ASIAN JOURNAL OF BIOMEDICAL & PHARMACEUTICAL SCIENCES

e-ISSN: 2249-622X

REVIEW

Iontophoresis: A Functional Approach for Enhancement of Transdermal Drug Delivery

Prabhakar Panzade*[1], Prashant Puranik[2]

[1]Shri Bhagwan College of Pharmacy, CIDCO, N-6, Aurangabad - 431003 (MS) India

[2] Government College of Pharmacy, Vedant Road, Osmanpura, Aurangabad - 431005 (MS) India

Article Details
Received:
29th July 2012
Received in revised form:
18th Aug 2012
Accepted:
20th Aug 2012
Available online
10th Sept 2012

OPEN ACCESS

Online ISSN 2249–622X
http://www.jbiopharm.com

ABSTRACT

The skin has been used as a port for systemic delivery of therapeutic agents since several decades. The composition of stratum corneum renders it a daunting barrier to the topical and transdermal administration of therapeutic agents. The number of drug molecules for transdermal delivery is limited owing to the physicochemical restrictions. Iontophoresis is an effective technique for physically facilitating transport of solutes across skin for both local and systemic effects. The principle distinguishing feature is the control afforded by iontophoresis and the dose can also be titrated for individual patients by adjusting current. It is believed to be future method of choice for the systemic delivery of protein and peptide drugs which normally can only be delivered by parenteral therapy. This review describes the mechanism of iontophoretic permeation enhancement, how to select drug, formulation and defining dose in iontophoresis. The effect of permeation enhancers on iontophoretic flux of drugs has also been described. Present review also provides an insight into applications of iontophoresis, challenges in delivery and future prospect for the iontophoresis. The technique has been observed to enhance the transdermal permeation of ionic drugs several folds.

Keywords: Iontophoresis, non-invasive, stratum corneum, electrically assisted delivery, permeation enhancer.

INTRODUCTION

The skin is the largest organ of the human body, with surface area of about 2 m^2. Historically, the skin was viewed as an impermeable barrier but in recent years, it has been increasingly recognized that intact skin can be used as a port for topical or continuous systemic administration of drugs. [1] For drugs which have short half-lives, a transdermal route provides a continuous mode of administration, somewhat similar to that provided by an intravenous infusion. However, unlike an intravenous infusion, delivery is non-invasive and no hospitalization is required. A rationale to explore this route exist only for drugs that are subjected to an extensive first pass metabolism when given orally or those that must be taken several times per day. Even then, only potent drugs can be administered through this route since there are economic and cosmetic reasons to not exceed the patch size beyond a certain limit. [2]

Iontophoresis

The stratum corneum is the principle barrier for absorption of drugs through the skin and restricts the permeation of hydrophilic, high molecular weight and charged compounds into the systemic circulation. However many therapeutically active drug molecules are hydrophilic and possess high molecular weights for example, peptides. [3]

Iontophoresis simply defined as the use of small amounts of physiologically acceptable electric current to drive ionic (charged) drugs into the body. [4-5] It is non-invasive technique which uses mild electric current to enhance and facilitate transdermal delivery of variety of drugs. [6] The drug is driven into the skin by electrostatic repulsion [7], by using the electrode of same polarity as the charge on the drug. Besides the benefits of bypassing the hepatic first pass metabolism and better patient compliance, it has some additional advantages as, delivery of ionized and

*Corresponding author: Panzade Prabhakar S. |Shri Bhagwan College of Pharmacy, N-6, CIDCO, Aurangabad – 431003, (MS) India. | E-mail – prabhakarpanzade@gmail.com|Mobile No. +919028446534

unionized drugs, enabling continuous or pulsatile delivery of drug, permitting easier termination of drug delivery, restoration of the skin barrier function without producing severe skin irritation, improving the delivery of polar molecules as well as high molecular weight compounds, ability to be used for systemic delivery or local (topical) delivery of drugs, offering better control over amount of drug delivered and reducing considerably inter-individual and intra-individual variability since the rate of drug delivery is more dependent on applied current than on stratum corneum characteristics. Thus, because of many advantages associated with this system, it has been area of growing interest in the local and systemic delivery of many drugs.

