A Method to Measure the Solubility of Drugs in Ointment Bases

Naoyoshi Kobayashi* and Izumi Saitoh

Received April 23, 1998; accepted August 20, 1998

The solubility of a drug in an ointment base is an important factor determining the efficacy of the formulation. However, it is difficult to measure the solubility of drugs in ointment bases. Thus, a rapid and simple method to determine the solubility of drugs in ointment bases was investigated.

Using oxybenzone as a model drug, the bleeding liquid which leaked out from various ointments was collected, and the drug concentration in the bleeding liquid was measured. The drug concentrations in the bleeding liquid collected from soluble type ointments in which the drug is dissolved in bases were in accord with that in the ointments. On the other hand, the drug concentrations in the bleeding liquid collected from crystal dispersion type ointments in which drug crystals are dispersed in bases were the same in spite of the variance in total drug concentrations in the ointments. It was confirmed by microscopic examination that crystals do not flow out into bleeding liquid in the crystal dispersion type ointment. It was also confirmed that the solubility of the drug obtained in the present study was in a solubility range consistent with microscopic examination. Furthermore, an increase in the drug solubility was detected by this method when the drug solubility in the base was raised by adding a detergent into the base. And the results from this method were in accord with the results from microscopic examination. These results suggest that the drug concentration in bleeding liquid represents the solubility of the drug in an ointment.

Key words: ointment; oxybenzone; drug solubility in semisolid formulation; corn filtration method

Katz and Poulsen,1) suggested that the absorption of a drug from an ointment is a result of interaction between the skin, drug, and base, and the absorption is dependent on two major factors—the skin and formulation factors. Formulation factors include the solubility of the drugs in the base, the oil–water partition coefficient, the state of existence, the crystal form, the particle size, and molecular weight etc.2) In order to improve the efficacy of formulations, Ostrenga et al.3) suggested that it is important for drugs to be dissolved in bases. Therefore, it is necessary to evaluate the solubility of the drugs in the base for the development of a formulation with high efficacy. Furthermore, the solubility of a drug in a base is required for theoretical deliberation on the release profile of crystal dispersion-type ointments, using Higuchi’s equation and also for analyzing skin permeability in a steady state.4)

However, it is very difficult to measure the solubility of drugs in bases of semisolid formulations. Saitoh et al.5) suggested that drug concentration in bleeding liquid is an important parameter for the efficacy of ointments. We examined the possibility that the solubility of a drug in a base can be estimated by measuring the drug concentration in the bleeding liquid. The method we used for measuring the drug solubility in a base by measuring drug concentrations in bleeding liquid will be referred to as the corn filtration method hereafter.

Materials and Methods

Materials and Reagents Oxybenzone (Wako Pure Chemicals, Tokyo, Japan) was used as a model drug along with two ointment bases (ointment I, ointment II). The base of ointment I consists of white petrolatum (JP) and liquid paraffin (JP). Sorbitan trioleate (Nikkō Chemicals, Tokyo, Japan) was added to the base of ointment II. Other reagents used were of special or HPLC grades, except for betamethasone dipropionate(JP).

Preparation of Ointments White petrolatum or white petrolatum with sorbitan trioleate was stirred and melted by heating at 80 ± 5 °C, then stirred sufficiently to obtain homogeneous samples and cooled to 48 ± 2 °C. Separately, oxybenzone, a model drug, and liquid paraffin were adequately mixed in a mortar and a homogeneous suspension was obtained. The suspension was poured into the ointment bases and stirred until the temperature of the whole ointment reached room temperature.

Collection of Bleeding Liquid According to the method by Saeki and Yasumori,6) samples were placed in a stainless steel corn mesh (opening: 45 μm) in an incubator kept at 37 ± 1 °C for approximately 20 h and the liquid which leaked out was collected as the bleeding liquid.

Microscopic Examination About 20 mg of the samples were mounted on a glass slide, covered with a coverslip, placed in an incubator kept at 37 ± 1 °C for more than 24 h, and observed for the existence of crystals of the drug at ×100 using a polarizing microscope (POH-13, Nikon, Tokyo, Japan). The drug solubility in a base was estimated by observing the state of existence of the drug in the ointments.

Measurement of Drug Concentration in Ointment and Bleeding Liquid About 0.1 g of ointment or bleeding liquid was weighed and placed in a test tube, then 5 ml of internal standard solution (chloroform solution of betamethasone dipropionate) was added followed by shaking for 10 min to disperse the ointment. Then after addition of 20 ml of methanol and shaking for 10 min, the samples were filtered through a 0.45 μm filter (Kanto Chemical, Tokyo, Japan) and the drug concentration was measured by the liquid chromatography internal standard method.

The measurement conditions were as follows: HPLC (510 type pump, 712 type auto-sampler, 481 type UV/visible detector, Japan Waters Inc., Tokyo, Japan), column; Nova Pack C-18 (4 mm I.D.×15 cm, Japan Waters Inc., Tokyo, Japan), mobile phase; CH3OH–H2O (7:3, v/v), flow rate; 0.8 ml/min,
and absorbance wavelength: 288 nm.

Results and Discussion

Microscopic Examination on the State of Existence of a Drug in Ointments and Bleeding Liquid

1) Microscopic Examination on Ointments: A microscopic examination was performed on ointment I, which contained oxybenzone at concentrations of 0.11—15.1%, at 37 °C.

