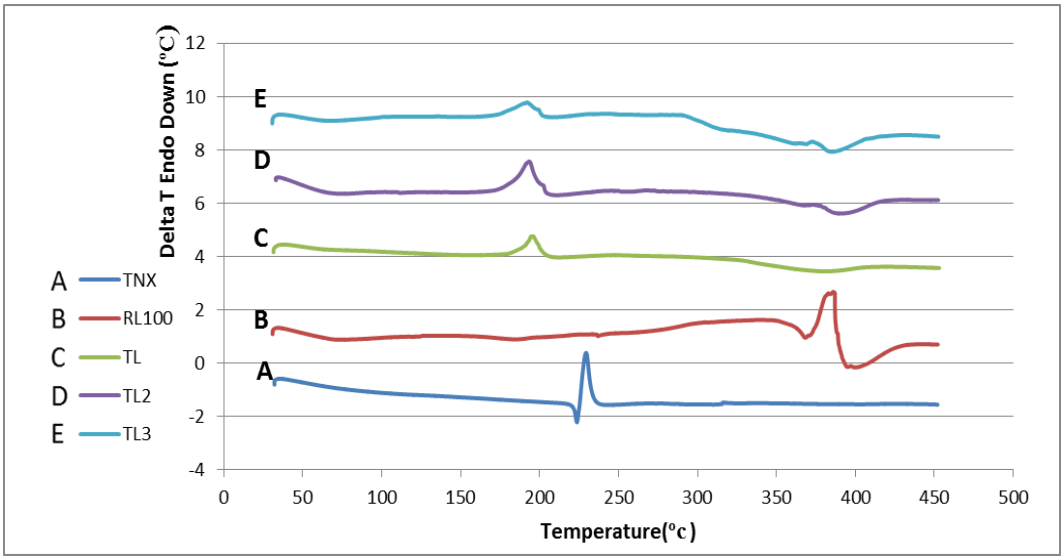

Fig. 8 DTA spectrum of TNX (A), Eudragit RL100 (B), their solid dispersion 1:1(C), 1:2(D),1:3(E)

Eudragit RL100 showed an endothermic peak around 357ºC which decomposed at 374ºC, TNX-Eudragit RL100 solid dispersions exhibit lower intensity exothermic peaks the maximum temperature values shift towards lower temperatures.

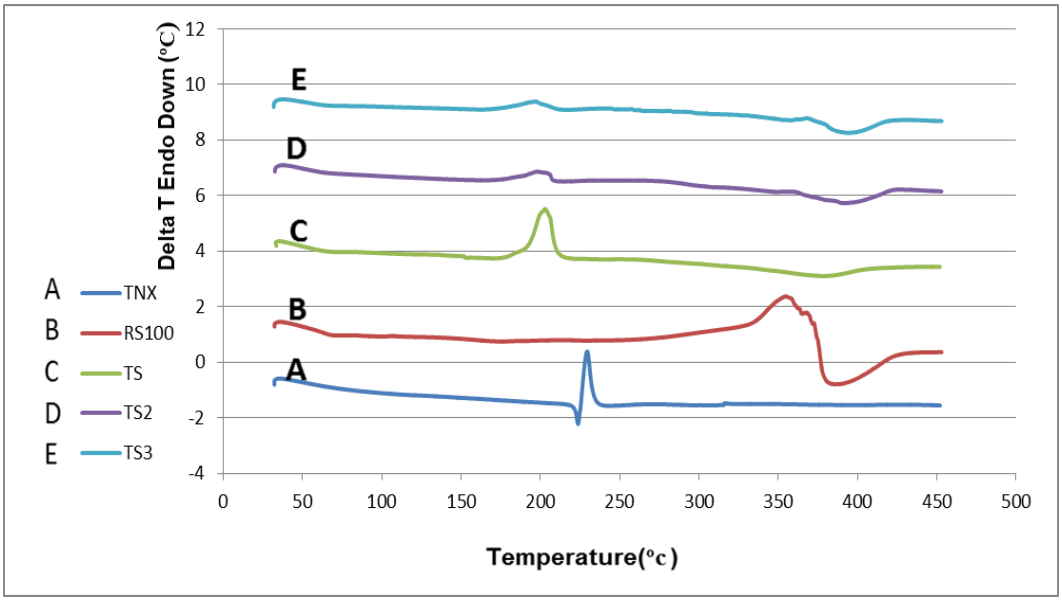

Fig. 9 DTA spectrum of TNX (A), RS100 (B), their solid dispersion 1:1(C),1:2(D),1:3(E).