The iontophoretic technique is based on the principle of electrostatic repulsion "like charges repel and opposite charges attract each other". The drugs cross the skin barrier by simple electronic repulsion of like charges. Thus, anionic drugs can cross the skin by using a negatively charged working electrode. Similarly, cationic drugs enter the skin more effectively when a positively charged electrode is used. While delivering anionic drug across biological membrane, it is placed between the negative electrode (cathode), and the skin. The drug ion is then attracted through the skin towards the positive electrode (anode) by the electromotive force provided by the cell. In case of cationic drug, the electrode polarities are opposite. The mechanism of iontophoresis is shown in Figure 1.

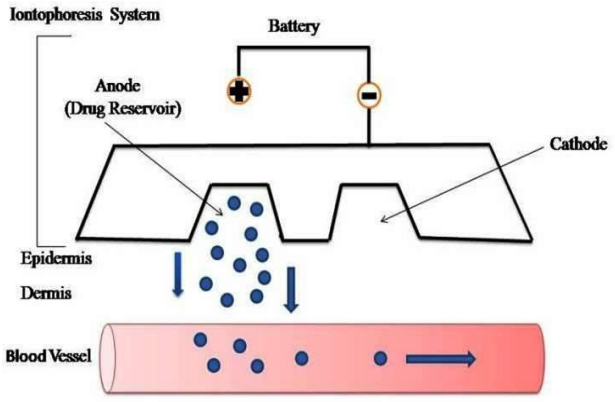

Figure 1. Mechanism of iontophoretic drug delivery

Once the drug has passed through the stratum corneum, it reaches to its site of action by rapidly going into the circulation. The electric circuit is completed by the movement of endogenous counter ions from within the skin. *In vitro* iontophoretic studies conducted on peptides have shown an increase in the passive permeability of skin post iontophoresis. This shows that the alteration of the skin barrier function due to current passage *in vitro* is one of the mechanisms for enhanced permeability following iontophoresis. [8]

Neutral molecules have been observed to move by convective flow as a result of electro-osmotic and osmotic forces on application of electric current. [9] Electro osmosis is the bulk flow of fluid occurring in the same direction as the flow of counter ions when a voltage difference is applied across a charged, porous membrane. This flow involves motion of fluid without concentration gradient and is a significant factor affecting iontophoresis. At physiological pH, human skin has a slight negative charge and counter ions are usually cations. Therefore, flow occurs from anode to cathode electroosmotically, thus enhancing the flux of cationic drugs.

Although normal iontophoresis is done with the help of continuous DC current, pulsed waveform of DC has also been used, which has been able to produce significant and rapid delivery of drugs e.g., penetration of thyrotrophic releasing hormone (TRH) was significantly increased when given by pulsed form than by continuous current. [10-12] A pulsed waveform allows the skin to depolarize and return to its initial state before the onset of next pulse. This is because stratum corneum acts as a capacitor and this polarization may reduce the magnitude of current applied as the constant current. Also pulsed waveform prevents the skin from developing polarization potential which reduces the efficiency of iontophoresis. Unlike pulsed waveform direct current develops permanent polarization leading to decrease in efficiency of iontophoresis. Moreover, pulsed current has been found to be less damaging to the skin, so that patient can tolerate higher levels of current if pulsed DC at high frequency is used. [13-15]

Iontophoretic devices

Iontophoresis devices are generally designed to deliver small amounts of therapeutically active materials for a given time. The device is generally operated at a constant voltage so that the current can be varied, depending upon the resistance of the skin being treated. This reduces the chances of electric shocks thus increasing patient compliance and acceptability. [16-17]

The salient features for an iontophoretic device include safety, convenience, reliability, cost and portability. Iontophoretic devices may be of the disposable or reusable type. In reusable system, the drug may be contained in a hydrogel pad, which can be replaced as required. For disposable systems, perhaps microprocessors can be removed and transferred to another patch to keep cost low. Some iontophoretic devices are listed in TABLE I. [18-21]

Sr.No.	Iontophoretic System	Manufacturers	Active pharmaceutical ingredient	Application
1	Lidosite®	Vysteris Inc.	Lidocaine	Anaesthetic
2	Iomed Phoresor® II	Iomed Inc.	botulinum	hyperhidrosis
3	E-Trans, Activa Tek	Activa Tek Inc.	Fentanyl HCl (Ionsys)	Postoperative pain management
4	Phoresor®	Iomed Inc.	Lidocaine and epinephrine (Iontocaine)	local dermal anesthesia
5	Ocuphor™	Iomed Inc.	---	Retinal diseases
6	Dupel®	Empi Inc.	---	Home, sports medicine and clinical settings.

