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SOLID DISPERSION OF TENOXICAM WITH SKIMMED MILK VIA FREEZE-DRYING

DONDURARAK KURUTMA YÖNTEMİ KULLANILARAK TENOKSİKAMIN AZ YAĞLI SÜT İLE KATI DİSPERSİYONUNUN HAZIRLANMASI

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The physical mixture (PM) and solid dispersion (SD) of tenoxicam with skimmed milk (SM) were prepared and investigated. Improvement of solubility of tenoxicam was achieved by preparing its SD with SM which can be used due to its amino acid and surface active agents contents and also for treatment of gastric disturbance. Lyophilization technique was used to prepare the SD. Data obtained indicated that SD of tenoxicam with SM showed almost 23 times the solubility of the plain drug. Results of the dissolution rate determination studies also have revealed that the incorporation of tenoxicam into SM significantly enhanced the dissolution rate of the drug compared with PM and the free from.

Differential scanning calorimetry (DSC), X-ray powder diffraction, infrared (IR) spectroscopic and scanning electron microscopic (SEM) analysis also elucidated the formation of SD of tenoxicam with SM.

Tenoksikamın az yağlı süt (SM) ile fiziksel karışımı (PM) ve katı dispersiyonu (SD) hazırlanmış ve incelenmiştir. Tenoksikamın çözünürlüğü, içerdiği amino asidler ve yüzey aktif maddeler nedeniyle ve gastrik rahatsızlıkların tedavisinde kullanılan az yağlı süt ile katı dispersiyonu hazırlanarak arttırılmıştır. Katı dispersiyonu hazırlamak için liyofilizasyon tekniği kullanılmıştır. Elde edilen veriler, az yağlı süt ile hazırlanan tenoksikam katı dispersiyonunun saf maddeye kıyasla 23 kat daha fazla çözünür olduğunu göstermiştir. Dissolusyon hızı tayininin sonuçları ise az yağlı süt ile hazırlanan katı dispersiyonun, fiziksel karışım ve serbest maddeye kıyasla dissolusyon hızının önemli ölçüde arttığını göstermiştir.

Diferansiyel taramalı kalorimetrik (DSC), X-ışını toz difraksiyon, kızıl ötesi (IR) spektroskopik ve taramalı elektron mikroskobik (SEM) analizler, az yağlı süt ile tenoksikam arasında katı dispersiyonun oluştuğunu göstermiştir.

Keywords: *Tenoxicam; Skimmed milk; Physical mixture; Solid dispersion; Solubility; Enhancement in dissolution*

Anahtar kelimeler : *Tenoksikam; Az yağlı süt; Fiziksel karışım; Katı dispersiyon; Çözünürlük; Disolusyonda artış*

Introduction

Tenoxicam is a nonstreoidal antiinflammatory agent which is used in the treatmant of rheumatoid arthritis. It is not freely soluble in water (1) and has local or systemic disturbance in gastro-intestinal tract (2). In order to improve the solubility of drugs in water, addition of surface active agents and formation of water soluble salts (3) and to enhance dissolution and absorption rate, reduction of particle size and increasing wettability have been attempted (4). For reducing particle sizes of drugs, solid dispersion (SD) and to form SD, freez-drying method have been proposed(5,6). In order to eliminate or diminish gastro-intestinal disorders of nonsteroidal drugs, amino acids have been suggested either as additive in the peroral application (7) or in the form of its amino acid salts(8).

In this study, as the carrier for SD, skimmed milk (SM) has been chosen due to its surface active agent and amino acid contents additively milk has been proposed against gastric disturbance of non-steroidal drugs with antiinflammatory effect (9-11).

Materials

Tenoxicam (F. Hoffmann-La Roche) and all other reagents and chemicals were of analytical grade; SM with maximum 1% fat and 4% carbonhydrate content. Tenoxicam was purchased and used in micronized form.

Photometer: Hitachi U-1100, Tokyo UV double beam spectrophotometer flow cell; dissolution apparatus: Erweka, Germany; peristaltic pump: Desaga STA, Desage, Heidelberg, Germany; potentiometer recorder: Servogor, type RE 541BBC Metrawatt Nürnberg, Germany; Netz apparatus: Type Voltaraft NG 15 Conrad Hirschau; Computer: IBM-compatible AT 486/33 with VGA graphic card, J. Friedrichs, Münster, Germany; Lyophilisation apparatus: Lyovac GT 2 (Leybold Heraeus).

