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Determination of the physical state of salicylic acid in hydrogel formulations by X-ray diffractometry

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Summary

Hydrogel topical formulations containing salicylic acid (SA) are available for the treatment of warts. An X-ray diffractometric method was developed to determine the physical state of the SA in one of these products. Formulations were prepared with high SA concentrations (26–45% w/w) so that a fraction of the incorporated SA was undissolved. A fixed weight of each formulation was loaded into an X-ray sample holder and the integrated intensities of two peaks of SA were determined. The intensity of each of these peaks was linearly related to the weight percent of SA in the formulation. The intercept on the x-axis was the solubility of SA in the matrix at room temperature and was found to be about 20% w/w. The use of the two X-ray peaks provided two independent solubility values and these were in good agreement. Based on scanning electron microscopy, the solubility of SA was determined to be close to 19% w/w at room temperature.

Introduction

Hydrogels are polymeric materials which swell when placed in contact with water and have the ability to retain water within their structure (Ratner and Hoffman, 1976). This ability combined with their good biocompatibility makes them useful for a variety of drug delivery applications (Roorda et al., 1986). The physical state of the drug in these delivery systems depends on the solubility of the drug in the matrix. There are two possible situations: (a) the drug is dissolved in the matrix or (b) a fraction of the incorporated drug is dissolved and a fraction is dispersed in the matrix. Knowledge of the physical state of the drug is required to model appropriately the drug release kinetics from these dosage forms (Baker, 1987).

Theeuwes et al. (1974) developed an ingenious differential scanning calorimetric (DSC) method to determine the solubility of drugs incorporated into a silicone polymer matrix. The method was based on the measurement of enthalpy of fusion of the crystalline drug in the matrix and therefore provided the solubility of the drug at its melting

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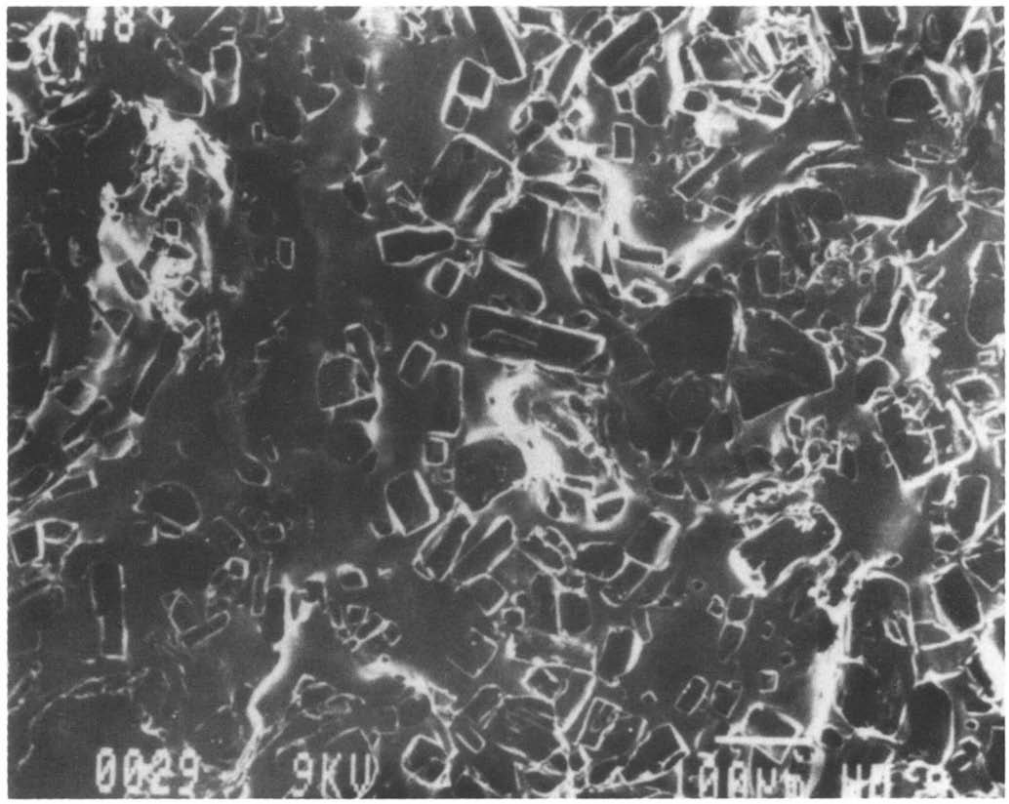