TABLE 1.Some Iontophoretic Devices

Drug delivery pathways in iontophoresis

Skin appendages which include sweat glands and hair follicles are considered to be major pathways of drug transport during iontophoresis. [22] During iontophoresis, the greatest concentration of ionized species is expected to move into some regions of the skin where there is damage, or along the sweat glands and hair follicles, as the diffusional resistance of the skin to permeation is lowest in these regions. Thus, pore pathway is generally assumed for iontophoretic delivery.

A non appendageal pore pathway has also been suggested recently [23-24] which probably implies the current flow through "artificial shunts" as a result of temporary disruption of the organized structure of stratum corneum. A potential-dependent pore formation in the stratum corneum has been reported and is also attributed to the flip-flop movements in polypeptide helices.

Intercellular or transepidermal transport may also occur concurrently with follicular transport but the contribution of this flux to the total is likely to be small. [25]

The skin is believed to be a cation selective membrane facilitating the transport of positively charged ions. The negative charge on the skin is as a result of greater number of protein amino acid residues carrying negative charges (e.g. carboxylic groups) as opposed to positive charges (e.g. amine moieties). The permselectivity of the skin induces a net volume flow during iontophoresis, and this induced volume flow during iontophoresis is in the direction of positive ion transport supporting the belief of cation selectivity of skin. [26]

Iontophoresis and chemical enhancers

Chemical enhancers:

The use of chemical penetration enhancers is one of the more widely techniques for increasing transdermal drug transport. Many different chemicals are able to modify the penetration enhancing characteristics of different drugs into the skin but actually few have been incorporated into marketed products due to safety concerns. Their mechanisms of enhancement may be increase in permeability of stratum corneum by acting as solvents to dissolve the skin lipids or to denature the skin proteins. Some enhancers can modify drug solubility parameters in the vehicle or in the skin to increase the drug penetration. In addition, these compounds will affect the partitioning of the drug from the applied formulation. [27]

An ideal enhancer must be nontoxic, nonirritating, non-allergenic, pharmaceutically inert and compatible with most drugs and excipients. Azone and oxazolidinedione are considered to be among the most promising enhancers. However, no single agent meets all the desirable attributes of an enhancer. A combination of enhancers may thus be required.

For most chemical enhancers, the strength of activity depends on their concentration. Toxicity of enhancers may limit their use in transdermal formulation. There are evidences of showing synergistic effects between the chemical enhancers and iontophoresis. e.g. buspirone hydrochloride [28] atenolol [29], nicorandil [30], nicardipine. [31] In addition, one can reduce the concentration of individual enhancers required to achieve

the desired enhancement by combining two or more enhancers within the same formulation.

Iontophoresis in combination with chemical enhancers:

Although the use of iontophoresis results in much higher drug delivery if compared with conventional passive delivery, it still has limitations as a technique. Chemical enhancers can be given in combination with iontophoresis to achieve even higher drug penetration. [32] It not only increases transdermal transport, a combination of chemical enhancers and iontophoresis also reduce the side effects such as irritation caused by high concentration of enhancers or stronger electric forces. The combined effects of enhancers and iontophoresis depend on the physicochemical properties of the penetrant, enhancer and their behavior under the influence of an electric field. [33] Thus, use of iontophoresis and enhancers may results in increase or decrease in flux depending on the drug.

