Sheabutter V: Effect of Particle Size on Release of Medicament from Ointment

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Abstract □ An ointment prepared from fat (sheabutter) obtainable from an indigenous (African) fruit released medicaments faster than either of the two ointment bases recommended by the British Pharmacopoeia. Reduction in particle size of crystalline medicaments incorporated in ointments increased surface area and transfer from the ointment to the substrate, possibly due to greater dissolution in the base, and, therefore, increased the availability of medicament at the ointment–substrate interface.

Keyphrases □ Sheabutter ointment—drug release compared to other ointments effect of particle size □ Drug release—sheabutter ointment compared to others, effect of particle size □ Particle size—effect on drug release from sheabutter ointment, compared to other ointments □ Ointments—sheabutter compared to others, drug release, effect of particle size

The aim of any formulation is to produce a finished product that is not only elegant and acceptable to the consumer but also possesses maximal therapeutic efficacy. An ointment may be intended to act solely on the skin surface to produce a local effect or to penetrate the skin. Regardless of its intended site of action, the ultimate desire is the rapid release of the active medicament from the base. The development of an ointment must include tests for medicament release in addition to product stability, washability, *etc.*

Ointments consist primarily of the excipients (base) and the active medicament. In the current work, the physicochemical forms of both the base and medicament were varied, and the influence of such variations on release was studied.

Agar diffusion (1), dialysis (2), and radiometry (3) have been used to evaluate release from ointments. Since the *in vitro* agar diffusion technique is reputed to correlate fairly well with adsorption through the skin (4), it was used in these studies.

EXPERIMENTAL

Ointment Bases—White soft paraffin BP, simple ointment BP, and sheabutter ointment prepared from sheabutter (75% w/w), arachis oil (25% w/w), and hard paraffin BP (10% w/w) were used. Sheabutter (5) is a fat obtained from the fruit of an indigenous (African) tree, *Butyrospermum parkii.* The arachis oil used was a local product; it complied with the BP monograph on a weight per milliliter basis. Hard paraffin BP was incorporated in the base to increase consistency.

Medicaments—Salicylic acid[1] and benzoic acid[1] were recrystallized from water and then dried in a desiccator for 24 hr prior to use.

Fractionation of Medicament—The medicament was dried at 70° for 1 hr and the dry crystals were sieved mechanically through a set of brass sieves, 420–75 μm. The collected fractions were stored for ointment preparation.

Preparation of Medicated Ointments—An appropriate amount of medicament that passed through a specific sieve was triturated with the base. The finished product was packed in previously sterilized collapsible tubes and stored at 28–30° until required.

[1] Laboratory chemical grade, May & Baker.

Table I—Size of Crystals Recovered from Ointments

Sieve Number	Sieve Size, μm	Crystal Size, μm: Benzoic Acid: Paraffin	Benzoic Acid: Simple	Benzoic Acid: Sheabutter	Salicylic Acid: Paraffin	Salicylic Acid: Simple	Salicylic Acid: Sheabutter
36	420	251	234	207	270	250	205
60	250	150	146	132	150	148	129
100	150	123	116	105	130	120	110
200	75	67	65	64	66	66	62

Microorganisms—*Escherichia coli* (NCTC 5938) and *Staphylococcus aureus* (NCTC 8532) were subcultured as previously described (6) and standardized nephelometrically to contain ~10^9 organisms/ml. The suspension was stored at 4° and used for a maximum of 2 weeks.

Size of Crystals Recovered from Ointments—The particle size of medicament in each ointment was determined. To recover the crystals from the finished ointment, the solvent should dissolve away the base without affecting the medicament. The solvent selected by experimentation, turpentine oil for salicylic acid and *n*-hexane for benzoic acid, was first shaken mechanically with excess medicament for 1 hr to presaturate the solvent and was then filtered.

An aliquot of the medicated ointment (1 g) was then shaken together with 20 ml of the presaturated solvent as before. Presaturation ensured little dissolution, if any, of the medicament being recovered from the ointment. The crystals were then filtered off from the solution and dried on filter paper. Crystal samples were mounted under a calibrated microscope, and the size of 20 crystals was measured.

Release of Medicament from Ointment—*Through Seeded Agar*—Portions of 1 ml of the standardized bacterial suspension were thoroughly mixed with nutrient agar at 42° and poured into petri dishes to set. Circular holes of uniform diameter and depth were cut into the agar; sufficient ointment containing medicament of a specific particle size was squeezed out to fill the cups.