Eudragit RS100 showed an endothermic peak around 375ºC and decomposed at 332ºC, TNX-Eudragit RS100 solid dispersions exhibit lower intensity exothermic peaks the maximum temperature values shift towards lower temperatures.

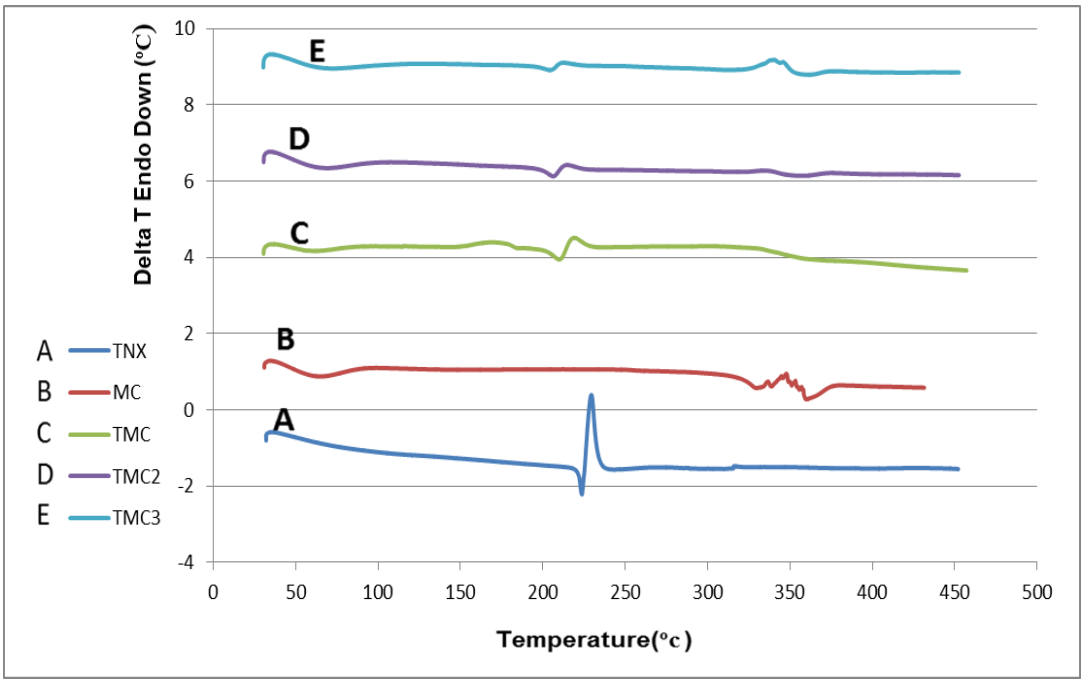

Fig. 10 DTA spectrum of TNX (A), MC(B),their solid dispersion 1:1(C),1:2(D),1:3(E)

Methyl cellulose showed three endothermic peaks around 63ºC, 330ºC and 361ºC, TNX- methyl cellulose solid dispersions exhibit lower intensity exothermic peaks the maximum temperature values shift towards lower temperatures.

In vitro drug release studies of tenoxicam and its solid dispersion using USP dissolution apparatus

The proper medium and appropriate rotational speed of the paddle or basket are of great importance in assuring that the test procedure is useful and discriminatory changing the agitation speed alters the measured release rates and affects the ability of an in-vitro test to distinguish in- vivo performance for both free drug and its solid dispersion formulations in several studies.[18]

Release studies were performed at various pH values (pH 1.0, pH 7.4) as tenoxicam shows pH dependent solubility corresponding to physiologic pH of GIT segments.[19]

In vitro release results required to measure the release of tenoxicam from its solid dispersion system in Eudragit RL100, Eudrgit RS100 and methyl cellulose in both 0.1N HCL pH (1.0) or phosphate buffer of pH(7.4) at different drug to polymer ratios were illustrated in Tables (3-8).