Method

Preparation of skimmed milk powder

After freeze-dring (SM was lyophilized until the sample's humidity reduced to maximum 3%. According to preliminary studies, lyophilization time was chosen as 72 h to reduce humidity), 25 ml SM yielded≅2.615 g* powder (*mean of 5 experiments). SM was sieved from 250 μm mesh sieves prior to preparation of SD and PM.

Preparation of the solid dispersions

500 mg tenoxicam was mixed in 25 ml SM in a water bath having 50°C temperature and stirred for 30 minutes by using a magnetic stirrer. It was freezed by keeping in fluid nitrogen bath and lyophilized for 72 hours. SD was sieved from 250 μm mesh sieves.

Preparation of the physical mixtures

500 mg micronized drug (particle size of 10 μm) was uniformly mixed with 2.615 g lyophilized SM using an agate mortar and pestle. The prepared mixtures were kept in a dessicator over calcium chloride (0% relative humidity) at room temperature.

Solubility studies of solid dispersions and physical mixtures

100 mg of tenoxicam, its SD and PM with SM equivalent to 623 mg (including 100 mg tenoxicam) under test was placed in a glass stoppered flask and 100 ml water was added. Then shaken in a water bath at 25°C for 15 h (USP XIX). The solution was filtered through blue ribbon filter paper (S&S) of pore diameter 0.45 μm. The dissolved drug was measured spectrophotometrically at 260 nm.

Dissolution rate determination

The dissolution rates of tenoxicam SD as well as the PM of the drug with SM compared with the plain drug were determined using the USP XXII Paddle method by a dissolution apparatus. 15 mg of pure tenoxicam or its equivalent of the SD or the PM with SM were sprinkled in 1000 ml of distilled water maintained at 37°C and stirred at 100 rpm. After certain time intervals, samples of the dissolution medium were withdrawn, filtered through Millipore membrane of 0.45 μm pore diameter and assayed for the drug content spectrophotometrically at 260 nm.

Differetial scanning calorimetry (DSC) studies

Samples weighing approximately 3 mg were palced in aluminium pans and analyzed using a Perkin-Elmer DSC-2°C calorimeter. The scanning speed was 10°C/min. In the range of 20-340°C.

X-ray powder diffraction analysis

X-ray diffaction patterns were recorded with a Philips PW 1710 diffractometer (The Netherlands). Cu Kα1 radiation (λ1-5418), nickel filter, 50 KV, 40 mA.

Infrared (IR) spectroscopic analysis

IR spectra as KBr discs were scanned on a Perkin Elmer 1600 series FTIR spectrophotometer.

Scanning electron microscopic analysis

Surface morphology of tenoxicam, its PM as well as SD with SM were analyzed by the scanning electron microscope (Joel 1200 EX-11, Tokyo, Japan).