The petri dishes were first kept in a refrigerator for 1 hr to minimize the growth of the microorganisms and to allow the ointment to diffuse through the agar. They were finally incubated at 37° for 24 hr.

Through Agar Containing Chemical Indicator—The medicaments, benzoic and salicylic acids, give color reactions with bromcresol purple and ferric chloride solutions, respectively. A 1-ml aliquot of the solution was added to 20 ml of nutrient agar, mixed, and poured into petri dishes to set. The ointment was extruded to fill cups made of the agar, and the dishes were stored at 37°.

As the medicament diffused through the agar, the pH of the medium changed from alkaline to acid and was manifested by a perceptible change in color. Since the color change was rapid, it was possible to follow the release rate by measuring the zone showing a change in color against time.

RESULTS

Size of Crystals Recovered from Ointments—Microscopic examination showed all particles recovered from the various ointments to be much smaller than the particles that originally passed through a specific

Table II—Solubility of Benzoic and Salicylic Acid Ointment Bases

Ointment	Medicament Solubility, % (w/w): Benzoic Acid: 70°	Benzoic Acid: 80°	Benzoic Acid: 100°	Salicylic Acid: 70°	Salicylic Acid: 80°	Salicylic Acid: 100°
Paraffin	6.0	8.0	20.0	0.5	1.0	6.0
Simple	10.0	12.5	25.0	1.0	1.5	8.0
Sheabutter	12.5	14.5	36.0	5.0	7.0	12.5

Table III—Influence of Particle Size on Release Rate of Benzoic and Salicylic Acids from Ointments Determined by Microbial Method

Sieve Size, μm	Inhibition Zone, mm					
	Paraffin		Simple		Sheabutter	
	E. coli	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*
	Benzoic Acid					
75	17.4	17.7	17.9	18.9	18.0	19.0
125	17.4	17.8	17.6	18.8	17.8	18.9
150	17.0	17.7	17.3	18.7	17.7	18.9
250	16.5	17.5	17.0	18.7	17.5	18.7
420	16.5	17.3	16.3	18.2	17.0	18.4
	Salicylic Acid					
75	16.0	17.5	17.5	18.0	18.0	19.0
125	15.8	17.3	17.4	17.4	18.0	18.5
150	15.7	17.0	17.0	17.0	18.0	18.5
250	15.5	16.0	16.2	16.3	17.5	18.2
420	15.0	16.0	16.0	16.0	17.0	17.5

sieve aperture (Table I). This observation led to the speculation that the ointment bases probably exerted some solvent action.

If it is assumed that all particles that pass through a specific sieve are spherical and uniform in diameter, the surface area of the particles equals $4\pi r^3/3$ or $\pi D^3/6$, where r and D are the radius and diameter of the particle, respectively, and π is a constant. The ratio of the surface area of the particle in the ointment and the surface area of the same particle passing through a specific sieve is given by:

$$\frac{\pi D_2{}^3/6}{\pi D_1{}^3/6} = D_2{}^3/D_1{}^3 \qquad \text{(Eq. 1)}$$

where D_1 is the diameter of the aperture through which a particle passes and D_2 is the diameter of the same particle after recovery from the ointment.

The percentage ratio equals $D_2{}^3/D_1{}^3 \times 100$. By plotting the log percentage ratio against the particle size, a straight line was obtained. Since the pattern was the same for both benzoic and salicylic acids, only the plot for benzoic acid is presented in Fig. 1. Linearity of the regression indicated that the medicament dissolved in the bases, dissolution being proportional to the surface area of the particles; *i.e.*, the finer the particles, the greater was their dissolution rate in all of the ointment bases studied.

Particles of the same original size incorporated in the ointments and subsequently recovered from them differed markedly in size from one ointment base to another (Table I and Fig. 1). For instance, benzoic acid crystals recovered from white soft paraffin were larger than those from either the simple or sheabutter ointment. Although differences in size were less marked with salicylic acid ointments, the results indicated that the crystals were larger in both white soft paraffin and simple ointments than they were in sheabutter.

Determination of solubility of the medicaments in the three ointment bases (Table II) seems to explain the differences observed in the crystal size in the different ointments.