Table (3) In vitro drug release studies of tenoxicam from its solid dispersion Eudragit RL100 in 0.1 N HCL (pH 1.0)

Time(min)	%Tenoxicam released			
	Drug :polymer ratio			
	Free drug	1:1	1:2	1:3
5	0.05±0.01	1.77±0.01	1.87±0.98	2.87±0.8
10	4.29±0.6	5.64±1.83	3.83±0.7	6.42±1.5
15	10.25±1.83	12.73±3.7	9.77±3.84	13.6±1.22
20	16.56±0.24	20.50±1.22	17.77±3.7	18.74±1.22
30	24.15±0.6	30.45±0.5	28.02±3.5	26.75±0.61
45	33.63±1.2	41.01±1.83	39.24±3.42	35.53±0.18
60	39.63±0.36	48.86±2.44	45.79±2.01	40.83±0.85
90	46.92±0.6	56.34±1.22	53.82±1.16	48.73±1.53
120	51.68±1.2	61.12±1.2	58.06±1.1	53.78±1.5

(Mean ±SD, n=3)

Table 4: In vitro drug release studies of tenoxicam from its solid dispersion Eudragit RL100 in phosphate buffer (pH 7.4).

Time(min)	%Tenoxicam released			
	Drug :polymer ratio			
	Free drug	1:1	1:2	1:3
5	7.20±5.0	11.95±3.51	8.83±0.8	8.92±0.09
10	14.62±0.53	25.02±2.98	25.33±2.80	23.98±2.5
15	32.19±0.8	42.42±1.58	40.04±1.40	33.72±1.40
20	45.46±4.7	54.03±0.88	46.07±2.63	38.15±1.5
30	66.82±2.01	63.82±0.70	51.39±1.05	43.37±1.93
45	76.76±3.68	70.31±0.26	55.64±1.7	46.96±1.9
60	80.62±0.18	73.31±0.35	58.11±0.70	49.62±1.3
90	82.13±1.05	76.16±1.32	61.62±0.18	53.14±0.88
120	82.49±0.44	77.88±0.35	63.64±0.70	56.14±1.40
150	83.66±0.45	78.24±0.70	63±0.88	55.88±1.05
180	83.93±0.44	78.99±1.58	63.92±1.32	59.87±1.0

(Mean ±SD, n=3)

Table 5: In vitro drug release studies of tenoxicam from its solid dispersion Eudragit RS100 in 0.1 N HCL (pH 1.0).

Time(min)	%Tenoxicam released			
	Drug :polymer ratio			
	Free drug	1:1	1:2	1:3
5	0.05±0.01	0.62±0.12	0.38±0.65	0.88±2.23
10	4.21±0.6	3.24±0.74	1.87±0.77	6.96±1.03
15	10.25± 1.83	8.33±2.05	6.32±0.65	16.70±0.56
20	16.56±0.24	10.52±12.8	11.06±1.16	22.88±1.03
30	24.15±0.6	18.74±2.76	17.24±2.3	32.56±1.78
45	33.63±1.2	26.68±1.17	23.13±1.99	38.14±0.34
60	39.63±0.36	30.93±1.41	28.01±3.87	42.68±1.02
90	46.92±0.6	37.08±1.04	34.81±4.97	48.32±1.78
120	51.68±1.2	40.08±0.43	39.28±4.97	51.01±1.02

(Mean ±SD, n=3)

Table 6: In vitro drug release studies of tenoxicam from its solid dispersion Eudragit RS100 in phosphate buffer (pH 7.4).

Time(min)	%Tenoxicam released			
	Drug :polymer ratio			
	Free drug	1:1	1:2	1:3
5	7.22±5.0	22.36±2.43	19.23±0.91	15±5.73
10	14.64±0.53	41.16±3.61	42.90±2.52	31.90±6.76
15	32.19±0.8	52.61±1.71	56.31±2.27	44.99±2.8
20	45.46±4.7	58.76±1.51	61.04±0.69	54.51±2.9
30	66.82±2.01	66.78±1.93	65.36±0.61	61.35±1.92
45	76.76±3.68	70.42±2.94	68.23±0.72	66.87±0.09
60	80.62±0.18	72.44±1.43	71.63±1.48	68.05±0.91
90	82.13±1.05	75.38±0.50	72.63±0.35	70.33±0.95
120	82.49±0.44	77.72±1.35	74.15±0.35	71.81±0.54
150	83.66±0.45	78.38±0.76	74.54±1.04	72.01±1.28
180	83.90±0.44	78.81±0.42	74.94±0.04	72.42±1.28
210	84.20±1.05	79.06±0.40	75.74±4.78	73.62±1.64
240	84.44±1.0	78.88±0.84	76.51±0.35	73.63±1.28

(Mean ±SD, n=3)

Table 7: In vitro drug release studies of tenoxicam from its solid dispersion methyl cellulose in 0.1 N HCL (pH 1.0).

