Iontophoresis in Oral Healthcare: Current Evidence and Future Directions

Dr. Mohamed Desouky [1] , Dr. Shabnamjot Kaur[2] , Dr. Ranning Duan[3] , Dr. Aysha Butt [4] , Dr. Monali Patel [5] , Dr. Soumya Joseph [6]

[1] BDS, Cairo, Egypt. mohammednhd@gmail.com
[2] BDS, Punjab, India. jotshabnam290@gmail.com
[3] BDS, Sichuan, China. rannieduan@gmail.com
[4] BDS, Bhopal, India. drayshabutt@gmail.com
[5] BDS, Gujarat, India. monalipatel288@gmail.com
[6] BDS, Kerala, India. soumyajoseph@live.com

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ABSTRACT

Iontophoresis is a physical drug delivery-enhancing technique that was introduced at the beginning of the preceding century. For decades, iontophoresis research was focused on studying delivery-enhancing mechanisms and was limited to a few therapeutic applications. The preparation used in iontophoresis should be soluble in water, of a small voltage, and prone to ionization. More mobility is seen with smaller particles. Iontophoresis could increase the diffusion of drugs into dentin, enamel, and other oral tissues. The chief drugs delivered or studied by iontophoresis in dentistry are non-steroidal anti-inflammatory drugs, local anesthetics, antibacterial drugs, and fluorides. Systemic and local drug administrations are the two basic classifications for drug delivery in the oral cavity. Improved local and systemic medicine administration is made possible by the non-invasive technology known as iontophoresis (IP). Iontophoresis was primarily researched for transbuccal medication administration in the oral cavity. For various drugs, buccal iontophoresis significantly improved drug delivery as compared to passive transport. To treat oral problems locally in the oral cavity, iontophoresis can improve drug penetration into the oral tissues. Iontophoresis has been tested for use in dentistry to cure hypersensitivity and periodontal disease as well as to create local anesthesia.

1. Introduction

Iontophoresis is a non-invasive procedure in which ions penetrate intact skin under the influence of an electric field. This technique uses a small electric current to enhance the delivery of charged molecules through biological tissues. Studies have shown that iontophoresis can be 10 to 2,000 times more effective than conventional passive drug delivery methods[1]. Etymologically, "iontophoresis" refers to the movement of ions, as it results from the migration of charged particles under an electrical field. “Ionto” in Greek means ‘ion,’ and ‘phoresis,’ means ‘to carry or transfer’[2].

1.1. Historical Background

The concept of iontophoresis dates back to 1747, when Pivati first described the phenomenon. Later, in the 18th century, Galvani demonstrated that electricity could induce the movement of metal ions. By 1879, Hermann Munk observed spontaneous cramps in rabbits exposed to strychnine solution for 20–25 minutes. In 1903, Leduc developed a method to transfer salicylic acid using an electric field, which helped relieve pain and accelerate wound healing. Initially, this phenomenon was referred to as "ion transfer" and later as "cataphoresis." By 1908, the term "iontophoresis" became widely used, and today, it is commonly known as electrically assisted drug delivery [1,2,3,4]. In dentistry, iontophoresis was first introduced in 1960 for treating dentin hypersensitivity[4].

1.2. Principle of Iontophoresis in Dentistry

The primary objective of iontophoresis is to deliver drugs to the subsurface of a lesion. Several dental treatments have been explored using iontophoresis, including anti-inflammatory drug administration, local anesthetics, antibiotics, fluoride, endodontic treatments, and aphthous ulcer therapies.

The fundamental working mechanisms of iontophoresis include:

1. Electrophoresis – Based on the principle that opposite charges attract while like charges repel, facilitating the movement of charged drug molecules.
2. Electro-osmosis – The movement of both ionic and neutral drug molecules within a solvent under the influence of an electric charge, allowing the drug to diffuse from a high-concentration surface to a lower-concentration subsurface across a charged membrane.
3. Electroporation (Electro-permeabilization) – The application of an electric field increases the permeability of biological membranes by modifying pore size and charge distribution, thereby enhancing drug penetration[1-4].

1.3. Components of an Iontophoresis System

The iontophoresis system consists of [5]:

Two electrodes: A positive electrode (anode) and a negative electrode (cathode).
A drug solution: The drug must be water-soluble and capable of ionization.
An electric current source: Provides the necessary voltage for drug movement.

1.4. Factors Affecting Iontophoresis Efficiency

Several factors influence the effectiveness of iontophoresis, including [1-4]:

1.4.1. Drug-related factors:

Molecular size: Smaller molecules move more efficiently.
Solubility in water: Water-soluble drugs facilitate better ionization.
Charge: The drug’s ionization tendency affects its movement.
pH and concentration: Optimal pH and drug concentration impact delivery efficiency.

1.4.2. Electrical factors:

Voltage type: Although alternating current (AC) provides a more stable flux across membranes, direct current (DC) is more commonly used in practice.