Effect of Particle Size on Release of Medicaments from Ointments by Biological and Colorimetric Methods—Sizes of inhibition

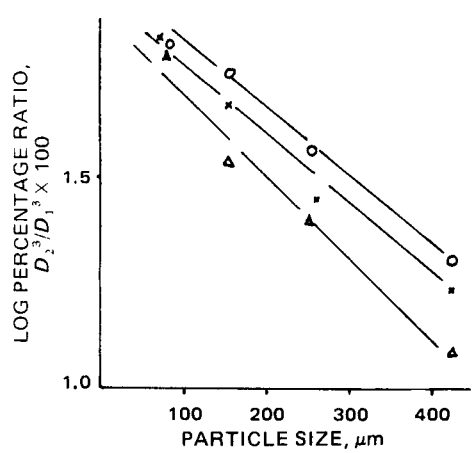

Figure 1—*Relationship between particle size and percentage diameter ratio (log) of benzoic acid crystals. Key: O, white soft paraffin; ×, simple ointment; and Δ, sheabutter ointment.*

Table IV—Influence of Particle Size on Release Rate of Benzoic and Salicylic Acids from Ointments Determined by Color Zones

Ointment	Sieve Size, μm	Color Zone, mm			
		0	8	16	24
	Benzoic Acid				
Paraffin	420	10.0	22.8	27.8	31.0
	75	10.0	27.8	32.6	35.4
Simple	420	10.0	25.6	29.4	30.0
	75	10.0	29.4	33.6	34.8
Sheabutter	420	10.0	28.0	36.2	38.8
	75	10.0	31.8	40.0	44.0
	Salicylic Acid				
Paraffin	420	10.0	23.6	29.0	32.0
	75	10.0	27.0	33.4	36.6
Simple	420	10.0	28.0	33.4	36.0
	75	10.0	30.0	36.4	40.6
Sheabutter	420	10.0	30.5	38.4	44.0
	75	10.0	35.4	44.7	50.4

zones produced by drug diffusion against microorganisms were determined (Table III). All ointments containing larger crystals of either benzoic or salicylic acid released their medicaments poorly; those containing smaller particles showed increasingly better release.

The colorimetric method was quicker and more sensitive than the biological procedure, so it was practically possible to follow the release rate over time. At any specified time over the experiment, release from ointments containing smaller crystals was relatively better than that from ointments containing larger crystals. This observation corroborated the results obtained using the biological approach. Since the pattern was the same for all three ointments, only that for sheabutter ointment is illustrated in Fig. 2; the overall results are summarized in Table IV.

DISCUSSION

The degree of fineness of solid medicaments incorporated in ointments may affect the grittiness and the aesthetic appearance of the final product. The BP recognizes this fact and recommends the use of finely sifted powder in ointments.

The current work shows that the ultimate fineness of crystalline par-

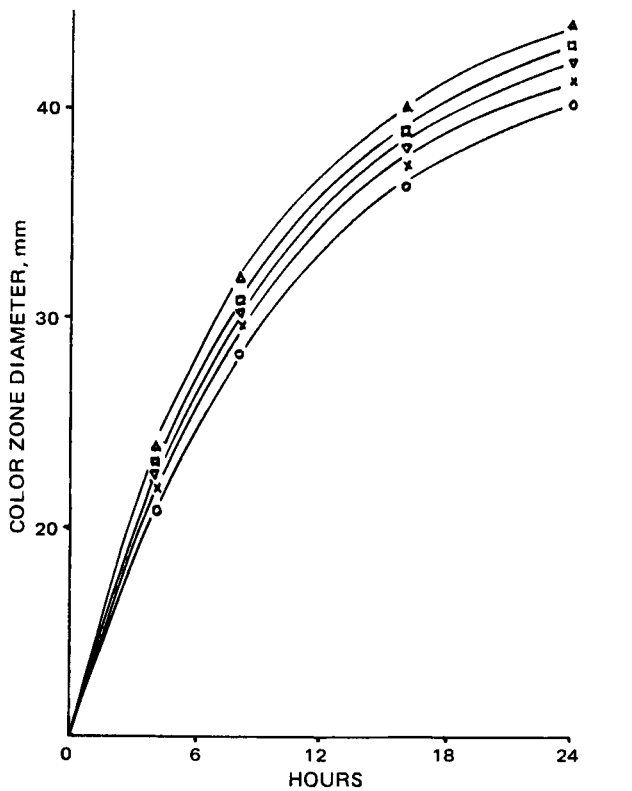

Figure 2—*Release of benzoic acid of different particle sizes from sheabutter ointment. Key (sizes in micrometers): Δ, 75; □, 120; ▽, 150; ×, 250; and O, 420.*