Drug selection in iontophoresis:

The drug candidates should be storable in liquid or dry form in the patch and should be stable. It should be soluble in aqueous media and be charged. The isoelectric point should be in the range of smaller than 4 or greater than 7.4. The iontophoretic device should deliver the drug in following manner

20-50 mg drug/day of molecular weight of 300 Da, 2-5 mg drug/day of molecular weight of 1000 Da and 100 µg drug/day of molecular weight of 5000 Da. [34]

Formulation in iontophoresis:

There may be difference in amount of drug loaded in device and amount actually crossed the skin. The amount that device can accommodate depends on device and technology while the amount that traverses the skin depends on formulation and drug. The charged drug should be selected. It is possible to transport neutral molecules with electro-osmosis and iontophoresis. The charged molecules have two forces acting on it, electrorepulsion and electro-osmosis which helps drug to pass into the skin.

Generally, aqueous or gel formulation suited for iontophoresis. The gel is suitable formulation as is matches with the contours of skin and stable. Gels also have other advantages over liquids, such ease of fabrication into the device, suitability with the electrode design, doformability into skin contours, better occlusion, and better stability. Moreover, high proportion of water employed in gel formulation can provide electroconductive base for clinical use. [35-36]

How to define dose in iontophoresis:

For iontophoresis the dosage is measured in milliamp-minutes because it is based on the current and that is the type of dosage. An iontophoresis treatment is set to deliver a current (For e.g. 2 mA) and patient is treated for short period of time (For e.g. 10 min session or 20 mA min dosage). Typically, solutions that are placed on electrode are about 1.5 mL in volume and range in concentration from 2-5%. The administration can be continuous or bolus using microprocessor and appropriate circuitry. As current controls the amount of drug delivered, administration can be programmed to provide the bolus dose immediately and then a slow maintenance dose over a period of time.

Challenges in delivery:

The main goals in iontophoresis that should be met are delivery of appropriate dose throughout the dosing interval, ensure system is safe, adhere effectively and is not irritating. The third objective is to develop a product that is elegant, cost effective and acceptable by patients. Proper planning is required to achieve these objectives. Sometimes, there is pH change across skin layers and the charge on molecule of interest changes as it travels through the skin and as a result drug may not traverse the skin. Extensive preformulation is required to understand the physical and chemical characteristics of the drugs. [37]

The cost of the device could be reduced by using the reusable type of systems in which hydrogel pad can be replaced with other. Also microprocessor from disposable device can be used for another system to keep the cost low.

APPLICATIONS

Hyperhidrosis:

Hyperhidrosis is a fairly common disorder and socially uncomfortable. [38] Iontophoresis is most widely used in the treatment of plantar and palmar hyperhidrosis. In this treatment affected region is placed in the tap water and the current passed at strength just below the threshold for discomfort, for approximately half an hour. The procedure is believed to be safe and effective. [39]

Diagnosis of cystic fibrosis:

Iontophoresis devices have also been used in the diagnosis of cystic fibrosis. Iontophoresis devices are prescription devices approved for the diagnosis of cystic fibrosis by iontophoresis of pilocarpine. Pilocarpine has a stimulatory effect on the eccrine secretion, the chloride content of which is used to assist in the diagnosis of cystic fibrosis. The technique is now universally accepted as the safest and least stressful way to stimulate the sweat. The use of pilocarpine iontophoresis to diagnose cystic fibrosis has been approved by FDA and is commonly used by pediatricians. [40]

Anaesthesia:

Local anesthesia is often required in conditions like superficial wound excisions, local skin biopsies, eyelid surgery, abscess incision, or in patients who are averse to the use of hypodermic needles. The disadvantages of injecting a local anesthetic include pain, distortion of tissue, potential systemic absorption. The usefulness of

iontophoresis to achieve local anesthesia has been well documented. The advantages of iontophoresis induced anesthesia include no tissue distortion, adequate local and little systemic concentrations of the drug and the procedure is painless. Based on a controlled study employing lidocaine, Gangarosa reported that skin anesthesia was best obtained with solutions containing 1% and 4% lidocaine with addition of epinephrine prolonged the duration of anesthesia. [41]

Facilitation of underlying deep tissue penetration of compounds:

The use of iontophoresis to facilitate underlying deep tissue penetration of drugs after topical application will be most beneficial in the treatment of osteoarthritis, soft-tissue rheumatism, tendonitis and other deep rooted local inflammatory conditions associated with sports injuries or other minor accidental injuries. Glass *et al* have demonstrated the penetration of dexamethasone in tissues below the applied site in monkeys. [42] The drug was observed at sufficient tissue depths including tendinous structures and cartilaginous tissue. Iontophoresis of water soluble glucocorticoids dexamethasone, hydrocortisone and prednisolone up to a depth of 1.25 cm below the applied was also demonstrated by some researcher. [43]

Applications in physical therapy:

Corticosteroids are the primary drugs used with iontophoresis in physical therapy. Corticosteroids are widely used because they possess a profound anti-inflammatory effect and are available in relatively inexpensive forms designed both for oral and topical administration. Several corticosteroids are available as water-soluble salts, rendering the corticosteroid molecule negatively charged and therefore available to move under the influence of a negative current field. Dexamethasone is often administered by iontophoresis, in combination with lidocaine, in the treatment of musculoskeletal disorders. This corticosteroid has frequently been administered from the positive electrode (it presumably is carried through the skin by the elec-troosmotic effect, because it is a negatively charged ion). DeLacerda used dexamethasone (1 mL of 0.4% dexa-methasone mixed with 2 mL of 4% lidocaine in aqueous solution administered from the anode at a dosage of 5mA for 10 minutes) to treat patients with myofascial shoulder girdle syn-drome and found that iontophoresis produced the most rapid improvement in range of motion, compared with treatment with ultrasound or muscle relaxants. He used a current of 5 mA for 15 minutes, applied over trigger points. [44] Other glucocorticoids administered by iontophoresis have been used in the treatment of patients with temporo mandibular trismus and paresthesia and for Peyronie's disease.[45]

Historical Uses in Physical Therapy

Hyaluronidase:

Hyaluronic acid, a gelatinous substance that exists in many body tissues, is a major constituent of the "ground substance" of connective tissue. It restricts diffusion of certain substances through the tissues. Hyaluronidase is an enzyme that hydrolyses hyaluronic acid, reducing its viscosity. [46] Hyaluronidase carries a positive charge and migrates most rapidly at a pH of 5.4. For these reasons, it is applied in 0.1-mol/L solution with an acetate buffer by iontophoresis to an edematouse limb. [47]

Vasodilators:

Two potent vasodilators, histamine and mecholyl (acetyl-beta-methylcholine chloride) have been administered by iontophoresis for a variety of disorders. Kling and Sashin compared the efficacy of these two vasodilators and determined that mecholyl produced less vasodilation. They also used histamine iontophoresis for patients with a number of conditions, particularly arthritis. The authors reported reduced pain and increased range of motion. Because there was no change in joint swelling, it is possible that the improvements noted were largely due to pain modulation. Kling and Sashin also reported improvement in patients with conditions associated with vasospasm, such as Raynaud's disease. [48]

Clinical Applications in Other Disciplines

Dentistry:

Dentistry, probably to an even greater extent than physical therapy, has used iontophoresis. Beginning in the late 19th century, dentists applied local anesthetics to their patients prior to oral surgical procedures. Gangarosa described the use of iontophoresis for three basic applications in dentistry: treatment of hypersensitive dentin (eg. in teeth sensitive to air and cold liquids) using negatively charged fluoride ions; Treatment of oral ulcers (Canker Sores) and herpes orolabialis lesions ("fever blisters") using negatively charged corticosteroids and antiviral drugs, respectively; and The application of local anesthetics to produce profound topical anesthesia, as is done in some physical therapy applications. Gangarosa studied herpes labialis treatment by an antiviral compound the idoxuridine. He concluded that it is extremely effective with reduction of healing time to 3-4 days (normal 9-10 days). There was found to be an immediate loss of discomfort and acceleration of all subsequent stages of the lesion, including coalescence of vesicles, rapid oozing, appearance of a small scab, lack of spread of lesions and rapid healing. Methyl prednisolone sodium succinate used for treatment of lichen planus. [49]

Dermatology:

Earlier, simple ions and heavy metals were most frequently used drugs but later interest has been shifted towards iontophoresis as drug delivery system for wide variety of medications, ranging from steroids to antibiotics to local anaesthetics. [50] Iontophoresis with tap water or anticholinergic compounds has been used for the treatment of patients with hyperhidrosis of the palms, feet, and axillae. Iontophoresis has been used for treatment of various dermatologic conditions *viz.* fungal infections, viral infections, ulcers, aphthous stomatitis, lichen planus and anaesthesia. There are reports of treatment of various miscellaneous conditions like hyperkeratosis with fissuring of palms and soles, vitiligo, scleroderma, lymphedema, patch testing and sweat test. There are reports of successful treatment of dermatophytosis with copper sulfate, [51] herpes simplex with iodoxuridine [52] and plantar warts with sodium salicylate. [53]

Otorhinolaryngology:

Iontophoresis is a preferred method for obtaining anesthesia of the tympanic membrane prior to simple surgical procedures involving that structure. Iontophoresis of zinc has also been used for the treatment of patients with allergic rhinitis.

Ophthalmology:

Iontophoresis has been used experimentally to deliver antibiotics into the eye. The principal disadvantage of this technique is the time required for direct contact of the electrode with the eye. [54]

FUTURE PROSPECT:

There is too much to look forward for iontophoretic drug delivery system. There is enormous opportunity for iontophoresis because many products present in market are very difficult to deliver by passive diffusion. Also the onset of action of such products is very slow as compared to active diffusion and takes considerable time until therapeutic dose is reached. The crucial to the success of iontophoresis is to develop products that are cost effective to the consumer. Circus is exploring the use of nanotechnology in various areas of drug delivery and is capable of delivering technology to transdermal delivery to improve the skin permeation. Future trends for transdermal technology will include delivery of multiple drugs from the same patch and delivery of new chemical entities that will require new adhesives with even broader formulating capabilities. A number of researchers are investigating iontophoresis for gene delivery. Other important near-term applications include neurology, women's health and dermatology.

CONCLUSION:

Iontophoresis is one of the more promising methods to enhance delivery of drugs with poor permeation profile through the skin. Iontophoresis dramatically enhances both the rate of release and extent of penetration of the salt form of the drugs. Without iontophoresis, such charged species are not able to penetrate the skin due to lipophilic nature of the skin. Iontophoresis is gaining wide popularity as it provides non-invasive and convenient means of systemic administration of drugs with poor bioavailability profile, short half life and multiple dosing schedules. Iontophoresis, in comparison to oral route, definitely provides benefits of improved efficacy and reduction in adverse effects. It is believed to be practical alternative to parenteral therapy. The major advantages of iontophoretic drug delivery system are rate of drug input can be controlled and optimized. Thus, iontophoresis may become an important alternative method of drug delivery in the near future.

REFERENCES:

1. Banga AK. Electrically assisted transdermal and topical drug delivery. 1st ed. USA:Taylor and Francis group; 1998.

2. Wang Y, Thakur R, Fan Q, Michniak B. Transdermal iontophoresis: combination strategies to improve transdermal iontophoretic drug delivery. Eur J Pharm Biopharm. 2005; 60: 179–191.

3. Blank IH. Penetration of low molecular weight alcohols into skin. I. Effect of concentration of alcohol and type of vehicle. J Invest Dermatol. 1964; 43: 415–420.

4. Sage BH. Iontophoresis. In: Swarbrick J, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology. 2nd ed. New York: Marcel Dekker; 1993.

5. Singh P, Liu P, Dinh SM. Facilitated transdermal delivery by iontophoresis. In: Bronaugh RL, Maibach HI editors. Percutaneous Absorption, Drugs-Mechanisms-Methodology. New York: Marcel Dekker; 1999.

6. Junginger HE. Iontophoretic Delivery of apomorphine: from *in-vitro* modeling to the Parkinson Patient. Adv Drug Deliv Rev. 2002; 54 Suppl: S57-S75.

7. BW Barry. Drug delivery routes in skin: a novel approach. Adv Drug Deliv Rev. 2002; 54 Suppl: S31–S40.

8. Dixit N, Bali V, Baboota S, Ahuja A, Ali J. Iontophoresis - An Approach for Controlled Drug Delivery: A Review. Curr Drug Del. 2007; 4: 1-10.