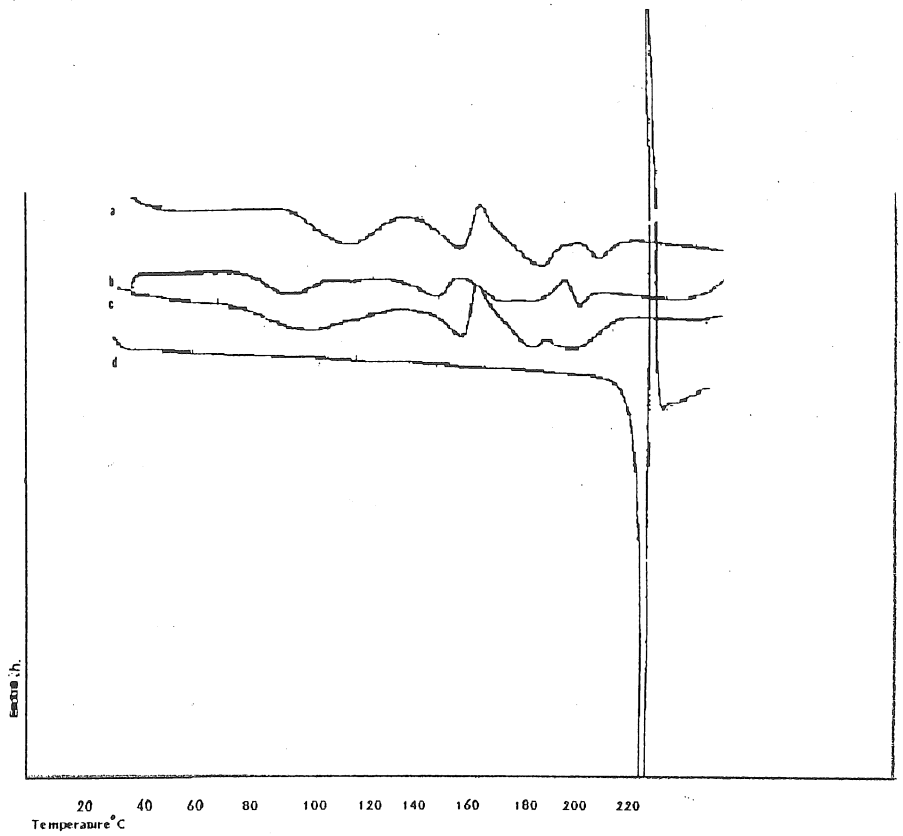


Fig. 1. DSC thermograms of **a**-solid dispersion of tenoxicam with SM **b**-physcal mixture of tenoxicam with SM **c**-SM **d**-tenoxicam