Fig. 1. SEM photographs of formulated patches containing (a) 45, (b) 37, (c) 26 and (d) 19% w/w salicylic acid.

point. Extraction of the drug from the matrix and partition coefficient determinations have also been used to determine the solubility of drugs incorporated in polymeric matrices (Scheuplein, 1965; Ghannam et al., 1986). These procedures are not necessarily simple and may not be applicable when the matrix is a complex multi-component system.

The object of this work was to develop an X-ray diffractometric method to estimate the solubility of salicylic acid (SA) incorporated in a hydrogel matrix. The solubility was also estimated by scanning electron microscopy in order to confirm the validity of the X-ray method.

Materials and Methods

Materials

Propylene glycol (PG) (Dow, MI), polyethylene glycol 300 (PEG) (Union Carbide, IL), salicylic acid (USP, Kalama, NJ), karaya gum (NF, Colony, NY) and Dowicil 200® (*cis*-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride) (Dow, MI) were used as received.

Methods

Trans-ver-sal® (Tsumura Medical, Chaska, MN), a commercially available hydrogel patch formulation used for the treatment of warts, was chosen for our studies. It contains 15% w/w SA. The matrix in this dosage form contains karaya gum, a gummy exudate obtained from the tree *Sterculia urens*.

Preparation of the patch formulations Hydrogel patch formulations containing 19, 26, 29, 32, 35, 37, 39, 41, 43 and 45% w/w SA were prepared according to the method outlined earlier (Reever et al., 1988). At each composition, three batches were prepared. In the formulations prepared for X-ray analysis, the particle size of SA was controlled. The SA used passed through a