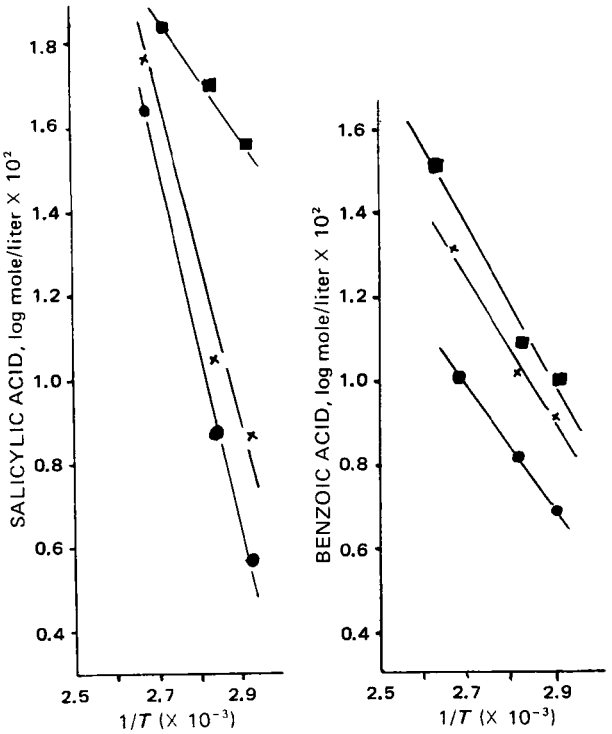

Figure 3—*Plots of logarithm of molar solubility of salicylic acid (left) and benzoic acid (right) in ointment bases* versus *the reciprocal of absolute temperature. Key:* ■, *sheabutter ointment;* ×, *simple ointment; and* ●, *paraffin ointment.*

ticles in a formulated ointment may differ from that originally incorporated. Medicaments recovered from white soft paraffin, simple, and sheabutter ointments were far smaller than they were before incorporation (Table I). Since the medicaments were incorporated in the bases by trituration, it may be argued that the diminution in particle size resulted from the mechanical process of mixing the base and medicament together, a process that may, indeed, produce some comminution. While trituration may account in part for the observation, the particles recovered from the ointments were not only smaller than they were when originally added but they varied in size from one base to another, suggesting the influence of the base.

Subsequent investigation (Table II) showed both benzoic and salicylic acids to be partially soluble in the three ointment bases. While it was practically impossible to determine the solubility of the medicaments in paraffin ointments at temperatures below 70° because the bases are semisolid, results recorded at all temperatures where the bases were completely melted established both acids to be less soluble in paraffin than in either simple or sheabutter ointment. The solubilities of benzoic acid and salicylic acid in the bases at elevated temperatures when plotted (on the log axis) against temperature ($1/T$) gave straight lines (Fig. 3), indicating the same order of solubilities in the ointment bases at room temperature as at the elevated temperatures. Therefore, this result confirms that the particle size was greater in the base in which it is least soluble and smaller in the one in which it is most soluble: that the particle size in the sheabutter ointment is smaller than the particle size in the simple ointment, which is smaller than the particle size in the paraffin ointment.

Particle size and, therefore, the surface area of medicament incorporated in the ointments increased the release rate markedly. Efficacies of both benzoic and salicylic acid ointments increased persistently, albeit slightly, as the particles became smaller (Table III). These observations were confirmed by a colorimetric method devised to detect the release rate, the superior sensitivity of the latter technique making the influence of particle size on release appear even more pronounced than was possible to observe using the microbial technique (Table IV and Fig. 2).

The reason for the observed differences in efficacies of ointments containing the same amount of medicament but of different particle size is not clear, but the cause seems to be linked with biological availability. Availability itself may be related to the transfer rate of medicament from an ointment base to the biological substrate under treatment, represented in this *in vitro* technique by nutrient agar. Medicament transfer across the ointment–substrate interface only occurs in solution; with solid medicaments, transfer depends on the amount of medicament in solution at the interface. Since smaller particles with larger surface areas dissolve much more readily than larger particles (Fig. 1), the smaller crystals conceivably dissolve in the oleaginous ointment bases and build up relatively higher concentrations at the interface for partitioning to the substrate. The current work suggests that when the total amount of particulate medicament incorporated in ointments is fixed, then efficacy depends primarily upon availability, which is itself controlled by particle size and surface area.

Besides the influence of the physical state of the medicament, the ointment bases contributed significantly to efficacy. For instance, similar amounts of medicament of the same degree of fineness showed much greater activity in sheabutter ointments than in either simple or paraffin ointments (Tables III and IV). The present finding corroborates an earlier report (6) that sheabutter ointments containing chloramphenicol, ammoniated mercury, *etc.*, were far more efficacious than simple or paraffin ointments containing the same medicaments.

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