Prospects of iontophoresis in cardiovascular drug delivery

ABSTRACT

Clinical benefits, industry interest, regulatory precedence, and strong market potential have made transdermal research the fastest growth area in drug delivery. As most drugs permeate poorly through skin, a major challenge is achieving the therapeutic level by enhancement of permeation rate. Iontophoresis, utilizing a minimal amount of current, is found to affect the skin permeation process drastically. Ideally suited for protein drugs, attempts have been made to utilize the technology for accelerating the low-molecular-weight drugs for chronic administration. However, because of the difficulty associated with the energy supply, commercialization was not feasible until recent times. Fortunately, the unprecedented growth of microelectronics has bridged this lacuna and brought the technology right into limelight. This article analyses the advantages of electrically assisted drug delivery in relation to passive permeation, with special reference to some cardiovascular drugs, for which there is already a demand in the market.

Key words: Cardiovascular, flux, iontophoresis, passive permeation, transdermal

Introduction

Worldwide, the pharmaceutical industry is facing multiple challenges. The ever-changing safety regulations related to the drug use demands the development of dosage forms, which would be able to deliver drugs at specific sites, preferably through non-invasive routes in a rate-controlled manner. The biotechnologically produced protein drugs also need parallel delivery devices because of their inherent instability in gastrointestinal tract. Presently, the pharmaceutical research is focused on the development of improved delivery routes for the existing drugs. In this context, dermal delivery has generated a lot of interest. In the last decade, 40% of the drug delivery candidates under clinical evaluation in United States belonged to the transdermal category.[1] However, the route was thought to be of questionable worth for the hydrophilic drugs, as they resulted in inadequate skin permeation.[2] The outermost skin layer, a thin matrix of dehydrated dead keratinocytes (10-15 μm), is designed by nature to minimize the trans-epidermal water loss. Only small molecules, neutral and lipophilic, can pass through them in limited quantity.[3] The permeants experience high resistive force while traversing the complicated lipophilic–hydrophilic serial pathways of the skin. For most of the molecules, the skin resistance is too high to be overcome by the concentration gradient, which is the driving force of passive permeation. Enhancer molecules can increase the permeation rate, but are prone to cause irreversible skin damage and irritation.[4] Physical propulsion of the drug molecules into the deeper layers of the skin was thought to be a safer alternative.

The first reports of iontophoresis had appeared in the turn of the century when Leduc demonstrated the technique by delivering strychnine and cyanide into rabbits in 1908.[5] But reports of burns and skin damages associated with the use of electric current created dubious repercussions about the utility of the process for routine administration of drugs.[6,7] The interest was revived only after some 60 years by the pioneering work of a group of researchers who had shown that drug permeation could be safe and successfully enhanced by using low-intensity controlled current, bringing the electrically assisted drug delivery back into the
limelight. Against intravenous infusions, current-induced controlled delivery is projected to have higher patient compliance, as it is associated with minimum of histological damage and spares the recipient of psychological trauma of needle.

Last two decades have seen biotechnologically produced proteins, added to the repertoire of drugs, which due to their macromolecular nature are unstable and unable to pass the gastro-intestinal barrier. But, the problem looked less complicated when it was discovered that they could slip through the aqua-filled pores when repelled by an electric force. Data obtained from the studies of smaller molecules also projected iontophoresis, an electrically driven delivery device, as a promising tool for route of non-invasive drug administration. Lidocaine has already reached the US market as an iontophoretic patch. Needing an additional energy source, the iontophoretic devices are bound to be expensive compared to the passive patches. Hence, to be commercially viable, iontophoretic delivery must have certain advantages over their passive counter parts. Analysis is normally done on this aspect before selecting a candidate for the iontophoretic system development.

The pharmaceutical journals are an abundant reservoir of both simple and iontophoretic studies. But, fewer attempts have been undertaken to compare and evaluate the data obtained from the processes. In this review, we attempt to examine and analyze the prospects of iontophoretic research as well as potential benefits of the technique above and over that of passive permeation, with special reference to cardiovascular drugs.