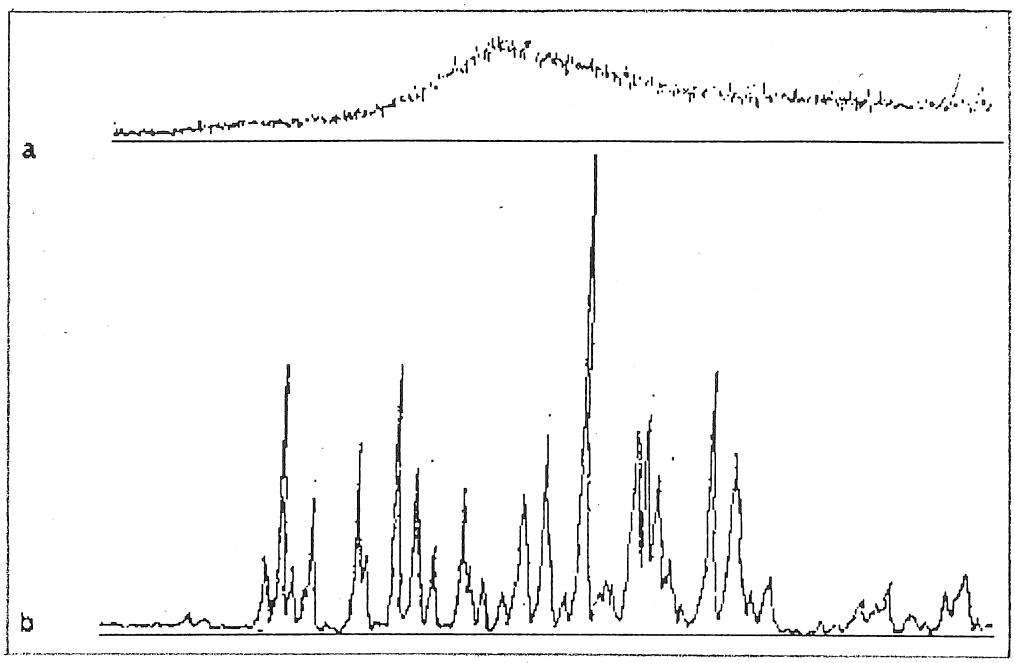


Fig.2.1. X-ray powder diffraction spectra of **a**-SM **b**-tenoxicam

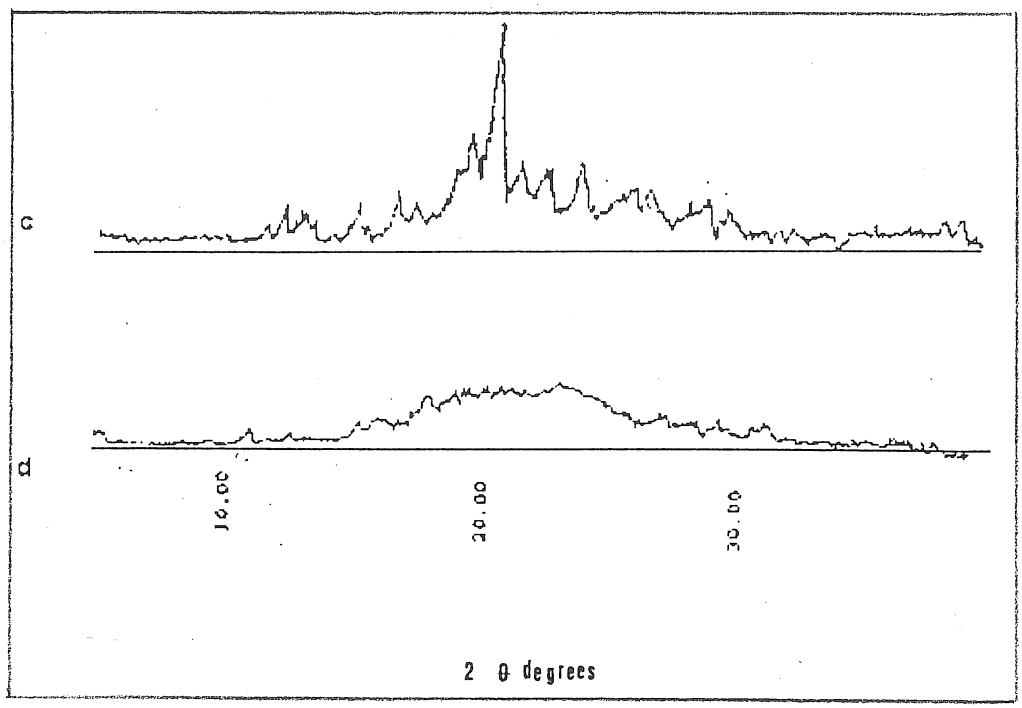


Fig.2.II. X-ray powder diffraction spectra of c-physical mixtre of tenoxicam with SM d-solid dispersion of tenoxicam with SM

Results and Discussion

The rate determining step in the absorption process for drugs of low solubility is generally the dissolution rate of such drugs in the gastrointestinal fluids. The formation of SD of the drug with a water-soluble carrier is one of the several techniques that can be used to improve the dissolution properties of low soluble or hydrophobic drugs. In this study, SM was used as the carrier, differential scanning calorimetric (DSC), X-ray powder diffraction, infrared (IR) spectroscopic and scanning electron microscopic (SEM) analysis were performed to determine the physicochemical properties of PM and SD in comparison with the plain drug. These techniques have been known to be used for the assessment of mo-

lecular interactions occurring between solid components of pharmaceuticals (12-15).

In order to get further evidence on the possible interaction between tenoxicam and SM, DSC studies were performed on PM and SD of tenoxicam with SM, as well as their individual components. As shown in Fig.1, the DSC curve of tenoxicam showed one endothermic peak at about 225°C, corresponding to its melting point, while SM exhibited a