Time(min)	%Tenoxicam released			
	Drug :polymer ratio			
	Free drug	1:1	1:2	1:3
5	0.05±0.01	0.06±0.24	0.43±0.03	1.95±0.61
10	4.21±0.6	1.46±0.24	1.77±0.18	3.09±0.61
15	10.25±1.83	2.72±0.37	3.23±0.12	4.89±0.31
20	16.56±0.24	4.04±0.24	4.59±0.49	6.56±1.4
30	24.15±0.6	7.34±0.79	6.56±0.03	10.19±1.77
45	33.63±1.2	10.06±0.98	10.25±0.18	16.08±4.88
60	39.63±0.36	12.97±1.16	13.16±0.79	18.66±2.99
90	46.92±0.6	16.69±1.5	18.52±1.3	26.43±3.17
120	51.68±1.2	20.92±1.8	23.00±1.4	33.08±2.75

(Mean ±SD, n=3)

Table 8: In vitro drug release studies of tenoxicam from its solid dispersion methyl cellulose in phosphate buffer (pH 7.4).

Time(min)	%Tenoxicam released			
	Drug :polymer ratio			
	Free drug	1:1	1:2	1:3
5	7.22±5.0	9.65±0.61	9.57±2.98	7.94±1.3
10	14.62±0.53	18.22±0.09	14.21±2.1	17.71±0.88
15	32.19±0.8	30.30±0.26	20.58±2.63	24.61±1.53
20	45.46±4.7	36.08±1.22	26.84±9.9	31.37±1.40
30	66.82±2.01	47.12±0.7	35.08±5.3	40.05±0.7
45	76.76±3.68	56.82±1.75	42.39±2.1	49.76±0.88
60	80.62±0.18	63.93±0.88	50.07±7.9	56.09±0.53
90	82.13±1.05	71.35±2.0	56.07±4.2	65.41±0.44
120	82.49±0.44	75.42±3.33	62.11±10.5	71.07±0.79
150	83.66±0.45	76.12±0.88	65.92±4	75.79±1.22
180	83.91±0.44	76.03±0.7	68.73±8.77	78.49±1.8
210	84.21±1.05	76.61±0.66	72.23±0.008	80.88±2.10
240	84.44±1.0	77.51±0.79	73.68±4.6	82.95±2.80

(Mean ±SD, n=3)

At pH 7.4 there was no significant difference in the total percentage released of tenoxicam from the three solid dispersion systems. The release of tenoxicam from Eudragit RL100 (1:1) was 78.99%, while the release from Eudragit RS100 (1:1) was 78.88%;on the other hand, the release of tenoxicam from methyl cellulose(1:3) was 82.95%, the ratio of (1:1) tenoxicam to Eudragit RL100, (1:1) tenoxicam to Eudragit RS100 and (1:3) tenoxicam to methyl cellulose were the best ratios which achieved maximal release at alkaline pH(7.4).

