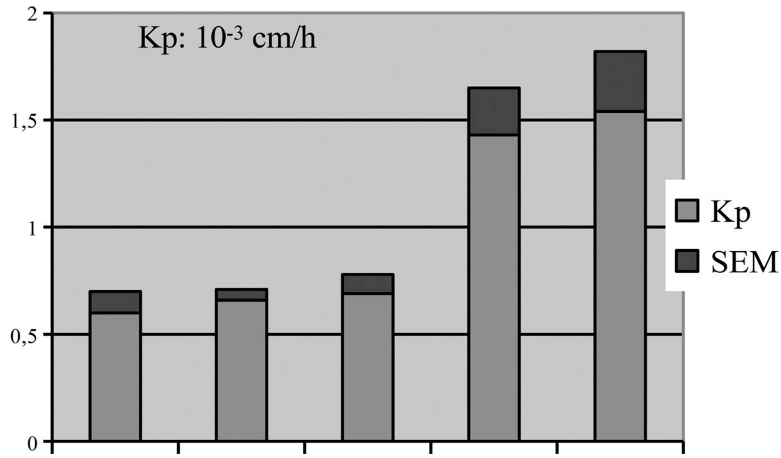

FIGURE 43.2 High-frequency phonophoresis of digoxin. Ultrasound (3.3 kHz, 3W/cm^2) provoked an increase both in transdermal transport and temperature in donor compartment. Similar heating outside the skin with an electrical resistance resulted in similar increase in transdermal transport. (Redrawn from reference 39.)

skin (17) and in isolated epidermal sheets (7), the rise in temperature in the donor compartment was less and cannot explain the 10- to 100-fold increases in percutaneous absorption. Merino et al. (44) reported an increase in temperature of 20°C of mannitol solution exposed to 20 kHz at 15 W/cm^2 for 2 hours. However, only 25% of the transdermal transport enhancement was attributable to this rise in temperature. The same group also studied the migration of a hydrophilic tracer (calcein) by using confocal microscopy and compared with adequate heating control, again showing a greater efficacy of 20 kHz ultrasound than simple heating (45).

43.4.1.2 Heating within the Skin

When an ultrasound wave penetrates through the skin or other structure, it decreases gradually as it propagates. This phenomenon of attenuation is explained by three mechanisms i.e., absorption, reflection, and dispersion, and it depends on the frequency of the wave and the density and heterogeneity of the structure. Part of this ultrasound energy is finally converted into heat. Due to its heterogeneity, the attenuation coefficient of the skin is four times higher than that of other soft tissues (46, 47). It is known that in-depth penetration of ultrasound is inversely proportional to frequency: 50% of energy penetrates up to 10 cm beneath the SC using 90-kHz ultrasound, whereas the same amount of energy only penetrates to 2 cm using 1-MHz ultrasound. In-depth transmission might support vasodilatation of dermal capillaries allowing systemic diffusion. Asano et al. (48) showed an increase of 6°C at 1 W/cm^2 and an increase of 11°C at 2 W/cm^2 by introducing a thermal probe beneath the skin of rats exposed to ultrasound (1 MHz, 1 to 2 W/cm^2, continuous mode). Using a 20-kHz ultrasound probe, the intradermal temperature measured *in vivo* just beneath sonicated skin increases only by a few degrees Celsius during sonication (2, 49).

43.4.2 Cavitation

43.4.2.1 Description

Cavitation is the production of microbubbles in a liquid when a large negative pressure is applied to it. When a medium is exposed to ultrasound, the transmitted waves alternatively compress and stretch its molecular structure. If a sufficiently large negative pressure is applied to the liquid so that the distance between the molecules exceeds the critical molecular distance necessary to hold