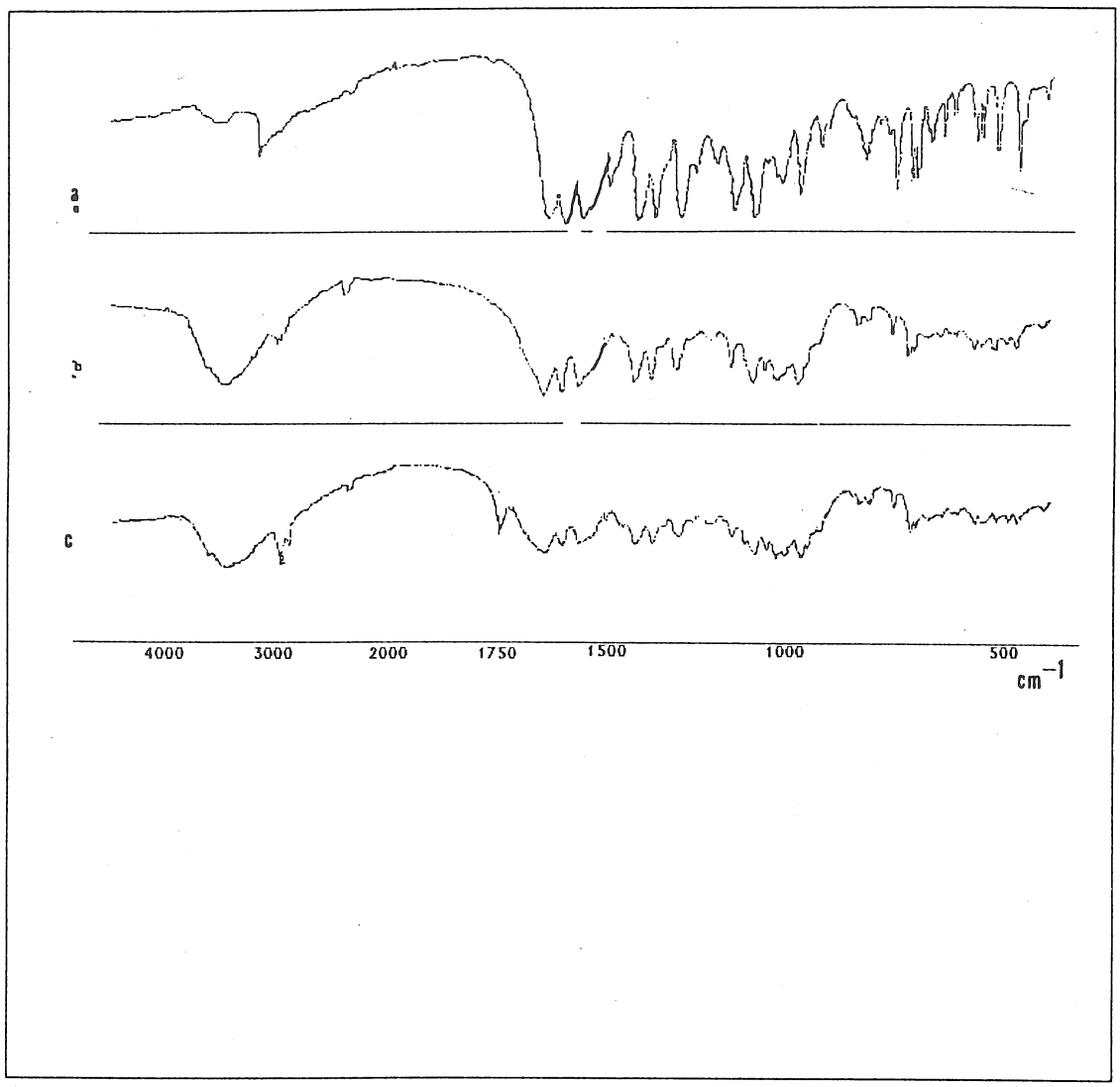
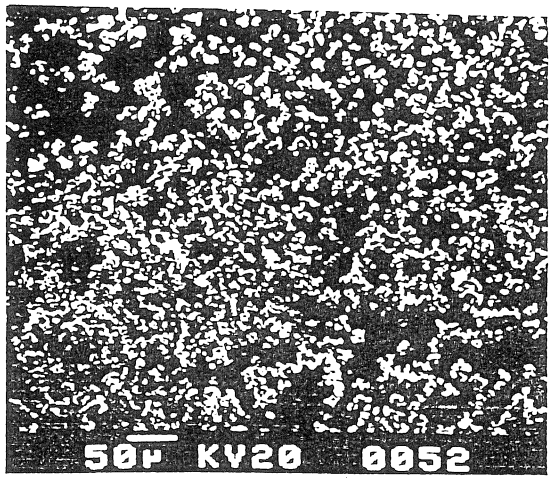
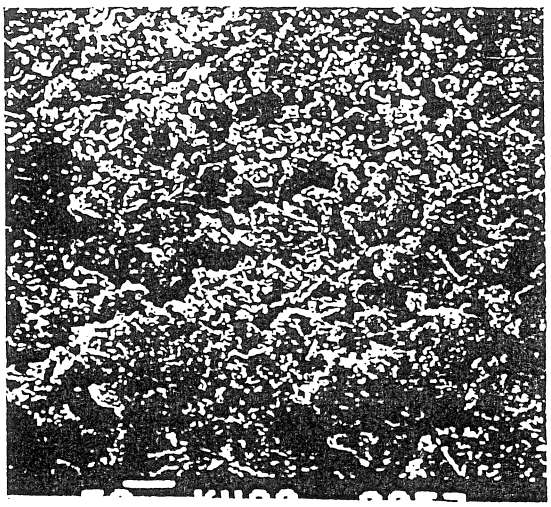


Fig. 3. IR spectra of **a**-tenoxicam **b**-physical mixture of tenoxicam with SM **c**-solid dispersion of tenoxicma with SM