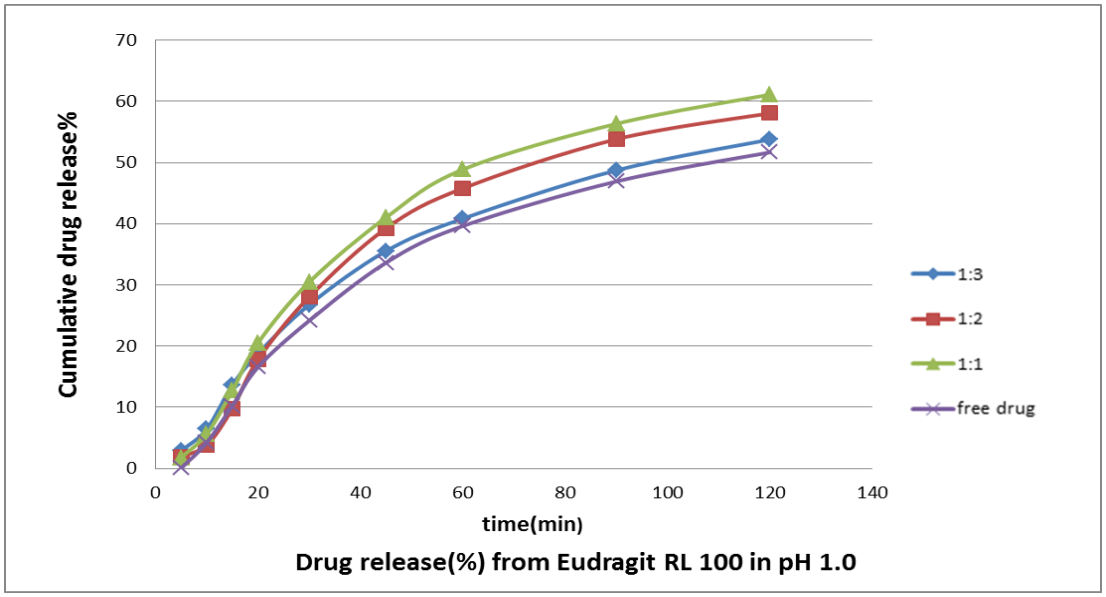

Fig. 11a at pH1.0.

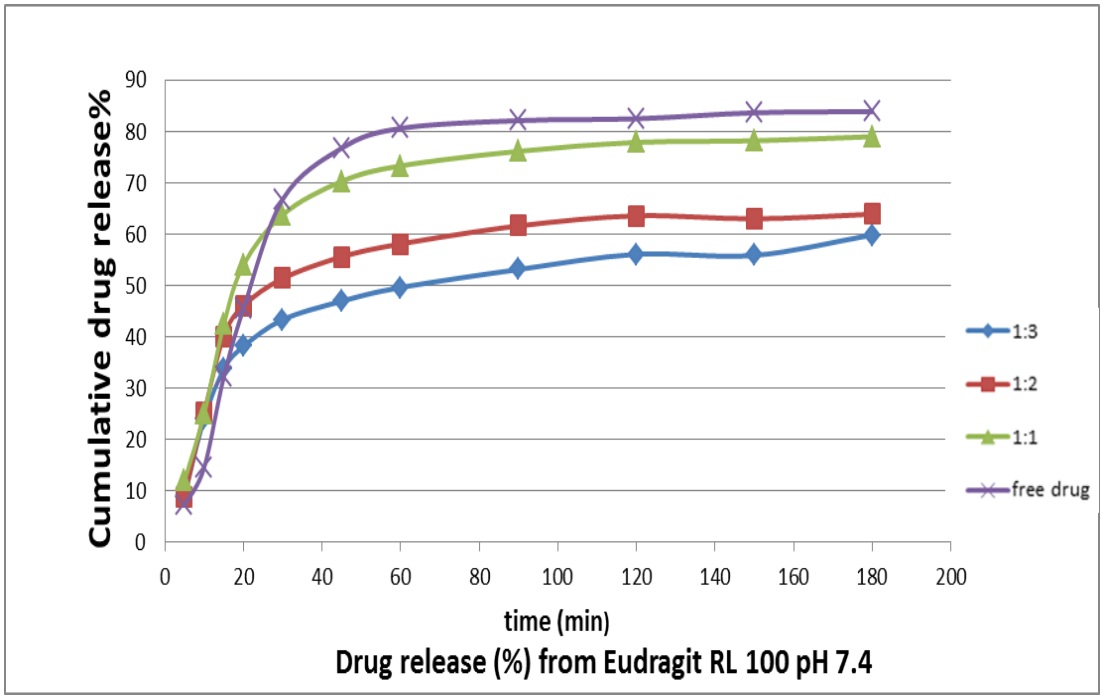

Fig. 11b at pH 7.4.

Release of tenoxicam from its solid dispersions using Eudragit RL100 at pH 1.0(a) and pH 7.4(b) in a drug to polymer ratios of (1:1, 1:2, 1:3).

(Fig. (11) shows the release of tenoxicam from its solid dispersion systems with Eudragit RL100 at drug to polymer ratios of (1:1, 1:2, 1:3) in 0.1N HCL (pH 1.0)(Fig. 11a) and phosphate buffer (pH 7.4) (Fig. 11 b).

At these pH values, it is clear that the total percentages released of tenoxicam from its solid dispersion systems with Eudragit RL100 were about 61.12, 58.06 and 53.78% at acidic pH (pH 1.0) at drug to polymer ratios of (1:1, 1:2, 1:3**)** respectively.(Fig. 11a).

This is because Eudragit RL100 is insoluble at acidic pH**.** The drug to polymer ratio(1:1) shows the largest percentage released this is probably due to incomplete coating of the drug particles at this ratio.