The results are shown in Table 1. At concentrations below 2.93%, the drug was dissolved in the base, while drug crystals were observed at concentrations above 3.42%. These observations suggested that the solubility of the drug to ointment was in a range of 2.93—3.42%.

The same microscopic examination was also performed on ointment II, in which sorbitan trioleate was added in order to increase the solubility of the drug in the base. The results are shown in Table 2. At concentrations below 3.46%, the drug was dissolved in the base, while drug crystals were observed at concentrations above 3.94%. These observations suggested that the solubility of the drug to ointment II was in a range of 3.46—3.94% and confirmed that the addition of a detergent increased the solubility.

2) Microscopic Examination on Bleeding Liquid: A microscopic examination was performed at 37 °C on bleeding liquid which were collected by the cone mesh filtration method from the ointments examined microscopically at 1). The microscopic examination results are shown in Table 1. The drug was found to be dissolved in the bleeding liquid collected from both the soluble and crystal dispersion types of ointment, confirming no flow of drug crystals into the bleeding liquid.

Moreover, the results from examination on ointment II are shown in Table 2. Irrespective of drug concentration contained, no flow of drug crystals into the bleeding liquid was confirmed in ointment II as well as ointment I.

The results from microscopic examination on bleeding liquid confirmed no flow of drug crystals dispersed in an ointment into the bleeding liquid in cases of both ointment I and II. Thus, it was suggested that the solubility of a drug in a base can be determined by measuring the drug concentration in the bleeding liquid.

Estimation of Solubility by Corn Filtration Method

Drug concentrations in the ointments and bleeding liquid used in the previous section were measured. The relationship between the drug concentrations in the ointment and the bleeding liquid for ointment I is shown by squares in Fig. 1. The drug concentration in the bleeding liquid increased in accord with that in the ointment in a range of ointment drug concentration up to about 3% (slope: 1.01, correlation coefficient: 0.999). And in a concentration range above about 3%, the drug concentration in the bleeding liquid was constant at about 3.1%. Thus, the solubility of the drug in the base is estimated to be 3.1%.

Moreover, the relationship between the drug concentrations in the ointment and the bleeding liquid for ointment II is shown by circles in Fig. 1. In accord with the results from ointment I, which did not contain a detergent, the drug concentration in the bleeding liquid showed clear saturation. But the solubility in ointment II was raised to about 3.5%, presumably reflecting an increase in the solubility of the drug in the base due to the addition of a detergent. Though the detergent-induced increase in the solubility of the drug in the base was not so marked (from 3.1 to 3.5%), it was meaningful to detect such a small change.

Comparison between Microscopic Examination and Corn Filtration Method

Since the solubility of drugs in semisolid formulations is an important parameter, a number of methods have been reported, i.e.: a microscopic examination method by observing the existence of a drug in a base; an estimation based on the results from in vitro drug release test; a method by measuring drug concentration in a base after immersing the base in a drug suspension for a particular duration; a calculating method based on partition coefficient and water solubility; and a theoretical method. These methods are complicated or inefficient.

The bases used in the present study were petrolatum-liquid paraffin bases with and without a detergent. There were almost no polarizing materials that were indistinguishable from needle crystals of the drug in these bases, making observation of drug crystals by a microscopic examination relatively easy. Thus, the microscopic examination was considered to be able to measure the solubility with some accuracy. Therefore, two different methods, the microscopic examination and corn filtration method, were compared. As shown in Table 1 and 2, the solubility of the drug in ointment I and II measured by the microscopic examination are 2.93—3.42% and 3.46—3.94%, respectively. On the other hand, as shown in Fig. 1, the solubility of the drug to ointment I and II measured by the corn filtration method are 3.1% and 3.5%, respectively. The results on both ointment I and II showed that concentrations determined by the corn filtration method were in a concentration range consistent with the microscopic examination. Moreover, the drug concentrations in the ointment and the bleeding liquid corresponded well in a drug concentration range where the drug was dissolved in the base.
the drug concentration in the bleeding liquid was almost constant in a range where the drug crystals were dispersed in the base. A sound correlation between the two methods was found.

However, Sugai\(^{11}\) pointed out that a microscopic examination is inappropriate for ointments containing polarizing materials such as cholesterol, which is commonly used as an ointment ingredient. Furthermore, in order to measure solubility, a consecutive procedure of preparing ointment and microscopic examination is required for obtaining the solubility. To obtain correct values, it is necessary to prepare and observe numerous samples. As for crystal dispersion ointments, the closer to solubility of the drug in the base, the more difficult to find the drug crystals. Thus, the solubility of the drug in the base was elevated from 3.1 to 3.5 % by adding a detergent. It is considered that great efforts are needed to detect such a small change by the microscopic examination. Taken these together, the microscopic examination has problems with accuracy, a range for applicable formulation, and operational difficulty.

On the other hand, the corn filtration method can measure the solubility of a drug in a base by preparing only one ointment containing a drug at an excessive concentration against the solubility and measuring the drug concentration in the bleeding liquid. Therefore, the corn filtration method is considered to be a rapid and simple method to determine the solubility of drugs in ointment bases.

References