Basic features of iontophoresis
An iontophoretic device needs an energy source in addition to the conventional drug reservoir. The source once activated generates the energy in programmed and controlled manner. Since the patches are to be worn on the body, the battery that provides current should be small, convenient to wear, and inexpensive, making the challenge formidable for the system developers. Fortunately, giant leaps in microelectronics have bridged that gap and made the theoretical approach a practicability. The technique works by principle of electrostatic repulsion of charges; hence, to be of use, the drug must be in the ionic form. Electric current creates a potential gradient across the skin tissue and from the drug reservoir placed below the active electrode, charged drug gets repelled. Positive ions were delivered by anode and negative ions by cathode [Figure 1]. The process is particularly beneficial for the drugs which produce positively charged ions. Skin has a net negative charge at physiological pH and cations cross the skin barrier better than the anions. For anions belonging to the molecular range of 35 - 500 Dalton, iontophoretic flux decreases with increasing molecular size. Since the permeability of stratum corneum in the presence of electric current is altered, uncharged water-soluble molecules can also permeate the skin by electro-osmosis. As carriers of electricity, hydrophilic drug that ionizes at physiological pH gets priority. These drugs permeate through the water-filled natural pores of the skin that takes them to the root of the pores, from where systemic uptake is very rapid. Since the

Commercially available passive patches carry small molecules and have evaded the interest of the iontophoretic researchers so far. The above molecules by virtue of their low molecular weight and good lipophilicity can permeate through the lipophilic skin matrix at an adequate rate without the assistance of active energy supply. The follicular area of the skin is only 0.1%, and small molecules can utilize both unbroken skin as well as the shunt pathway of the follicular route. Here, the use of electrolysis can result in no or minimal benefit. In iontophoresis, the follicular route because of its aqueous environment is predominantly utilized, though there is a nominal contribution from the passive flux too. Hence, the high-molecular-weight drug that cannot accommodate into the narrow slits of the unbroken skin gets a decided advantage in the iontophoretic process. In electrically repelled drug delivery, the total permeation is the sum of iontophoresis, electro-osmosis, and passive flux; the electrostatic repulsion being the predominant one. Moreover, for the biotechnologically produced peptide drugs, iontophoresis seems to be the ideal route for non-invasive, rate controlled, and reproducible drug delivery.

Approaches of iontophoretic research
Iontophoretic system development is a multidisciplinary research activity and can be broadly classified into several areas. While the energy supply device is a specialized microelectronic research zone, formulation development needs to address certain key issues; the pathways of cutaneous penetration be characterized, rate limiting steps in transdermal absorption be identified; the specific drug structure-penetration relation be understood; and the
Optimization of the iontophoretic delivery needs...
standardization of various parameters, the condition of the skin, the formulation excipients, but the most important and investigated area is the mode and duration of energy supply. Mode of energy supply influences the flux and hence investigation is carried out for the desired current density as well as the pattern of energy supply. Switching iontophoresis, i.e., switching of the polarity of electrodes on transdermal absorption was one of the approaches adopted. It was seen that verapamil permeation was greater at certain switching interval and permeability coefficient and cumulative amount both improved significantly. Increasing the current density usually increases mass transport, but a limiting value of 0.5 mA/cm² is thought to be safe and satisfactory in most of the cases.

For the formulation parameters, optimization is usually done with ionic strength, pH, buffer types, special adjuvants, and the membranes incorporated in the formulation. In case of captopril, iontophoretic flux was significantly affected by factors like pH, ionic strength, drug concentration, etc. Use

Table 1: Transdermal permeation data of certain cardiovascular agents by passive and iontophoresis

| Drugs         | Study type (Skin used) | Passive permeation | Iontophoresis |
|---------------|------------------------|---------------------|---------------|
|               |                        | Donor solution/ system | Flux/plasma concentration | Donor solution/ system | Flux/plasma concentration |
| Metoprolol Tartrate<sup>28</sup> | In vivo (microporous membrane) | 1.7 mmol/g loaded in ion-exchange fiber | 54.3 ± 4.10 (µg/cm²/h) | In vivo (microporous membrane-using 0.1mA/cm²) | 97.6 ± 5.10 (µg/cm²/h) |
| Propranolol Hydrochloride<sup>29,30</sup> | In vivo (Human) | 50 mg/ml solution in cation-anion exchange fibers | 0.26 ± 0.07 (µg/cm²/h) | In vivo (Human-0.5mA/cm²) | 50 mg/ml solution in cation-anion exchange fibers | 43 ± 7.00 (µg/cm²/h) |
| Nadolol<sup>29</sup> | In vivo (Human) | 16.27 mg/ml aqueous solution | 107.71 (µg/cm²/h) | In vivo (Human-0.5mA/cm²) | 5% (m/v=50 mg/ml) solution in cation-anion exchange fibers | 49 ± 7.00 (µg/cm²/h) |
| Timolol maleate<sup>21,32</sup> | In vivo (Human-stratum corneum) | 40 mg/ml solution | 3 ± 2 (µg/cm²/h) | In vivo (Human stratum corneum - 0.5 mA/cm²) | 40 mg/ml solution | 240 ± 49 (µg/cm²/h) |
| Captopril<sup>33</sup> | In vivo and In vivo (Rat) | Hydrogel | No captopril detected | In vivo and In vivo (Rat) | Hydrogel | 0.9 µg/ml in plasma after 1h |
| Atenolol<sup>30,31</sup> | In vivo (Mice) | 22.90 mg/ml in methanolic solution | 76.57 (µg/cm²/h) | In vivo (Human stratum corneum -0.25 mA/cm²) | 40 mg/ml | 54.45 (µg/cm²/h) |