At pH 7.4(Fig. 11 b) there was complete but delayed release of the drug from the enteric drug-polymer solid dispersion systems where 78.99, 63.9 and 59.87% were released at drug to polymer ratios of (1:1, 1:2, 1:3**)** respectively.(Fig. 11b).

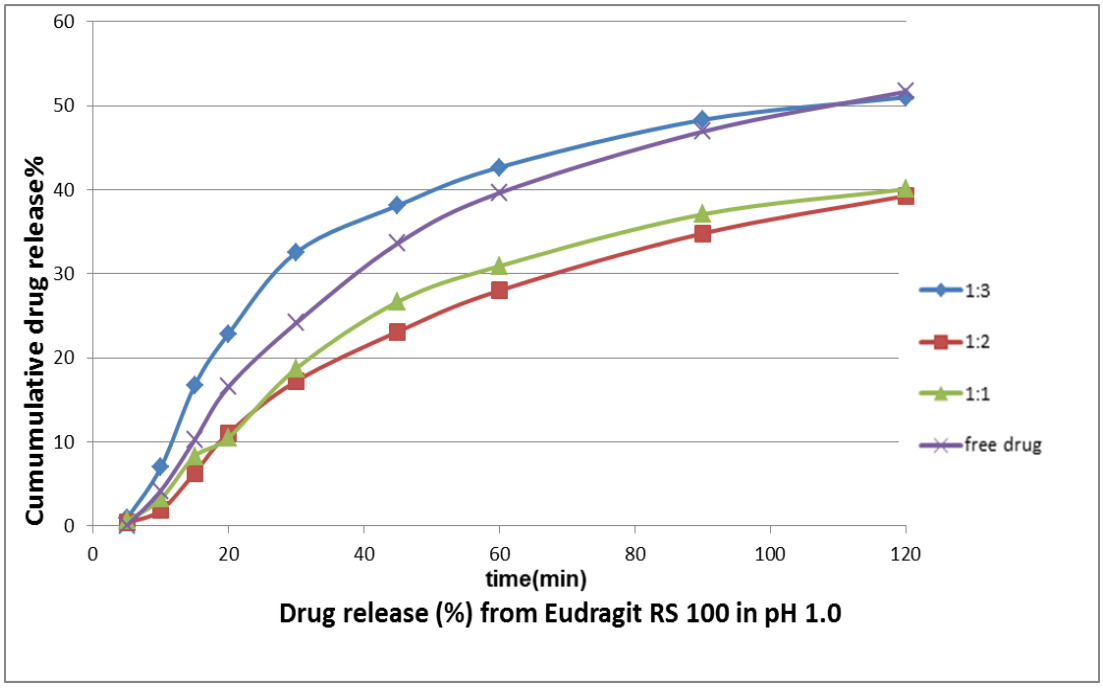

Fig. 12a at pH 1.0.

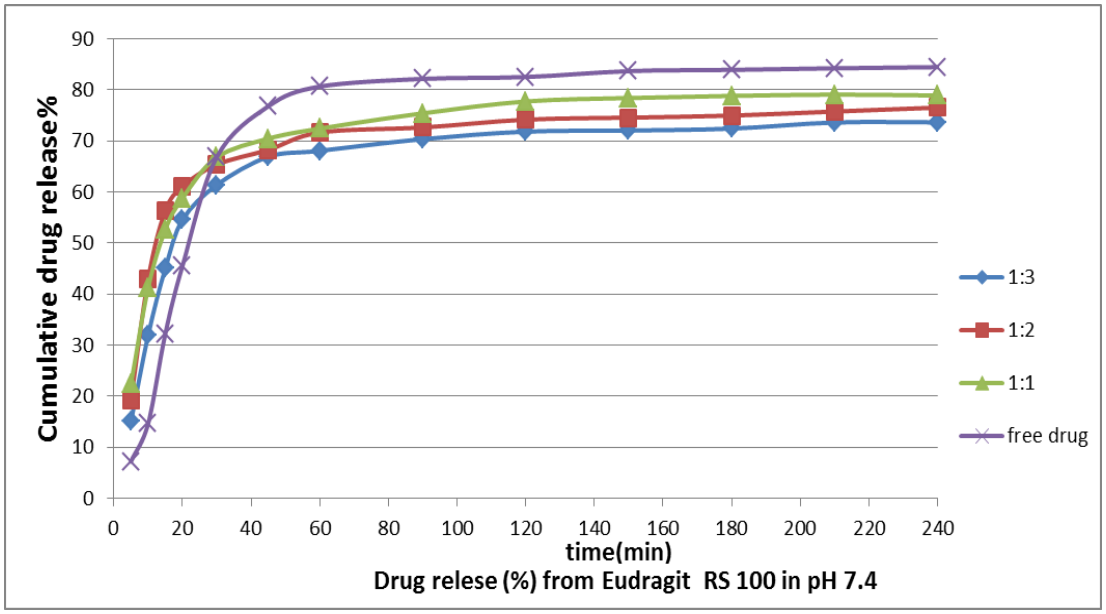

Fig. 12b at pH 7.4.

