Acta Pharmaceutica Turcica
XLII (4) (153-158) 2000

AN APPROACH TO INCREASE LIBERATION OF INDOMETHACIN

İNDOMETAZİN'İN LİBERASYONUNU ARTIRMAK İÇİN BİR YAKLAŞIM

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The physical mixture and solid dispersion of indomethacin with skimmed milk were prepared to improve aqueous solubility of the drug amino acids and surface active agents exist in the milk. The presence of amino acids also reduces gastric disturbance possibly originating from the drug. Solid dispersions were prepsred by lyophilization and the data obtained from solubility studies revealed that aqueous solubility of the drug can be improved 25 times when formulated as a solid dispersion. Results of dissolution studies indicated that the dissolution rate of a solid dispersion of indomethacin is much taster than that of its physical mixture and plain drug. Formation of a water-soluble indomethacin-skimmed milk complex was investigated employing scanning electron microscopic, differential scanning calorimetric, IR spectroscopic and Xray powder diffraction analysis.

Indcmetazinin sudaki çözünürlüğünü artırmak için az yağlı süt ile fiziksel karışımı ve katı dispersiyonu, hazırlanmıştır. İlacın çözünürlüğünün artması, sütte bulunan amino asitler ve yüzey aktif ajanlar sayesinde olabilmektedir. Ayrıca amino asitler ilacın gastrik rahatsızlığını da azaltmaktadır. Katı dispersiyon liyofilizasyon tekniği ile hazırlanmıştır. Çözünürlük çalışmalarına göre, ilacın sudaki çözünürlüğü katı dispersiyon ile 25 kat artmıştır. Dissolüsyon çalışmaları sonuçları, indometazinin katı dispersiyonunun dissolüsyon hızının fiziksel karışım ve serbest ilaca kıyasla daha çabuk olduğunu göstermiştir. Suda çözünen indometazin az yağlı süt kompleksinin oluşumu, taramalı elektron mikroskop, diferansiyel taramalı kalorimetri, IR spektroskopisi ve X-ışını toz difraksiyon analizleri ile araştırılmıştır.

Keywords: *lndomethacin; Solid dispersion; Physical mixture; Skimmed milk; Solubility in water*

Anahtar Kelimeler: *Indometazin; Katı dispersiyon; Fiziksel karışım; Az yağlı süt; Suda çözünürlük*

Introduction

Indomethacin (IND), a non-steroidal antiphylogistic/anti-inflammatory drug possesses poor water solubility(1) end has local and/or systemic gastric irritation(2). Enhancement of water solubility was achieved by addition of surface active agents and by formation of water-soluble salts(3). Reduction of particle size increasing wettability have been used to improve dissolution and absorption rate of poorly water soluble drugs(4). Recently, solid dispersions of IND with several carriers have been proposed(5-7). To prevent gastric disorders of IND, addition of amino acids to peroral dosage forms(8) or formation of amino salts(9) of the drug have been investigated.

In this study, skimmed milk (SM) was employed as a carrier to form a solid

dispersion (SD) as it composed of amino acids and surface active agents(10) enhancing water-solubility(11) and reducing gastric disturbances of nonsteroidal drugs with anti-inflammatory effect(12, 13). Since SM is a natural and non-toxic component, it can be a candidate as an excipient in peroral and parenteral drug dosage forms. Scanning electron microscopic (SEM), Differential Scanning Calorimetric (DSC), IR spectroscopic and X-ray powder diffraction analysis were performed to determine the physicochemical properties of physical mixture (PM) and SD containing IND and SM in comparison with the plain drug. These techniques have been used for the assessments of molecular interactions occurring between solid components of pharmaceuticals(6,7). Solubility and dissolution rate determinations have been performed to evaluate the solubility and enhancement of dissolution of IND.

Materials

Indomethacin (Deva, Turkey), skimmed milk containing maximum 1 % fat, about 4.7% carbohydrate, 3.3% proteine and minerals other reagents used were of analytical grade.

Method

1. *Preparation of skimmed milk powder: SM* was lyophilized until the humidity of the sample was reduced to maximum 3.0%. Based on the preliminary studies, lyophilization time was determined as 72 hours to reach to this humidity value. 2.615 g yield of lyophilized SM powder was obtained from 25 ml of SM (mean of 3 experiments).

