

THE EFFECT OF SODIUM LAURYL SULFATE ON THE RELEASE OF INDOMETHACIN
FROM AGAR BEADS

AGAR KÜRELERDEN İNDOMETAZİNİN SALIMI ÜZERİNE SODYUM LAURİL SÜLFATIN
ETKİSİ

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In this study, agar beads containing indomethacin were prepared at 1:1 polymer-drug ratio and the release of the drug was investigated. Sodium lauryl sulfate was added to the formulations at different ratios. All the prepared formulations gave prolonged release. It was observed that sodium lauryl sulfate increased the release of drug considerably. In vitro release studies exhibited a \sqrt{t} dependence indicating a diffusion controlled process from the matrix formulation. A desired release profile was obtained by adding sodium lauryl sulfate to the formulations.

Bu çalışmada indometazin içeren agar küreler 1:1 polimer-ilaç oranında hazırlandı. Formülasyona değişik oranlarda sodyum lauril sülfat ilave edilerek ilaç salımına etkisi incelendi. Hazırlanan tüm formülasyonlarda uzatılmış salım elde edildi. Sodyum lauril sülfatın indometazin salımını belirgin derecede arttırdığı gözlemlendi. Matris yapısındaki formülasyonlardan ilaç salımlarının difüzyon kontrollü bir şekilde \sqrt{t} kinetiğine uygun olarak gerçekleştiği saptandı. Formülasyonlara sodyum lauril sülfat ilave edilerek istenen salım profili elde edildi.

Keywords: Indomethacin; Agar beads; Release studies; Sodyum lauryl sulfate

Anahtar kelimeler: İndometazin; Agar küreler; Salım çalışmaları; Sodyum lauril sülfat

Introduction

In recent years the interest to controlled-release dosage forms has increased because of their advantages such as prolonging drug action and avoiding excessive drug concentrations in plasma and tissues. For this purpose, some natural polymers such as agar, agarose and alginate were also used for encapsulation purposes. These materials form gels when used in adequate concentration upon cooling to about 40°C and they remelt on heating to about 85°C (1-3). Nakano *et al* showed (4-6) in their studies that agar can be used successfully in controlled-release dosage form design. In another study, different concentrations of agar solution were used in the preparation of sustained-release agar beads containing phenobarbitone sodium. It has been reported that the Higuchi kinetic model

described fully the pattern of dissolution (7). In a previous study, it was shown that agar was also a suitable polymer for sustained-release of indomethacin and the release rates were inversely related to drug contents in the formulations (8).

Indomethacin is a non-steroidal anti-inflammatory drug used for arthritis in conventional and retard capsule forms. Conventional dosage form results in side effects on gastrointestinal and central nervous system in some patients due to the high initial plasma concentration. It is probable that a sustained-release dosage form would reduce the severity of these side effects (9-13).

In this part of the study, agar beads containing indomethacin were prepared by adding sodium lauryl sulfate (SLS), a hydrophilic lubricant, to the formulations

and its effect on the release of indomethacin was investigated.

Materials

Indomethacin (Fako, Turkey), agar (Oxoid), sodium lauryl sulfate (Merck), Tween 80 (İlsan-İltaş, Turkey). The other chemicals used were of analytical grade and used as received.

Methods

1-The preparation of agar beads

The method by Nakano *et al* (4) was applied by modifying. Cold paraffine was used instead of ethyl acetate (4) to solidify agar beads and more spherical beads were thus obtained (8). Agar beads were prepared at 1:1 agar-polymer ratio and also 1:1:0.25 and 1:1:0.025 agar-indomethacin-SLS ratios. SLS was added to the formulation to examine its effect on the release of the drug. The formulations were prepared as three batches. To determine drug contents in the agar-indomethacin formulations, the assay procedures were repeated as explained previously (8).

2-In vitro release studies

The release tests were carried out in 500 mL of pH 6.2 phosphate buffer at 37 \pm 0.5 $^{\circ}$ C. Rotating paddle method was used at 100 rpm. Tween 80 (0.02%) was added to the dissolution fluid to overcome the poor wettability of indo-methacin (14, 15). Accurately weighed agar beads containing 25 mg indomethacin were used for the release studies. Five mL aliquots were taken. These aliquots were spectrophotometrically (Shimadzu Double-Beam 150-02) assayed directly at 318 nm. The withdrawn samples were returned to the

beakers after measurements. The dissolution tests were done for 24 hrs and for the first 8 hrs, the samples were measured with one hour intervals. Each determination was carried out in triplicate and the mean values were reported.