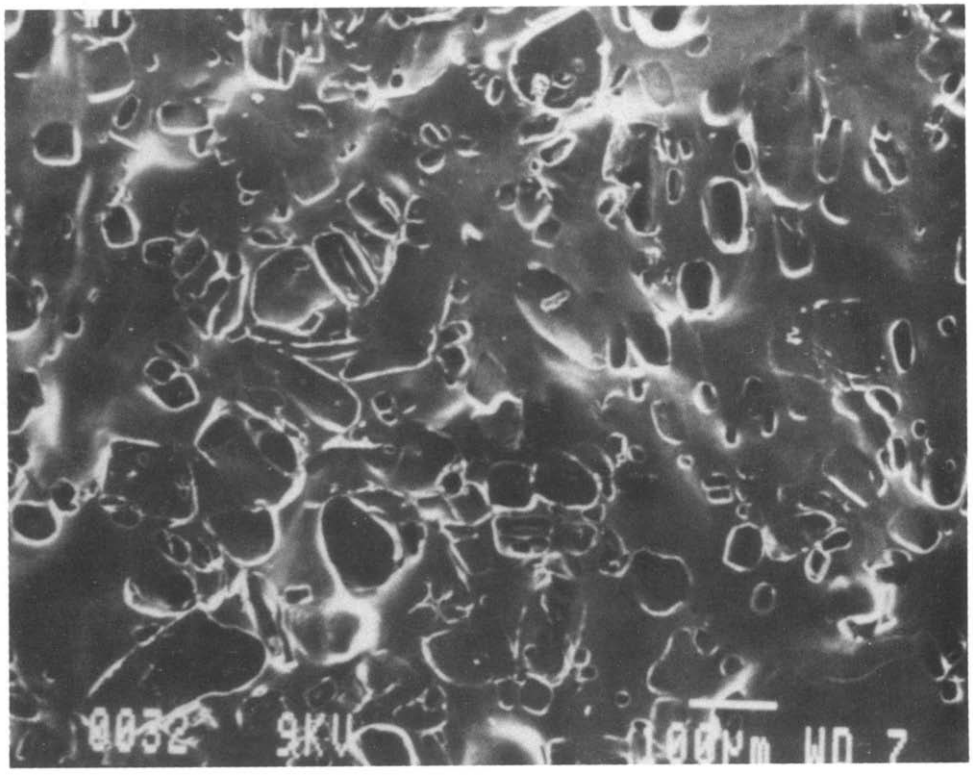


Fig. 1 (b).

200 mesh but was retained in a 325 mesh sieve. Microscopic examination revealed that all the particles were < 75 μm (longest dimension) in size.

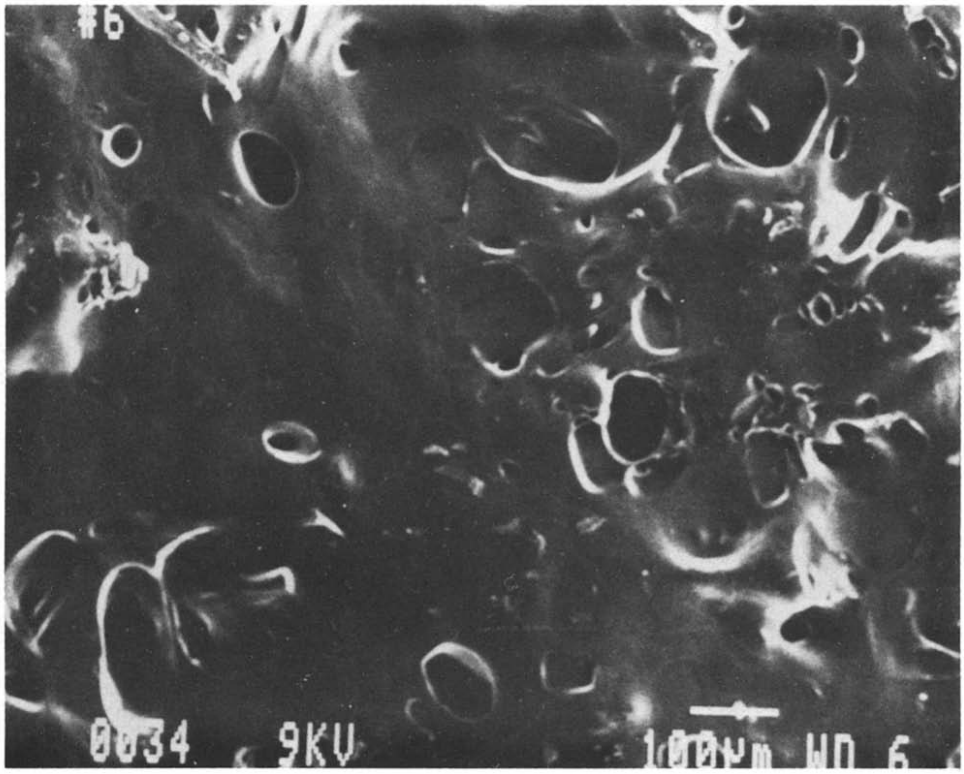
Scanning electron microscopy (SEM) The patches were coated under reduced pressure ($\sim 10^{-5}$ Torr) with carbon (50 Å thickness) followed by gold (100 Å thickness) and observed under a scanning electron microscope (model 840 II Jeol) operated at 9 kV. SEM studies were carried out on formulations with 15, 19, 26, 37 and 45% w/w SA.