2. *Preparation of the solid dispersions:* For the preparation of the SD, 500 mg indomethacin was suspended in 50 ml of SM proceeded by pH adjustment to 7.2. The suspension was then kept in a water bath applying magnetic stirring for 30 minutes at 50±2°C. The resultant solution was frozen at -20 ± 0.5°C and then, lyophilized.

3. *Preparation of the physical mixtures:* 500 mg of indomethacin was uniformly mixed with 5.182 g of lyophilized SM in a mortar by the aid of a pestle. The resultant PM was kept in a desiccator over calcium chloride at room temperature.

4. *Microscopic analysis:* Scanning electron microscopic analysis (SEM) was applied to determine surface morphology of IND, its SD, PM and SM using a Joel 1200 EX-11 (Tokyo, Japan) Model Scanning Electron Microscope.

For particle size analysis, shapes of the particles were drawn using microscope (Olympus SZH 10-11, Japan) with stereoscopic loop (triocular-side lighting) and diameters of these particles were measured. Mean particle sizes, were calculated by micromeritic method(14).

5. *X- ray powder diffraction analysis:* X-ray diffraction patterns of samples were investigated using Huber Corp. Diffraktionstechnik, Rimstig by Ca-K a_1-ray application

6. *IR spectroscopic analysis*: IR spectra of IND, SD, PM and SM were determined over the range of 4000-500 cm^{-1} using IR Spectrophotometer (Perkin Elmer 1600 Series FTIR Spectrophotometer) from KBr pellets.

7. *Differential Scanning Calonmetric analysis:* Differential scanning calorimetric (DSC) analysis of 5.5 mg of samples were performed placing the samples in aluminium pans of a Perkin-Elmer DSC-2°C calorimeter. 10°C min^{-1} of a scanning speed was applied within the temperature range of 20-250°C.

8. *Solubility studies:* 50 mg of IND, its SD and PM equivalent to 50 mg of IND were added into 25 ml of distilled water and shaken in a water bath at 25 ± 0.5°C for 15 h (USP XIX).

Samples were then withdrawn with a syringe filter (pore size 0.45 μm) and were assayed spectrophotometrically (Shimadzu Double Beam UV-150-02) at 318 nm for solubilized IND content. Determinations were done in triplicate.

9. *In vitro dissolution studies: In vitro* dissolution rates of IND incorporated into solid dispersions and physical mixtures were investigated using USP XXIII Paddle method. 25 mg of pure IND or its equivalent to SD or PM were sprinkled into 500 ml of distilled water at 37±0.5°C and stirring at 50 rpm. Samples were withdrawn at certain time intervals, filtered through Milipore membrane filter (0.45 μm) and assayed spectrophotometrically at 318 nm for the solubilized drug content. All experiments were done in triplicate.

Results and Discussion

The morphology of particles were performed by means of a SEM (Fig. 1, 2). Particles of solid dispersions of IND were mostly in amorphous form which lead to a conclusion that reduction in particle size was achieved. Results of particle size analysis, that particle sizes of IND, PM, and SD were as 39, 13 and 3.49 μm,, respectively.

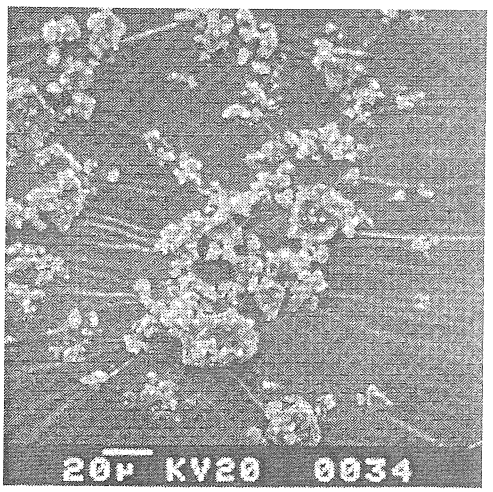
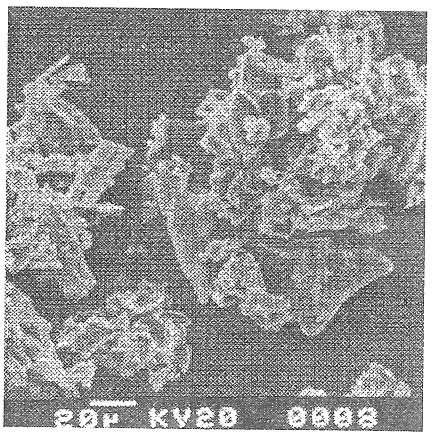
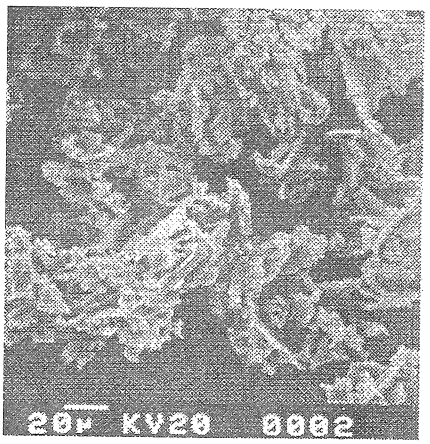