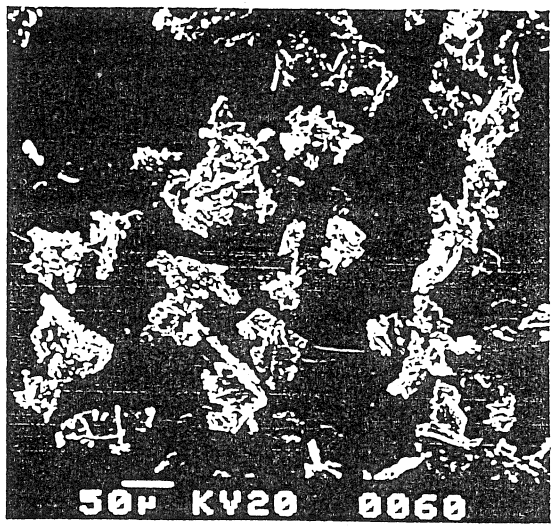
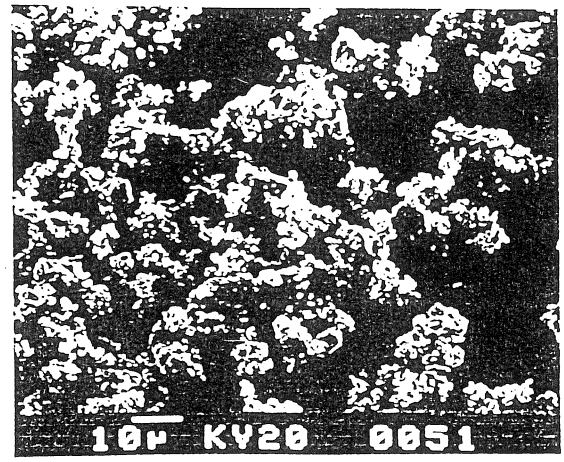
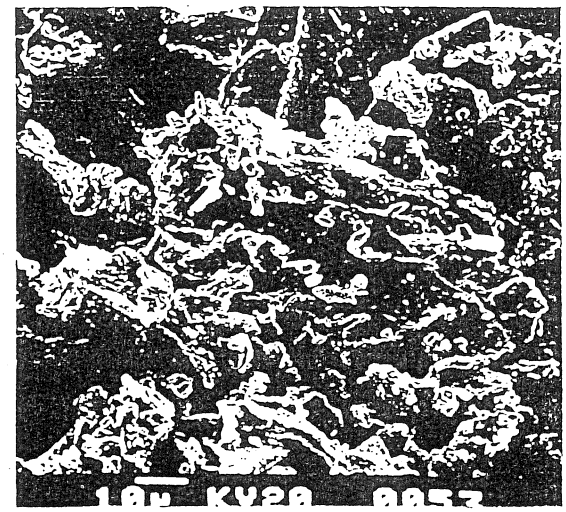


Fig.4. SEM pictures (200xmagnification) of **a**-tenoxicam **b**-physical mixture of tenoxicam with SM **c**-solid disperison of tenoxicam with SM





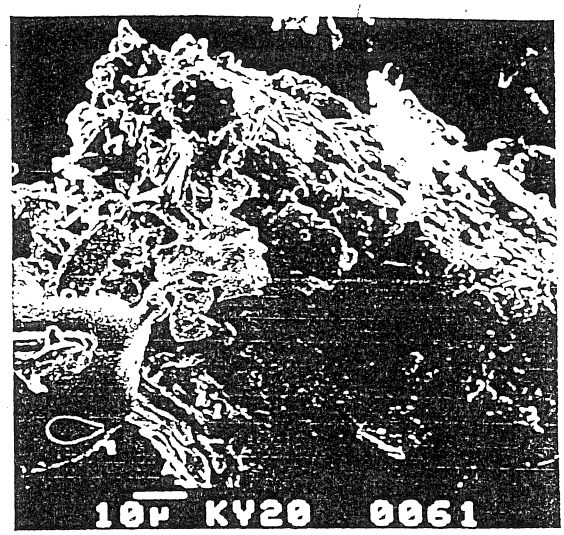


Fig.5. SEM pictures (1000xmagnification) of **a**-tenoxicam **b**-physical mixture of tenoxicam with SM **c**-solid dispersion of tenoxicam with SM

