**TABLE 43.3**
***In vivo* Studies of High- and Medium-Frequency Phonophoresis in Humans**

| Author and Year (Ref.) | F (kHz) | I (W/cm²) | Mode | Duration (minutes) | Molecule | Number of Patients | Effect |
|---|---|---|---|---|---|---|---|
| Benson 1991 (86) | 3000 | 1 | C | 5 | Nicotinates | 10 | Nonsignificant |
| McElnay 1993 (87) | 3000 | 1 | C | 5 | Nicotinate | 10 | Vasodilatation ×1.7 |
| Benson 1988 (88) | 750–3000 | 1–1.5 | C<br>P | 5 | Prilocaine<br>lignocaine | 11 | Significant increase in duration of anesthesia |
| Benson 1989 (89) | 750–3000 | 1.5 | C | 5 | Benzydamine | 10 | Nonsignificant |
| Williams 1990 (90) | 1100 | 0.25 | C | 5 | Anesthetic drugs | 6 | Nonsignificant |
| Griffin 1967 (91) | 1000 | 0–3 | C | 5 | Hydrocortisone | 102 | Reduced pain (68% vs. 28%) |
| Ciccone 1991 (92) | 1000 | 1.5 | P | 5 | Salicylate | 40 | Nonsignificant |
| Cagnie 2003 (4) | 1000 | 1.5 | C | 5 | Ketoprofen | 10 | ×10 enhancement transport in synovial tissue; however, no enhancement in fat |
| McElnay 1985 (25) | 870 | 2 | P | 5 | lignocaine | 10 | Nonsignificant |
| McElnay 1986 (93) | 870 | 2 | P | 5 | Fluocinolone acetonide | 12 | Nonsignificant |
| Durmus 2014 (94) | 1000 | 1.5 | ? | 10 | Capsaicin plus ultrasound<br>versus capsaicin plus sham ultrasound | 21<br>20 | Significant decrease of pain in the ultrasound group as compared with placebo group |
| Coskun Benlidayi 2018 (95) | 1000 | 1 | C | 5 | Ibuprofen gel plus ultrasound versus ibuprofen cream plus ultrasound | 30<br>31 | Significant decrease of pain in both groups and more pronounced in the gel group |

### 43.3.2 Low-Frequency Sonophoresis

This range of frequency has been investigated more intensively in recent years *in vitro* (Table 43.4), in some animal species *in vivo* (Table 43.5), and in humans (Table 43.6).

#### 43.3.2.1 *In vitro*

Using a 20-kHz ultrasound probe, diffusion of low-molecular-weight molecules across epidermal sheets was increased from 2- to 5000-fold (26). Moreover, the synergistic action of a chemical enhancer such as sodium lauryl sulfate has been shown with low-molecular-weight molecules (27). Although statistically significant, the enhancement ratio remains relatively low in some *in vitro* studies performed on mouse skin (28), especially for hydrophilic drugs (29). A significant increase was also demonstrated using 350-µm-thickness human dermatomed skin, including the epidermis and upper dermis, with enhancement ratios of 4 and 34 for caffeine and fentanyl, respectively, during sonication, and the lag time was shortened (30). Moreover, by using 20-kHz ultrasound, it was shown that large molecules such as poly l-lysine (51 kDa) could be delivered through human heat-stripped skin with an exponential enhancement of the drug transport with ultrasound exposure time (31).