Results and Discussion

The shapes of the agar beads obtained were generally spherical with an initial diameter ranging from 3 to 3.5 mm. After the drying process, beads of 1.14-1.50 mm in diameter (mean 1.32 \pm 0.110 mm; n=50) obtained by sieving were used in dissolution tests of the formulations. As seen in Table 1, indomethacin was thoroughly dispersed in agar solution during the preparation of formulations. The observed drug contents were found to be close to the expected ones.

Lubricants that are commonly incorporated in the formulation of solid dosage forms fall predominantly in the class of hydrophobic compounds (such as indomethacin). Consequently, the nature (hydrophobic or hydrophilic), quality and quantity of the lubricant added can affect the dissolution rate. The effect of lubricants on the dissolution rate of drugs depends on the properties of the granules. If the granules are hydrophilic, water-soluble lubricants have insignificant effect on the dissolution. On the other hand, if the granules are hydrophobic, the lubricant enhances dissolution rate(14). After release studies were performed, the cumulative release results of indomethacin were plotted as a function of time

Table 1. The assay results (n=3)

Formulations (agar:indomethacin:SLS)	Expected drug content%	Mean observed drug content % (\pm sd)
1:1	50	44.95(0.571)
1:1:0.25	44.44	44.48(0.321)
1:1:0.025	49.38	43.87(0.647)

(Fig. 1) and it was clearly observed that SLS, added as a hydrophilic lubricant, increased the release of indomethacin considerably. SLS enhanced the dissolution of indomethacin due to its hydrophilic character combined with surface activity, which increased the microenvironment pH surrounding the weak acid and increased wetting and better solvent penetration into the agar beads. Similar results were also obtained in previous studies and it was found that SLS increased the drug release (16-17). However, although the amount of SLS was increased tenfold, the release rate of drug was not affected with this increase. The release results were evaluated statistically for the chosen probability level ($p=0.95$). The difference between the release results obtained from the formulations with and without SLS was statistically significant, whereas there was no significant difference between the formulations prepared with two different ratios of SLS.

The release rate from a planar matrix is usually proportional to the square root of

time. It was found that the Higuchi kinetic model described fully the dissolution pattern of drug from agar beads(7). We have also observed that the release rates were also proportional to the square root of time. The determination coefficients were found to be 99.7-99.9%. The plots are shown in Fig.2.

As indicated in USP XXII (18), there are some limitations for the release of indomethacin from extended-release dosage forms for a dosing period of 24 hours. The releases were in the range of 10-32% by 1 hr, 20-52% by 2 hrs, 35-80% by 4 hrs, not less than 60% by 12 hrs and not less than 80% by 24 hours. In our previous study, we investigated the release of indomethacin from agar beads prepared at 2:1, 3:1 and 4:1 polymer-drug ratios. The release rates were inversely related to drug contents in the formulations. It was observed that when the USP release criteria were taken into consideration, only the formulations of 4:1 and 3:1 (except 2:1) ratios gave the acceptable release results. Also when lactose, as a

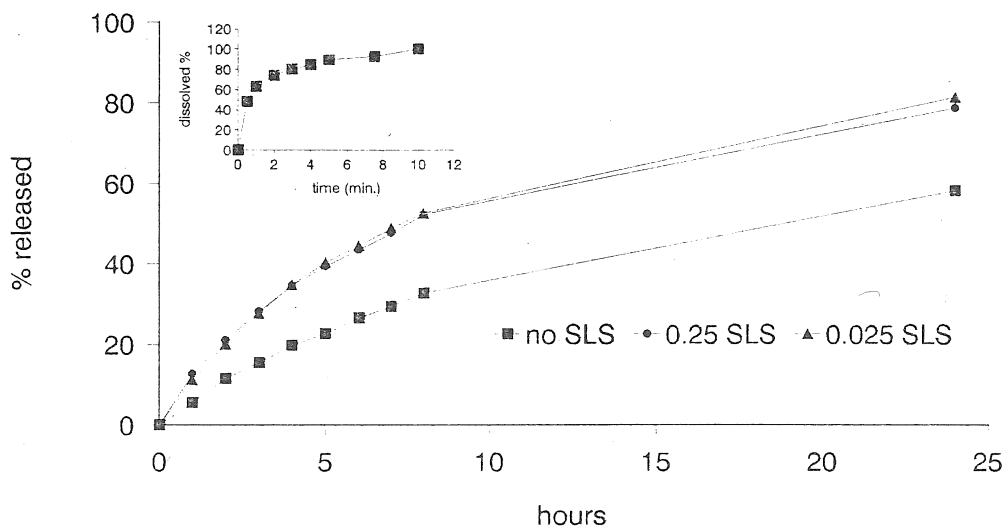


Fig.1. The release of indomethacin from agar beads prepared with and without SLS (insert: the dissolution profile of indomethacin powder)

