depends on the surface charge of the skin. Generally, at pH higher than isoelectric point of the skin (pI), the skin is known to carry a net negative charge and the direction of electro-osmosis is from anode to cathode (Vanbever et al., 1998a). The relative contribution of electro-osmosis compared to electrokinesis is many-fold lesser. However, in the case of neutral molecules and molecules with a low charge to mass ratio, electro-osmosis would be the predominant mode of drug transport during pulse application.

45.4 FACTORS AFFECTING DRUG DELIVERY BY ELECTROPORATION

Several factors such as electrical parameters, physicochemical properties of the drug, and formulation factors are known to affect drug delivery during electroporation (Denet et al., 2004; Singhal and Kalia, 2017).

45.4.1 Electrical Protocol

The electrical parameters include pulse waveform, voltage, pulse duration, pulse rate, and electrode polarity and design.

45.4.1.1 Pulse Waveform

Generally, explored waveforms include exponentially decaying pulses and square wave pulses. In exponential decay pulse, the set voltage decays over some time with a long voltage–time profile. The advantage of decaying pulses would be the ability to maintain long-lasting skin permeabilization, thereby promoting electrophoretic mobility. There are varied reports regarding the superiority of the type of waveform in terms of drug delivery efficiency (Denet et al., 2004; Vanbever et al., 1996a). *In vivo* studies have indicated that a square waveform is known to be more tolerant, as it did not induce any inflammation or necrosis (Dujardin et al., 2002).

45.4.1.2 Pulse Voltage, Pulse Duration, Pulse Number, and Pulse Rate

The drug transport across the skin can be controlled by monitoring the pulse voltage, pulse duration, pulse number, and pulse rate. A typical voltage applied during electroporation would usually range between 50 and150 V, although higher voltages have been employed during *in vitro* studies (Banga and Prausnitz, 1998). Generally, the drug transport across the skin is known to increase with increasing the pulse voltage, but less sharply at high pulse voltages.

For instance, the amount of terazosin hydrochloride delivered across rat skin was found to increase linearly with an increase in the voltage applied during electroporation (Sharma et al., 2000). Likewise, the flux usually increases linearly with an increase in pulse duration and pulse numbers. Similarly, an increase in the pulse length was found to increase the driving force required to transport the molecule across the skin (Weaver and Chizmadzhev,1996). Moreover, the pulse rate increases the transdermal delivery too. In addition, the onset time is reduced with an increase in pulse duration and rate. Studies in the past have indicated that a short duration (sub-μsec pulses) usually produced a high density of smaller pores, while longer pulses resulted in less dense, larger pores in the stratum corneum. The application of shorter pulses using large-area electrodes was found to be a safer option than larger pulses using small area electrodes. The amount of terazosin hydrochloride transported across the skin was found to increase linearly with pulse length and the number of pulses (Sharma et al., 2000).

The transdermal flux of calcein, a model fluorescent marker, was found to be a function of pulse length, pulse rate, electrode polarity, waveform, and total pulsing time (Prausnitz et al., 1993). It was observed that the transport number of the marker that ranged between 10^{-5} and 10^{-2} was found to depend on the voltage applied, while independent of pulse length, pulse rate, or waveform. Electroporation studies in the past have revealed that few low-voltages, long-duration pulses (50V, 200ms) were found to be more efficient to deliver the drug across the skin than many high-voltage, short-duration pulses (Vanbever et al., 1996a). However, long-duration pulses tend to cause significant local heating within the skin that could result in potential skin irritation.