Release of tenoxicam from its solid dispersions using Eudragit RS100 at pH 1.0(a) and pH 7.4(b) in a drug to polymer ratios of (1:1, 1:2, 1:3)

(Fig. 12) shows the release of tenoxicam from its solid dispersion systems with Eudragit RS100 at drug to polymer ratios of (1:1, 1:2, 1:3) in 0.1N HCL (pH 1.0)(Fig. 12a) and phosphate buffer (pH 7.4) (Fig. 12b).

At these pH values, it is clear that the free drug is not completely released at the acidic pH (pH 1.0), the total released of tenoxicam was about 51.68% at acidic pH (pH 1.0) .however, tenoxicam is completely released at pH value 7.4.

Total percentages released of tenoxicam from its solid dispersion systems with Eudragit RS100 were about 40.1, 39.28 and51 % at acidic pH (pH 1.0) at drug to polymer ratios of (1:1, 1:2, 1:3**)** respectively.(Fig. 12a).

This is because Eudragit RS100 is insoluble at acidic pH**.** The drug to polymer ratio (1:3) shows the largest percentage released.

At pH 7.4(Fig. 12 b) there was complete but delayed release of the drug from the enteric drug-polymer solid dispersion systems where 78.9, 76.5 and 73.6 % were released at drug to polymer ratios of (1:1, 1:2, 1:3**)** respectively.(Fig. 12b).

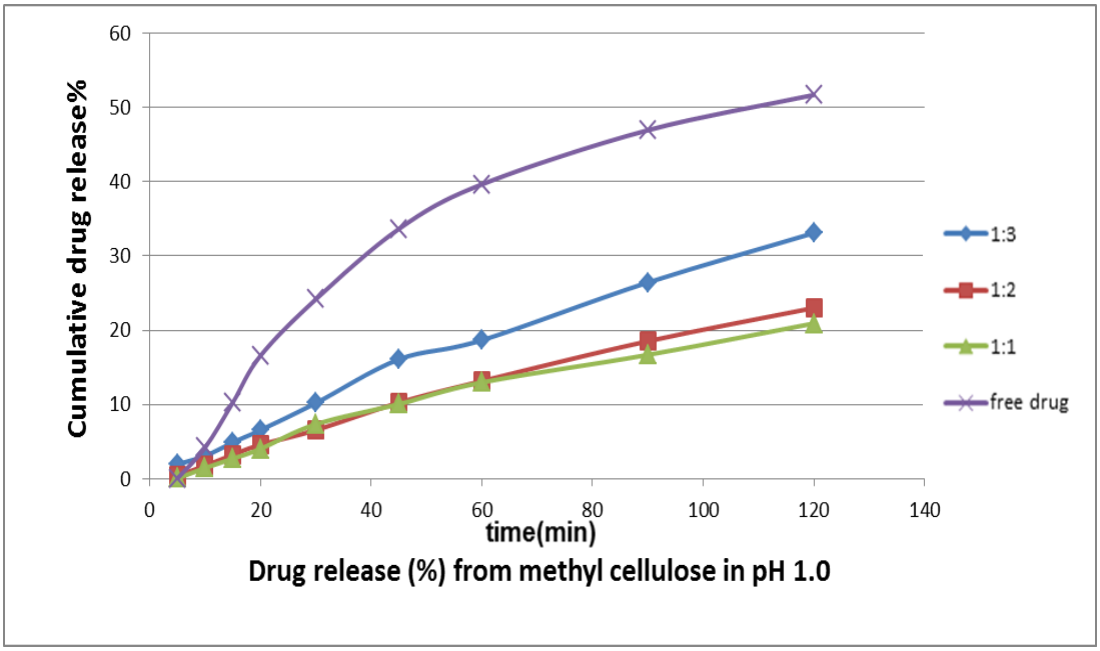

Fig. 13a at pH 1.0.