Table 2: Comparison of the iontophoretic flux with physicochemical parameters of certain cardiovascular agents

| Drug                  | Molecular weight | Solubility (Temp) | Log P* | Effect of iontophoresis on drug flux |
|-----------------------|------------------|-------------------|--------|-------------------------------------|
| Propranolol hydrochloride | 295.8            | 104.2 mg/ml (37°C)<sup>34</sup> | 3.56   | Significant enhancement (170 folds) in in vivo permeation |
| Captopril             | 217.3            | >100 mg/ml (25°C) | 1.02*** | Detectable plasma level of the drug by iontophoresis in contrast to no permeation in passive diffusion |
| Timolol maleate       | 432.5            | >33.3 mg/ml (25°C) | 1.91   | 80 folds enhancement in permeation |
| Metoprolol tartrate   | 684.8            | >1000 mg/ml (25°C) | 1.88   | A moderate enhancement of 1.8 folds |
| Atenolol              | 266.3            | 31.2 mg/ml (37°C)<sup>34</sup> | 0.16   | Widely fluctuating permeation profile |
| Nadolol               | 309.4            | 46 mg/ml ** (37°C) | 0.71   | A drastic 1225 times rise in the permeation rate was noted. |

*Partition Coefficient of free bases in octanol: water system, **Solubility determined in 50% aqueous Polyethylene glycol 400, ***Calculated value
of special adjuvants like ion exchange resins in the device is also found to be beneficial.\[26\] In certain cases, transdermal permeation shows stereo-selectivity. Certain researchers have tried to optimize the permeation by investigating this approach.\[30\] Manipulation of the association state and formation of the charged analogues may turn out to be a useful approach to enhance the iontophoretic delivery. Formation of the insulin analogues with extra negative charges had shown beneficial results in terms of 50 to 100 times flux enhancement.\[32\]

Skin hydration was found to be an important parameter that can enhance the permeation rate. Similarly, extracting the skin lipids by treatment with alcohol can facilitate the delivery. So, efforts are also on to optimize the permeation rate by this basal treatment.\[31\] Use of permeation enhancers in the donor vehicle to enhance the iontophoretic flux is another approach investigated by some researchers.\[33\] As electroporation and iontophoresis both have same common denominator of electro-repulsion, attempt is also being taken to enhance iontophoretic flux by decreasing the skin impedance by an initial electroporation.\[34\]

**Conclusion**

Drug delivery is not the only area where iontophoresis is thought to be of practical use. It has already found use in the diagnostic area. Reverse iontophoresis is used in the non-invasive monitoring of the glucose level for diabetics.\[29\] It is getting investigated for the development of a diagnostic test for the determination of phenylketonuria, a potentially fatal metabolic disease in infants.\[35\] The technique is also useful for assessing vascular functions.\[36\] Though the opponents of iontophoresis argue that electroporation can be a better substitute for active drug delivery rather than iontophoresis, the technique fares better in terms of both safety and efficacy. It also shows more promise than the micro-conduit technology, which uses the targeted impact of high-energy micro-particles on specified areas on skin surface to create pores for non-invasive sampling of analyte as well as drug administration.\[37\] The electroporation technique requiring much higher voltage, i.e., 100-1000V, can give rise to hazardous side effects and is likely to be a component of specialized healthcare zone, while the hi-tech micro-conduits technology is still in its infancy. On the other hand, iontophoretic systems involving low level of electricity can be constructed with a 9-volt button cell and can be easily commercialized. Cardiovascular agents because of their demand for chronic administration have already had an assured market for transdermal products. The advanced state of research in this field indicates that iontophoretic administration of such drugs is likely to be a reality in the near future.

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