9. Green PG, Flanagan M, Shroot B, Guy RH. Iontophoretic Drug Delivery. New York:Marcel Dekker; 1993.

10. Huang YY, Wu SM, Wang CY. Response Surface Method: A Novel Strategy to Optimize Iontophoretic

Transdermal Delivery of Thyrotropin-releasing Hormone. Pharm Res. 1996; 13: 547-552.
11. Makoto K, Toshio I, Kozo T. Evaluation of Skin Barrier Function Using Direct Current II: Effects of Duty Cycle, Waveform, Frequency and Mode. Biol Pharm Bull. 2002; 25(12): 1623-1628.
12. Stefania P, Tiziana P, Massimo G, Fabiola C, Simonetta V, Marco R. Transdermal Delivery of Heparin Using Pulsed Current Iontophoresis. Pharm Res. 2006; 23 (1): 114-120.
13. Clemessy M, Couarraze G, Bevan B, Puisieux F. Preservation of skin permeability during *in vitro* iontophoretic experiments. Int J Pharm. 1994; 101(3): 219-226.
14. Srinivasan V, Higuchi WI. A model for iontophoresis incorporating the effect of convective solvent flow. Int J Pharm. 1990; 60: 133–198.
15. Singh P, Maibach HI. Iontophoresis in drug delivery: basic principles and applications. Crit Rev Ther Drug Carrier Syst. 1994; 11: 161–213.
16. Jain NK. Controlled and Novel Drug Delivery. 1st ed. New Delhi:CBS publishers and distributors; 1997.
17. Singh P, Maibach HI. Iontophoresis: an alternative to the use of carriers in cutaneous drug delivery. Adv Drug Deliv Rev. 1996; 18: 379-394.
18. Kavanagh GM, Oh CS. BOTOX delivery by iontophoresis. Brit J Dermatol. 2004;151: 1093–1095.
19. Alza product literature www.alza.com. (4th Jan. 2012).
20. Iomed product literature http:// www.iomed.com. (4th Jan. 2012).
21. Chaturvedula A, Joshi DP, Anderson C, Morris R L, Sembrowich WL, Banga AK. *In vivo* iontophoretic delivery and pharmacokinetics of salmon calcitonin. Int J Pharm. 2005; 297: 190-206.
22. Chien YW. Transdermal route of peptide and protein drug delivery. New York:Marcel Dekker; 1991.
23. Cullander C, Guy RH. Sites of iontophoretic current flow into the skin: identification and characterization with the vibrating probe electrode. J Invest Dermatol. 1991; 97: 55-64.
24. Cullander C. What are the pathways of iontophoretic current flow through mammalian skin? Adv Drug Deliv Rev. 1992; 9: 119-135.
25. Yoshida NH, Roberts MS. Structure transport relationships in transdermal iontophoresis. Adv Drug Deliv Rev. 1992; 9: 239-264.
26. Pikal MJ, Shah S. Transport mechanisms in iontophoresis III. An experimental study of the contributions of electroosmotic flow and permeability change in transport of low and high molecular weight solutes. Pharm Res. 1990; 7: 222–229.
27. Adrian CW, Brian BW. Penetration Enhancers. Adv Drug Del Rev. 2004; 56: 603-618.
28. Meiden VM, Mohammad A, Michniak BB. Enhanced iontophoretic delivery of buspirone hydrochloride across human skin using chemical enhancers. Int J Pharm. 2003; 264: 73-83.
29. Bhaskaran S, Harsha SN. Effect of permeation enhancer and iontophoresis on permeation of atenolol from transdermal gels. Indian J Pharm Sci. 2000; 6: 424-426.
30. Krishnaiah YSR, Al-Saidan SM, Chandrasekhar DV, Rama B. Effect of Nerodilol and Carvone on in vitro Permeation of Nicorandil Across Rat Epidermal Membrane. Drug Dev Ind Pharm. 2006; 32: 423–435.
31. Krishnaiah YSR, Satyanarayana V, Bhaskar P. Enhanced Percutaneous Permeability of Nicardipine Hydrochloride by Carvone Across the Rat Abdominal Skin. Drug Dev Ind Pharm. 2003; 29 (2): 191-202.
32. Kaoru K, Kazuaki K, Misuzu W, Kiyoshi K, Akiyoshi S, Kentaro K. *In Vivo* Transdermal Delivery of Diclofenac by Ion-Exchange Iontophoresis with Geraniol. Biol Pharm Bull. 2009; 32(4): 684-687.
33. Thomas NS, Panchagnula R. Combination strategies to enhance transdermal permeation of zidovudine (AZT). Pharmazie 2003; 58: 895-898.
34. Green PG. Iontophoretic delivery of peptide drugs. J Control Release.1996; 41: 33–48.
35. Vikram K, Kiran B and Rahul T. Enhancement of Iontophoretic Transport of Diphenhydramine Hydrochloride Thermosensitive Gel by Optimization of pH, Polymer Concentration, Electrode Design and Pulse rate. Pharm Sci Tech. 2007; 8: E1-E6.
36. Stamatialis DF, Rolevink HH, Gironès M, Nymeijer DC, Koops GH. *In vitro* evaluation of a hydroxypropyl cellulose gel system for transdermal delivery of timolol. Curr Drug Deliv. 2004; 1: 313-319.
37. Rios M. Advances in trasnsdermal technologies. Pharm Tech. 2007; 31: 10.
38. Holzle E, Ruzicka T. Treatment of hyperhidrosis by a battery-operated iontophoretic device. Dermatologica. 1986; 172: 41-47.
39. Sloan JB, Soltani K. lontophoresis in dermatology. J Am Acad Dermatol. 1986; 15: 671-84.
40. Webster HL. Laboratory diagnosis of cystic fibrosis. Crit Rev Clin Lab Sci. 1983; 18: 313-338.
41. Gangarosa LP. Defining a practical solution for iontophoretic local anesthesia. Methods Find Exp Clin Pharmacol. 1981; 3: 83-94.
42. Glass JM, Stephen RL, Jacobsen SC. The quantity and distribution of radiolabeled dexa- methasone delivered to tissue by iontophoresis. Int J Dermatol. 1980; 19: 519-525.