1.4.3. Biological factors:

Tissue thickness: Thicker tissues may reduce drug penetration.
Inflammation: Inflamed tissues may have altered permeability.
Adipose tissue: Fat layers can affect drug movement.
Pore size and permeability: The presence of pores influences drug absorption.
Electrode placement: Proper positioning of electrodes affects efficiency.

2. Iontophoresis for Dentinal Hypersensitivity and Remineralization Therapy:

2.1. Iontophoresis for Dentinal Hypersensitivity

Dentin hypersensitivity occurs due to exposure of dentinal tubules from underlying dentin. The sensory nerve of the dentin becomes exposed due to factors such as attrition, abrasion, erosion, or abfraction. Additionally, loss of cementum from the root surface also contributes to tooth sensitivity. When enamel becomes thin, dentin responds to external stimuli such as thermal, tactile, osmotic, or evaporative factors. The most affected areas are the cervical region of the facial surface of the canines and premolars[6,7].

Iontophoresis can be efficiently used to treat dentin hypersensitivity. One study illustrates that the effect of fluoride iontophoresis is prolonged compared to topical fluoride application alone.

This occurs because 2% sodium fluoride iontophoresis, electrically driven fluoride ions, react with calcium in the hydroxyapatite to form fluorapatite, therefore blocking the dentinal tubules. There are varying hypotheses as to how iontophoresis results in the desensitization of dentin. According to one theory, reparative dentin is formed, which causes dead tracts in primary dentin. Another theory states the induction of paresthesia occurs by altering the sensory mechanism of pain conduction and blocking dentinal stimuli that induce pain through the micro precipitation of calcium fluoride across the dentinal tubules. Nanohydroxyapatite and pro-argin are effectively used to reduce dentin hypersensitivity. Iontophoresis can be a valuable adjunct for their improved delivery, enhancing and prolonging their effectiveness[8].

2.2. Iontophoresis for Remineralization

Iontophoresis is used in the initial carious lesion for the remineralization of enamel. In an analysis, three topical fluoride regimens, such as acidulated phosphate fluoride gel (1.23%), NaF varnish 2%, and a 5% solution with iontophoresis, were compared. Using a CLSM and digital microhardness tester, NaF with iontophoresis showed reduced lesion depth and increased fluoride absorption. Fluorinex is an iontophoretic device that aims to increase electrical conductivity in the tooth by preconditioning it with copper (II) chloride solution. Fluoritray uses a low direct electrical current, resulting in the diffusion of fluoride gel into the teeth and the elimination of the polarization effect. This leads to the active substitution of hydroxyl groups with fluoride ions. It was inferred that Fluorinex provided exceptional results in remineralization as compared to traditional APF gel application on incipient carious lesions[7].

3. Iontophoresis in Local Anesthesia and Endodontic Treatments

3.1. Local Anesthesia

Local anesthesia is a fundamental technique in dentistry that involves administering anesthetic medication near the nerves surrounding the treatment area to help mitigate the pain during oral procedures[9]. Although local anesthesia is a very efficient pain management technique, the traditional needle-and-syringe method can cause tremendous anxiety and fear in patients, particularly in pediatric patients. To ease this discomfort, numerous other methods of local anesthetic administration are present today, such as electronic dental anesthesia, jet injection, computer-controlled local anesthetic delivery devices, and many others, most of which still require a needle for application[10]. Iontophoresis is a non-invasive and effective alternative for the administration of local anesthetic without the use of a needle. It uses an electric current to deliver local anesthetics, like lignocaine, to deeper tissues following topical administration, thereby efficiently anesthetizing the region[11]. Iontophoresis enables the delivery of anesthetics to deeper layers of both hard and soft tissues[12]. A pilot study conducted in pediatric patients that used topical anesthetic spray on buccal and lingual mucosa via Iontophoresis proposed that a current intensity of 9.43 + 0.95 mA (I think the number is wrong) and duration of 4 to 6 minutes of applying LA through Iontophoresis is required to achieve optimal therapeutic anesthesia for dental surgical procedures in children. The study group also showed decreased anxiety and fear related to needle insertion[10]. Another study was conducted by Smitayothin et al. on the anesthetizing effects of lignocaine and epinephrine via Iontophoresis for caries removal. In this research project, after filling the teeth with lidocaine 20% and epinephrine 0.1%, a 200mA electric current for two minutes was applied. This research concluded that 87.5% of the teeth with caries were anesthetized through iontophoresis, and the immediate pain relief experienced after Iontophoresis application of lignocaine and epinephrine continued for 40 minutes. Another observation made in this study was that lidocaine could pass through the tooth structure by using alternating current (AC), thereby eliminating the need to numb the tissues in comparison to the traditional LA injections using a syringe and needle[1]. Yet, direct current (DC) facilitates quicker delivery of lidocaine as compared to alternating current (AC). It is also found that the new Low-dose lidocaine Iontophoresis System (LDIS) achieves rapid anesthesia in 10 minutes at a much lower dose than other commonly used anesthetics, thereby reducing the side effects. However, Iontophoresis has not been extensively studied on minimally permeable membranes, such as gingiva or palate[12].