Fig. 1. SEM picture (500 x magn.) of indomethacin



(a)



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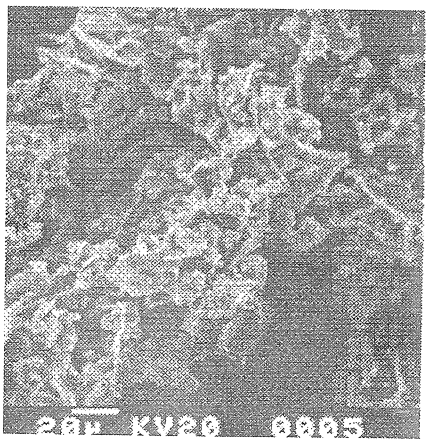

(c)

Fig. 2. SEM pictures (500 x magn.) of a) physical mixture of indomethacin with skimmed milk, b) solid dispersion of indomethacin with skimmed milk c) skimmed milk

The X-ray powder diffraction pattern of pure drug exhibited its characteristic diffraction peaks at various diffraction angles indicating the presence of cristallinity, whereas SM showed a diffraction spectrum that was typical for most amorphous materials with a few detectable diffraction peaks. In case of PM and especially SD, the absence and the reduction of major IND diffraction peaks indicates that an amorphous form existed in SD (Fig. 3). In X-ray diffraction spectrum of the PM, some crystals of IND were detected as the particle size is much bigger than in the SD. If ratio of IND reduces, the major peak of IND will disappear.

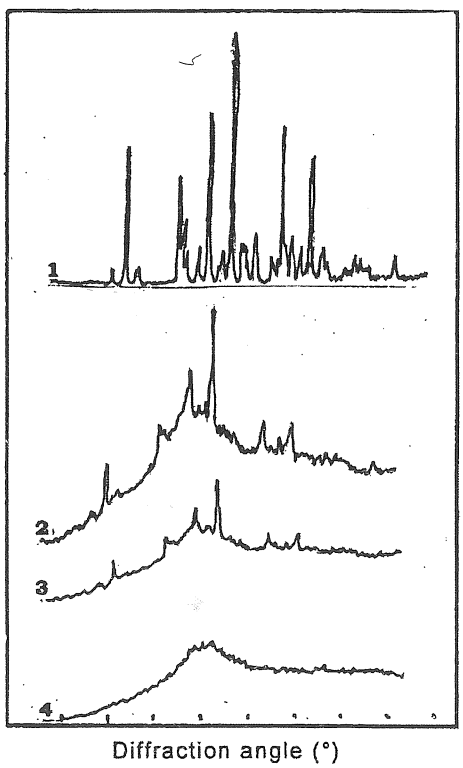

Fig. 3. Powder X-ray diffraction spectra of indomethacin (1), physical mixture (2), solid dispersion (3) and skimmed milk (4)

According to the IR spectroscopic analysis data, the obtained characteristic absorption bands for functional groups of IND (C=0 stretch; 1717 and 1691 cm^{-1}, aromatic C=C stretch; 1518 cm^{-1}, 0-CH3 deformation; 1454 cm^{-1}) showed changes compared to those obtained from SD and PM (Fig. 4). In the IR spectrum of SD, it is seen OH^- group at 3854 cm^{-1}. It is said that to be occured H^+ bond between IND with SM according to data of X-ray diffraction and IR analysis.