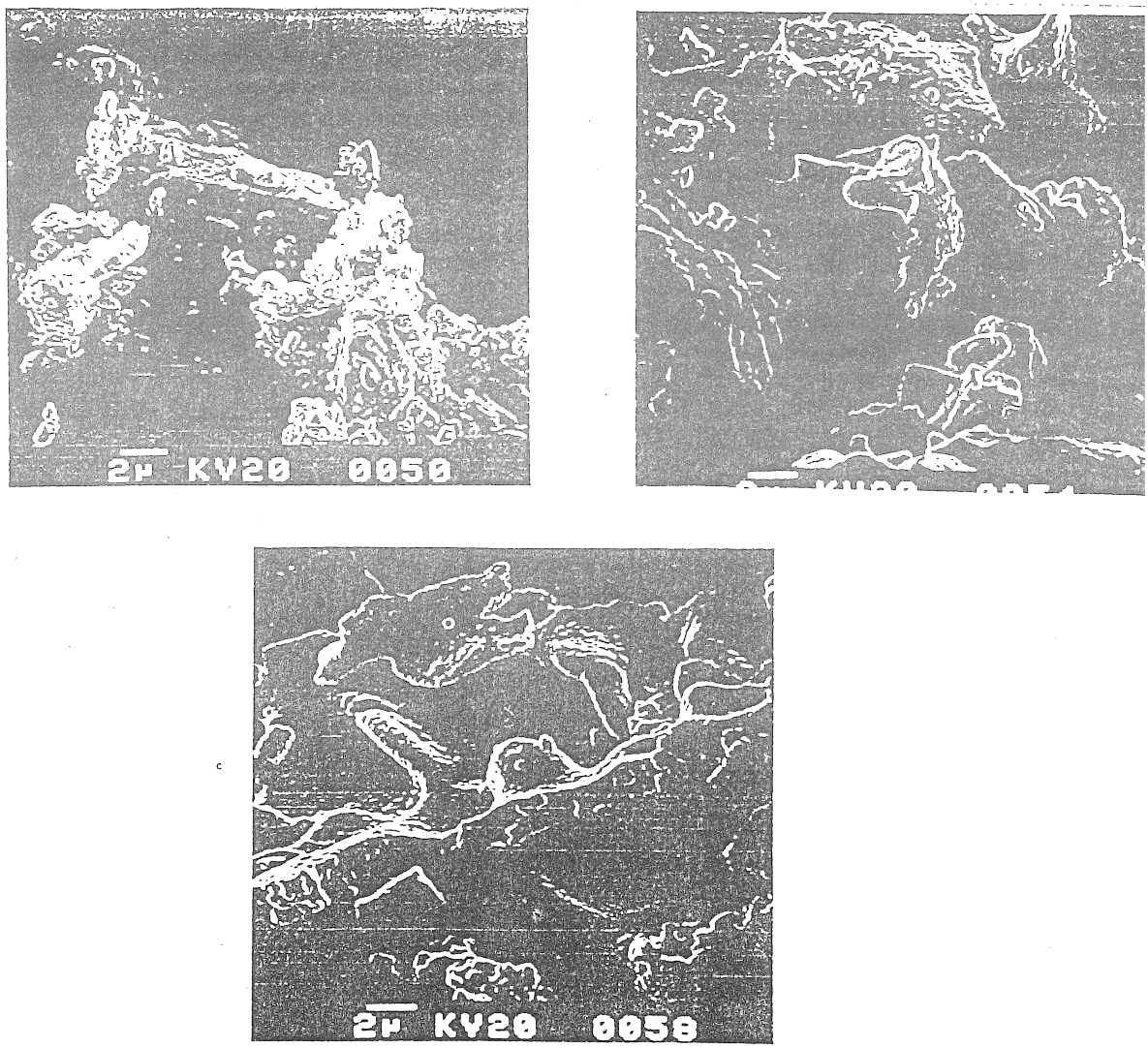


Fig.6. SEM pictures (5000xmagnification) of a-tenoxicam b-physical mixture of tenoxicam with SM c-solid dispersion of tenoxicam with SM

peak at 165°C. The DSC plot of the SD showed only one sharp peak at 167°C. Since value is for away from the melting point of tenoxicam, hence, it could be due to a bonding formed between tenoxicam and SM. Disappearance of the specific peak of the drug indicated that the drug has interacted with the carrier.