X-ray diffractometry All the patch formulations prepared (SA content ranging from 19 to 45% w/w) were subjected to X-ray diffractometry. A fixed weight (1.07 g) of each formulation was filled into an aluminum sample holder and exposed to CuKα radiation (45 kV $\times$ 30 mA) in a wide angle powder X-ray diffractometer (model D500, Siemens). The scanning was carried out from 23.5 to 32.5° 2θ at 1.2° 2θ/min. Two X-ray peaks of SA were chosen for the quantitative analysis. The first peak (hereafter referred to as peak I) included lines with d spacings of 3.58, 3.53 and 3.52 Å and the peak area was determined by integrating between 24.79 and 26.11° 2θ (Berry, 1982). The second peak (hereafter referred to as peak II) included lines with d spacings of 2.95, 2.91 and 2.88 Å and the peak area was determined by integrating between 30.03 and 31.68° 2θ. Background counts were usually obtained by integrating between 26.2 and 27.0° 2θ for peak I and 29.6 and 30.2° 2θ for peak II. The net intensities of peaks I and II were obtained after appropriate background subtraction (Klug and Alexander, 1974).

Results and Discussion

SEM analysis

When formulations with 26, 37 and 45% w/w SA were observed under the electron microscope,



(c)

Fig. 1 (c).

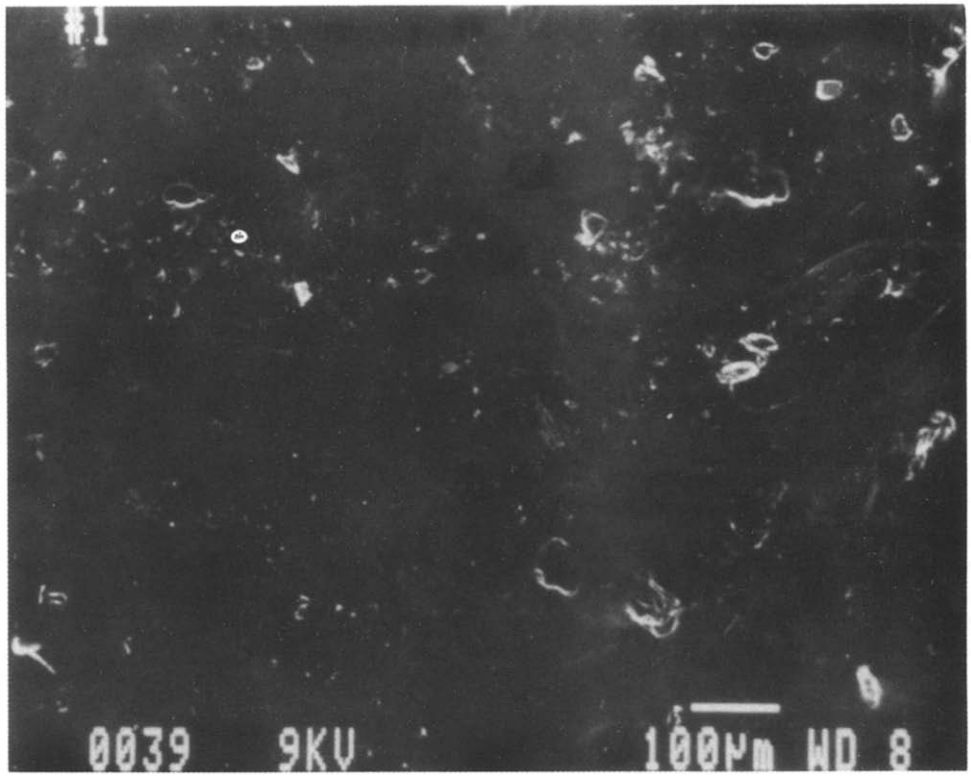
the presence of crystalline SA was evident in all of them (Fig. 1b and c). Increases in the SA load revealed a progressive increase in the amount of dispersed SA. In the formulation containing 19% w/w SA, only very few crystalline particles were seen (Fig. 1d). This suggested that the drug load was close to the saturation solubility of SA in the matrix. The SEM photograph of Trans-ver-sal® showed a dark blank screen and no evidence of presence of crystalline SA. Based on SEM, all the SA in the commercial formulation was concluded to be present in the dissolved state. The technique provided direct visual evidence of the presence of dispersed drug in the matrix.