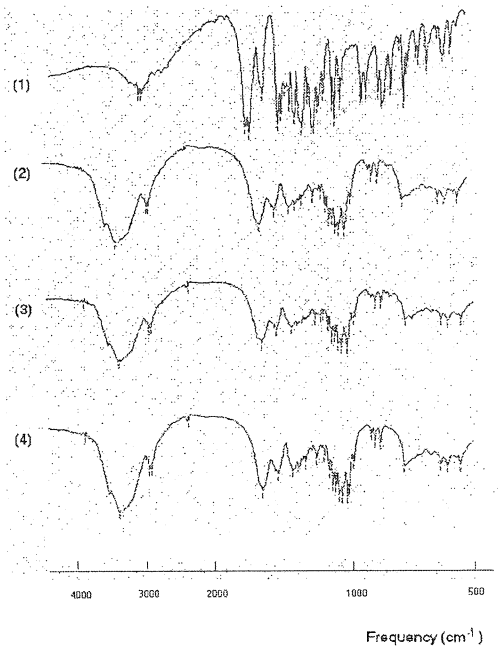

Fig. 4. Infrared spectrum of indomethacin (1), physical mixture (2), solid dispersion (3) and skimmed milk (4)

The thermographs of DSC showed that (Fig. 5) SM exhibited a peak at 168°C and IND had a sharp peak at about 162°C, corresponding to its melting point (1). Broad exothermic transition peaks were obtained for PM and SM at 158°C and 157°C, respectively and those for SD were smaller, broader and shifted to lower temperature than PM and IND. These data were in accordance with the postulate of almost amorphous (disordered) state of the SM and indicated that IND was penetrated through SM and hence, a physical complex was formed.

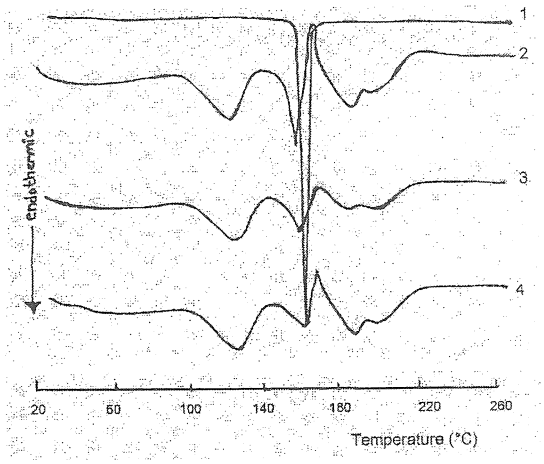

Fig. 5. DCS thermograms of indomethacin (1), physical mixture (2), solid dispersion (3) and skimmed milk (4)

Aqueous solubility of IND formulated in SD was also investigated. The data revealed that solubility of IND in SD (12.5 mg/100 ml) was 25 times and that of PM (4.8 mg/100ml) 10 times higher than the aqueous solubility of plain drug (0.50 mg/100 ml).

Dissolution studies were performed for IND powder, its PM, and SD. Data indicated that the dissolution rate of IND from SD was higher than that of PM and IND powder (Fig. 6). The liberation rate of IND from SD was rather slow within the first 10 min. and then increased reaching the value 76.17%±0.50 within 35 min. After 60 min., 98.89%±0.40 of the drug was dissolved in the dissolution medium whereas the amount of drug liberated from the PM and plain drug were only 30.50%±0.35 and 5.30%±0.21, respectively.

Based on these results it could be concluded that SD of IND formulated using SM has proved to be the most suitable form for IND due to high increased aqueous solubility and the dissolution of the drug. PM also showed more solubility and better dissolution profiles in comparison to the plain drug. Thus, it would be possible to formulate IND with SM in the form of SM, having suitable therapeutic dose and absorption profile for peroral and parenteral administrations.

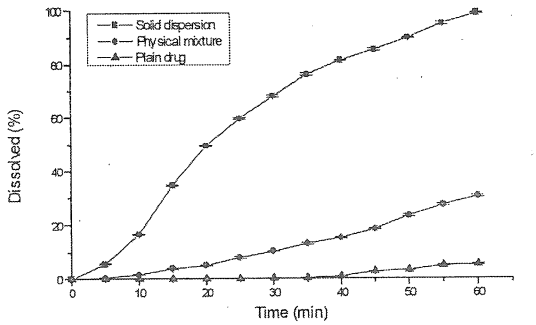

Fig. 6. Dissolution profiles of indomehacin (plain drug), its solid dispersion and physical mixture with skimmed milk in distilled water at 37±0,5°C

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Accepted 19.04.2000