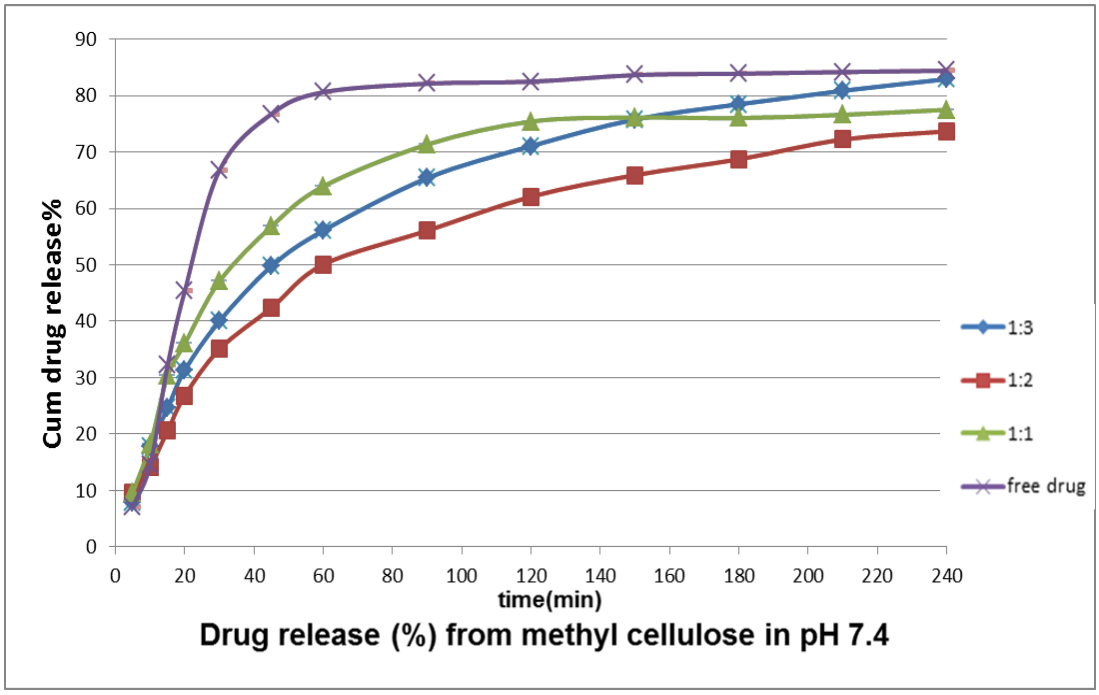

Fig. 13b at pH 7.4.

Release of tenoxicam from its solid dispersions using methyl cellulose at pH 1.0(a) and pH 7.4(b) in a drug to polymer ratios of (1:1, 1:2, 1:3)

(Fig. 13) shows the release of tenoxicam from its solid dispersion systems with methyl cellulose at drug to polymer ratios of (1:1, 1:2, 1:3) in 0.1N HCL (pH 1.0)(Fig.13a) and phosphate buffer (pH 7.4) (Fig.13b).

At these pH values, it is clear that the total percentages released of tenoxicam from its solid dispersion systems with methyl cellulose were about 20.9, 23 and 33.1 % at acidic pH (pH 1.0) at drug to polymer ratios of (1:1, 1:2, 1:3**)** respectively(Fig. 13a).

This is because methyl cellulose is insoluble at acidic pH**.** The drug to polymer ratio (1:3) shows the largest percentage released.

At pH 7.4(Fig. 13b) there was complete but delayed release of the drug from the enteric drug-polymer solid dispersion systems where 77.5,73.7 and 82.9 % were released at drug to polymer ratios of (1:1, 1:2, 1:3**)** respectively.(Fig. 13b).

CONCLUSION

The release studies of tenoxicam from its solid dispersion systems using different types of polymers

such as Eudragit RL100, Eudragit RS100 as well as methyl cellulose which prepared using solvent evaporation technique in order to reduce its gastrointestinal side effects show that,the ratios of (1:1)tenoxicam to Eudragit RL100,(1:1) tenoxicam to Eudragit RS100 and (1:3) tenoxicam to methyl cellulose were the best ratios used with maximal release at alkaline pH of the intestine.IR analysis indicated that there is no appearance of new peaks or disappearance of existing peaks, which indicating that there is no interaction between tenoxicam and the polymers used.

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