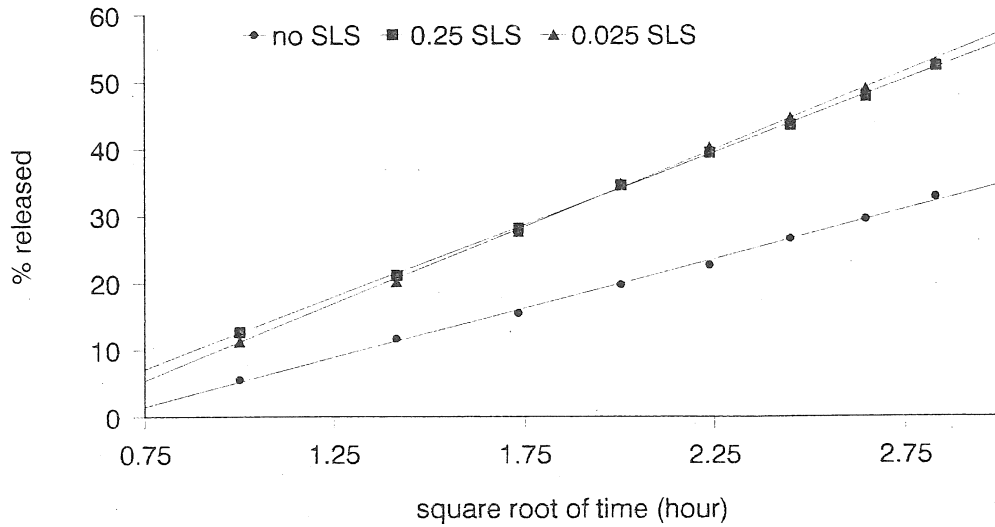


Fig.2. The release of indomethacin as a function of square root of time for three different formulations

water-soluble diluent, was added to the formulations of 1:1 at three different ratios to increase indomethacin release from beads, it was observed that only the formulation prepared at 1:3:1 agar-lactose-indomethacin ratio reached the USP lower release limits(8). In this study, the formulation of 1:1 ratio did not release the drug within the lower release criteria(Fig.3). However, we observed that SLS increased the release of drug considerably and the lower release criteria

could be reached with the formulations of 1:1 prepared by adding less amounts of SLS. The Higuchi release rates of three formulations were 13.6, 17.01 and 17.81 $\text{time}^{-1/2}$ for 1:1, 1:1:0.25 and 1:1:0.025 formulations, respectively. The release rate necessary for the lower release criteria stated in USP was also found to be 17.45 $\text{time}^{-1/2}$. According to these results, the formulations containing both ratios of SLS released the drug at desired release

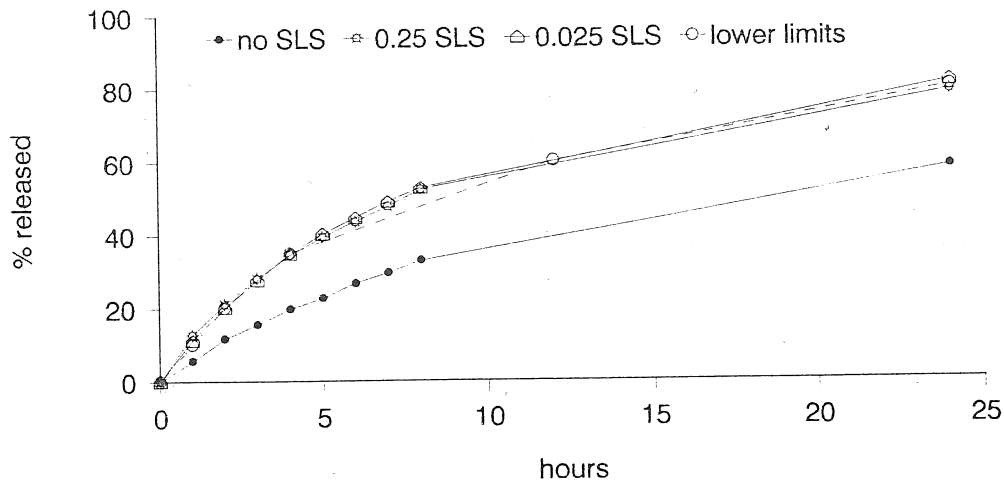


Fig.3. The comparison of the release profiles of three formulations with USP lower release criteria

rate when compared with the lower release rate. In addition, the ratio of 0.025 of SLS was sufficient to increase the release as desired. It was clearly observed that, addition of SLS to the formulations was found to be more effective than addition of lactose.

It can be concluded that SLS has a significant effect on the release of indometacin and when added to the formulations even at small amounts, a desirable formulation can be prepared at minimum drug-polymer ratios.

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