The X-ray powder diffraction pattern of tenoxicam shows its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity, whereas SM exhibits a diffraction spectrum, typical of mostly amorphous materials not showing any detectable diffraction peaks. As can be seen from Figure 2, in case of SD, absence and reduction of major tenoxicam diffraction peaks indicate that mostly a disordered state existed in the SD. In X-ray diffraction spectrum of the PM, it is possible to detect some crystals of tenoxicam since the

particle size is bigger than in the SD. However particle size of tenoxicam in PM and plain drug are similar. Based on these results, improvement in solubility and dissolution rate may be related to reduction of particle size and formation of an amorphous state in SD form and enzymes and the surface active agents content of SM in case of PM.

Figure 3 shows the IR spectra of tenoxicam, the PM and SD of tenoxicam with SM. In IR spectrum of the plain drug, the characteristic bands of tenoxicam at 1774, 1436, 1428, 1388, 1202 and 1151 cm^{-1} were observed. The C=O stretching band of 1774 cm^{-1} was found to be shifted to 1745 cm^{-1} in SD which might be formed due to a bond between the NH_2 group of SM's protein and C=O group of tenoxicam. The present results suggest the transformation of the drug into the amorphous ionic state in the SD with SM.

According to SEM results, Figures 4-6 reveal that in case of PM, the particle size of tenoxicam is nearly same and tenoxicam crystals could be seen on some SM particles in SD, tenoxicam particles are mostly in amorphous form which could be accepted as reduction of particle size was in a great order achieved. As can be seen from Table 1, solubility of tenoxicam in SD is (0.098%) nearly 23 times and in PM 8 times higher than the plain drug which has a solubility as 0.045 mg/ml (0.0045%) in water (1).

The dissolution profiles of SD and PM of tenoxicam with SM are graphically depicted in Figure 7. Tenoxicam as plain drug was also analysed but there wasn't any dissolution observed. Incorporation of tenoxicam with SM especially in SD from significantly enhanced the dissolution rate of the drug as compared to PM and the free form. Dissolution test results have also stated that in SD from, dissolution rate was higher and faster than in PM.

Due to these results, it could be concluded that, as expected SD with SM has found to be the most suitable form for tenoxicam in terms of solubility and dissolution in water whereas PM of tenoxicam with SM has given better results than the plain drug. On the other hand, according to our investigation in view of pharmacological activity an side effects of gastrointestinal disturbance on other nonsteroidal drugs with the same therapeutic activity, the pharmacological activity has been increased and the gastrointestinal disturbance has been decreased in a significant manner (10,11,15). These problems are also similar in case of therapy with tenoxicam so it could be possible to adapt these results to SD of tenoxicam with SM and the same advantages could be expected for tenoxicam. Therefore it would be possible to formulate tenoxicam with SM in SD having eventual decreased therapeutic dose less gastrointestinal disturbance for peroral and also parenteral applications.

Table. Solubility of tenoxicam as plain drug in solid disperisons and physical mixtures with SM in distilled water at 25°C.

Tenoxicam % w/v	From of the Drug	Solubility(%) ±SD
0.1	Solid dispersion with SM	0.098% ±1.12
0.1	Physical mixture with SM	0.035% ±0.09
0.1	Plain drug	0.0043%±0.07

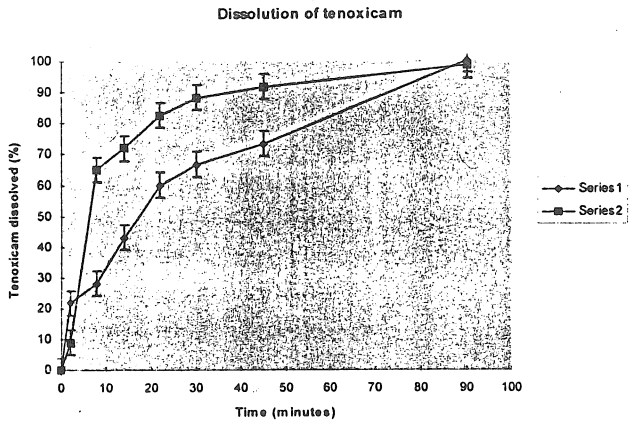


Fig.7. Dissolution profiles of tenoxicam in solid dispersion and physical mixture with SM in distilled water at 37°C
Series 1-Physical mixture
Series 2-Solid dispesion

Acknowledgement

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