During the preparation of the samples for SEM, the samples were subjected to a reduced pressure of $\sim 10^{-5}$ Torr, at room temperature, for about 1 h. This could have caused evaporation of the volatile components in the formulation and thereby altered the composition and in effect the physical state of SA in the samples. The weight change of some formulations was monitored following storage under the above conditions for 1 h. The observed weight loss was $6.65 \pm 1.23\%$ (mean $\pm$ S.D.; $n = 4$). Such a small weight loss was unlikely to alter the composition of the formulation significantly.

X-ray diffractometry

All of the observed peaks in the X-ray patterns of the formulations were due to diffraction by crystalline SA in the formulation (Berry, 1982). Therefore, none of the other ingredients in the formulation were crystalline.

The intensity of each of these two peaks (I and II) was plotted as a function of the weight percent of SA in the formulation (Fig. 2). The intercept on the x-axis provided an estimate of the saturation solubility of SA in the matrix at room temperature. Based on the results obtained from peaks I and II, the solubility was estimated to be 19.6 and 20.6% w/w, respectively. These two



(d)

Fig. 1 (d).

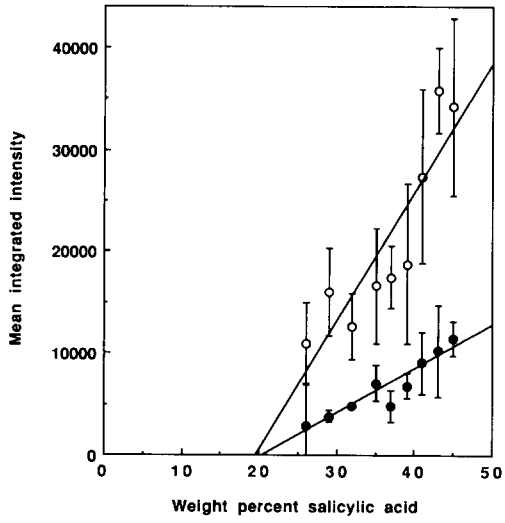


Fig. 2. Plot of the mean integrated intensity of the X-ray peaks as a function of the weight percent salicylic acid in the formulated patches ($n = 3$). Error bars represent standard deviations. The correlation coefficients of the regression lines were 0.89 (peak I) and 0.93 (peak II). (○) peak I; (●) peak II.

independent estimations of the solubility were in close agreement. Moreover, the results from the SEM analysis suggested that the solubility of SA in the matrix was around 19% w/w at room temperature. Thus, the results obtained from the SEM and X-ray diffractometric analysis were in good agreement.

The nature of the work necessitated a consideration of the sources of error in quantitative X-ray diffractometry which are listed below.

Diffraction line intensity Variations in particle size and microstrain can cause large variations in line shape, thereby affecting the maximum peak intensity (peak height). However, these variations will not affect the integrated line intensity (area under the peak). Therefore, in the measurement of diffraction line intensity, the integrated line intensity was measured (Cullity, 1978).

Preferred orientation The preferred orientation of the particles can lead to serious errors in the measured intensities of the lines (Klug and

Alexander, 1974). However, in the hydrogel formulations, the SA particles were observed to be embedded in a matrix (Fig. 1). This matrix had the consistency of a gel. It was therefore assumed that the SA particles were randomly oriented in the matrix.

Microabsorption When two substances of different mass absorption coefficients are mixed, possible errors due to microabsorption will need to be considered (Klug and Alexander, 1974). The mass absorption coefficient of a substance is defined as the weighted average of the mass absorption coefficients of its constituent elements (Cullity, 1978). For the purpose of mass absorption coefficient calculation, the formulation was considered to consist of the unknown component (SA) and the matrix (all the ingredients in the formulation other than SA). The mass absorption coefficients of SA and the matrix were calculated to be 6.82 and 7.58 cm^2/g, respectively (for CuKα radiation). The mass absorption coefficient of karaya gum was calculated on the basis of the following composition (in w/w): D-galacturonic acid (43%), D-galactose (13%), L-rhamnose (15%), acetyl group (8%) and water (17%) *. Since the mass absorption coefficients of SA and the matrix were quite close to one another, errors due to microabsorption were concluded to be negligibly small.

