

depends on the density of the propagation medium (ρ), the total pressure (p) equal to the sum of the atmospheric pressure, and the pressure created by the ultrasonic wave: $E = p^2 / \rho c^2$. The intensity usually used in sonophoresis ranges from 0.5 to 2 W/cm², and the increase in pressure is approximately 0.2 bar, with an intensity of 1 W/cm² in water (18).

43.3 ULTRASOUND-ENHANCED PERCUTANEOUS ABSORPTION: PHARMACOKINETIC DATA

43.3.1 MEDIUM- AND HIGH-FREQUENCY PHONOPHORESIS

43.3.1.1 *In vitro* Studies

In vitro studies have been performed in the last three decades to quantify the increase in cutaneous permeability induced by ultrasound (Table 43.1). Differences between studies are related to ultrasound conditions (frequency, continuous or pulse mode, duration, intensity), monitoring (or not) of

TABLE 43.1

***In vitro* Studies of High- and Medium-Frequency Phonophoresis across Rat, Mice, or Human Skin (list is not limitative)**

Author and Year (Ref.)	F (kHz)	I (W/cm ²)	Mode	Duration (minutes)	Molecule	Membrane	Effect
Vyas 1995 (81)	20000	3	P	15	Diclofenac	Mice skin	×2–30 enhancement
Machet 1996 (39)	3300	3	C	10	Digoxin	Hairless mice skin	Flux ×3, but heating resulted in the same effect
Meidan 1998 (20)	3300 1100	2.25	C	240	Hydrocortisone	Rat skin	×2.2 enhancement ×1.8
Meidan 1998 (74)	1100	2	C	5	Sucrose Mannitol Hydrocortisone	Rat skin	×4.5 enhancement ×4.1 ×7.7
Pelucio-Lopes 1993 (40)	1100	1.5	C	20	Azidothymidine	Human skin	Flux ×1 with a cooling coil
Hikima 1998 (21)	1100	4.3	C	10–30	Prednisolone	Hairless mouse skin	×2–5
Machet 1998 (41)	1100	1.5	C	20	Mannitol Estradiol Hydrocortisone	Hairless mice skin Human skin	Flux ×1 with a cooling coil Flux × 1 with a cooling coil
Brucks 1989 (38)	1000	1	C	240	Ibuprofen	Human epidermis	×3 enhancement
Mitragotri 1995 (22)	1000	2	C	300	7 molecules	Human epidermis	Flux ×13 estradiol, ×5 testosterone, ×4 cortisol, ×1.5 butanol, ×1.2 caffeine.
Johnson 1996 (23)	1000	1.4	C	1440	4 molecules with chemical enhancer	Human epidermis	Flux ×1 and ×75
Mitragotri 2001 (24)	1000	2	C	300	5 molecules	Human stratum corneum	×2–15 enhancement
Liao 2016 (82)	1000	2	P	5	Diclofenac	Rat skin	×1.1 enhancement ×1.3 enhancement with microbubbles