43. Murray W, Lavinc LS, Scifter E. The iontophoresis of C_{21} esteritied glucocorticoids: pre- liminary report. J Am Phy Thei Assoc. 1963; 43: 579-581.
44. Kahn J. Iontophoresis and ultrasound for postsurgical temporomandibular trismus and paresthesia. Phys Ther. 1980; 60: 307-308.
45. Rothfield SH and Murray W. The treatment of Peyronie's disease by iontophoresis of esterified glucocorticoids. J Urol. 1967; 97: 874-75.
46. Magistro CM. Hyaluronidase by iontophoresis in the treatment of edema. Phys Ther. 1964; 44: 169-175.
47. Popkin R. The use of hyaluronidase by iontophoresis in the treatment of generalized scleroderma. J Invest Dermatol. 1951; 16: 97-102.
48. Yoshida NH, Roberts MS. Structure transport relationships in transdermal iontophoresis. Adv Drug Deliv Rev. 1992; 9: 239-264.
49. Sachdeva S, Gupta R, Gupta G. Iontophoresis and Dentistry. J Indian Den Asso. 2011; 5: 46-48.
50. Rai R, Srinivas CR. Iontophoresis in dermatology. Indian J Dermatol Venereol Leprol. 2005; 71: 236-241.
51. Jersild O, Plesner N. Treatment of epidermatophytosis in the extremities in the extremities with iontophoresis of copper. Acta Derm Venereol. 1940; 21: 268-279.
52. Gangarosa LP, Merchant HW, Park NH, Hill JM. Iontophoretic application of iodoxuridine for recurrent herpes labialis: Report of preliminary clinical findings. Methods Find Exp Clin Pharmacol. 1979; 105-109.
53. Gordan NH and Weinstein MV. Sodium salicylate iontophoresis in the treatment of plantar warts (a case report). Phys Ther. 1969; 49: 869-870.
54. Costello CT, Jeske AH. Iontophoresis applications in transdermal medication delivery. Phys Ther. 1995; 75: 554-563.

Conflict of Interest: None Declared