Statistical accuracy of the counter measurements The magnitude of the statistical errors depends on the total number of photons counted (Klug and Alexander, 1974). The percent standard deviation in the net peak area, $100\sigma_P$, is given as:

$$100\sigma_P = \frac{100(N_T + N_B)^{1/2}}{N_T - N_B} \quad (1)$$

where N_T is the integrated counts for the peak (including the background) and N_B represents the integrated counts for the background. The percent standard deviation in the net area of peaks I and II was calculated for the formulations with SA concentrations ranging between 26 and 45% w/w. In the case of peak I, the highest value was 3.3%. For peak II, when the SA concentration was $\geq$ 29% w/w, the highest value was 8.9%. Based on these results, the statistical accuracy was concluded to be acceptable.

Sample thickness When the maximum diffracted intensity from a flat specimen is desired, the sample thickness must satisfy the condition (Klug and Alexander, 1974):

$$t \geq \frac{3.2 \sin \theta}{\mu^* \rho'} \quad (2)$$

where t is the thickness of the sample, θ is the incident angle of the X-rays, μ^* is the mass absorption coefficient of the sample and ρ' represents the density of the sample. Since 1.07 g of the formulation was loaded into a sample cell of volume 0.8 cm^3, the value of ρ' was 1.34 g/cm^3. The value of μ^* ranged from 7.58 cm^2/g (for the formulation containing 26% w/w SA) to 7.38 cm^2/g (for the formulation containing 45% w/w SA). Therefore, an intermediate value of 7.48 cm^2/g was used for the calculations. For 2θ values of 25 and 30°, t must be $\geq$ 0.7 and 0.8 mm, respectively. Since the depth of the sample holder was 2 mm, Eqn 2 was satisfied and there was no loss in intensity due to inadequate sample thickness.

The error bars in Fig. 2 indicate that there is a large variance associated with the estimation of the integrated intensity of the peaks. Two possible factors responsible for this observation are: (i) amorphous scattering of X-rays by the noncrystalline ingredients in the formulation and (ii) the complex nature of the system under study.

When SA was not included in the formulation, the gel did not form and the system remained in the liquid state. This indicated that SA was necessary for the formation of the gel. However, no irreversible interaction between SA and the other ingredients in the formulation is likely. This conclusion is based on earlier studies wherein we had demonstrated complete release of SA from the commercial formulation during 8 h of in vitro release studies (Venkatesh et al., 1991). SA prob-

* Technical information on karaya gum obtained from Colony Import and Export Corp., Garden City, NY, 1990.

ably forms hydrogen bonds with both PG and PEG and this interaction of SA with the hydrogen-bonding solvents is essential to form a stable cross-linked gel upon addition of karaya gum (Reever et al., 1988; Hymes and Rolf, 1987).

The X-ray pattern of the Trans-ver-sal® formulation contained no diffraction peaks and this confirmed that all the SA in this product was present in the dissolved state at room temperature.

Very few analytical techniques can distinguish between the dissolved and dispersed states of a drug in a hydrogel formulation. Therefore, the X-ray method developed, although approximate, is useful. It has not only aided in the identification of the physical state of SA in the matrix but also provided a reasonably good estimate of the solubility of SA in a complex system at room temperature. Further, the method is quick, simple, and nondestructive. The X-ray method is also capable of detecting any alterations in the solid state of the drug during processing. This is a unique advantage of this method.

In many transdermal dosage forms currently under development, the drug is incorporated in a polymeric matrix (Chien, 1987). The X-ray method developed can find application in the characterization of the physical state of the drug in these systems.

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