3.2. Endodontic Treatments

The effective outcome of endodontic treatments relies on multiple factors. However, inadequate disinfection of root canals is the primary cause of secondary infections[13]. Due to the complexity or anatomical variations of root canals, instruments, and medications may not always reach certain areas of the root canals, especially the apical areas. Iontophoresis can be used to successfully disinfect root canals and dentinal tubules. Persistent infections can give rise to oral pathological conditions, such as apical periodontitis, which can lead to endodontic surgeries, ultimately leading to long-term distress in patients. Even though new root canal disinfection alternatives (such as the usage of rotary and reciprocating instruments) and irrigation techniques (such as sonic irrigation and ablative laser) have emerged, they are not very efficient. Since the application of Iontophoresis is advantageous in other areas of dentistry and does not require puncturing of the tissues for drug delivery, endodontic treatments may also benefit from its potential uses. Biofilms adhered to the root canal should be removed for appropriate disinfection of the canals. Potassium iodide iontophoresis helps in the removal of gram-positive cocci in the biofilm, and silver iontophoresis aids in the removal of gram-negative bacteria. Cupral iontophoresis has also been found to have great antibacterial effects[1]. A study was conducted to determine the use of iontophoresis for increasing the penetration of drugs into root canals and dentinal tubules, using methylene blue as the dye. In this study, Iontophoresis at 0.5 mA for 15 minutes and 1.5 mA for 5 minutes was applied to the bovine root canals. This study concluded that iontophoresis increases the penetration of drugs, and variations in current density and application time significantly affect the spread of the dye. Effective delivery of methylene blue to the apical region was observed with 1.5mA for 5 minutes or 0.5mA for 15 minutes, thus indicating that longer application time can counterbalance lower application current[13]. The most common pathogens present in the root canals with refractory apical periodontitis are *Enterococcus faecalis, Candida albicans, Pseudomonas aeruginosa,* and *Bacillus subtilis*. An in vitro study conducted to research the bactericidal effects of iontophoresis suggested that iontophoresis with diamine silver fluoride solution removed all of the four bacteria, thereby suggesting that this is highly effective in the treatment of refractory apical periodontitis[14].

4. IONTOPHORESIS FOR TARGETED DRUG DELIVERY IN DENTISTRY

4.1. Buccal Iontophoresis- Transmucosal iontophoresis through the buccal route offers a viable alternative for systemic drug delivery. The buccal area's barrier characteristics, environment, and blood flow make iontophoretic delivery via this route particularly appealing for drugs that experience first-pass metabolism or cannot be absorbed through the gastrointestinal tract[15].

4.2. Palate Iontophoresis- To investigate the permeation mechanism of cornified oral mucosa, the barrier properties of the palate were evaluated for the iontophoretic transport of tetraethylammonium, salicylate, mannitol, dexamethasone, fluoride, and chlorhexidine. The findings indicated that the cornified epithelium acted as the primary barrier, limiting drug delivery. Iontophoresis improved drug delivery into and through the palate while also decreasing the transport lag time[16].

4.3. Non-Steroidal Anti-Inflammatory Drugs- Iontophoresis was used with salicylate, naproxen, and metronidazole, and drug concentrations were measured using a spectrophotometer. The penetration of sodium salicylate, naproxen sodium, and metronidazole through carious dentin was lower compared to healthy dentin. The ionized form of the drug exhibited greater penetration when delivered via iontophoresis.[17]

4.4. In Oral Ulcer Treatment- Iontophoresis can improve drug penetration into the enamel, dentin, and other oral tissues, making it useful for treating oral diseases. With antiviral drugs, it can be used to treat oral ulcers ("canker sores") with negatively charged corticosteroids and herpes orolabial lesions ("fever blisters")[7].

4.5. In Periodontal Diseases- In the treatment of periodontal diseases**,** sustained drug delivery systems for antibacterial and anti-inflammatory agents have been used. Iontophoresis of these agents to the gingiva and nearby tissues can help prevent systemic bacterial invasion and manage the progression of periodontal disease[17].

4.6. Targeted drug delivery in dentin-

Iontophoresis using metronidazole, salicylate, and naproxen was studied for dentin and was found to improve drug delivery through both intact and caries-affected dentin. In addition to treating dental caries, fluoride iontophoresis was proposed as a desensitizing treatment for cavity preparation, restoration cementation, and enamel hypoplasia. Iontophoresis was shown to enhance the delivery of fluoride into dentin [18].

5. TECHNOLOGICAL ADVANCES IN IONTOPHORESIS

5.1. Iontophoresis Assisted microneedles used in transdermal biosensing

This area focuses on the potential of iontophoresis-assisted microneedles used in biosensing applications. Microneedles differ in ranges from hundreds of micrometers to a few millimeters in length and penetrate the skin's outermost layers to access ISF, allowing continuous monitoring of analytes such as glucose, lactate, and physiological parameters that are crucial for diabetic management and metabolic disorders [19,20]. A microneedle is inserted into the skin as an active electrode to extract biomarkers, with a distant reference electrode completing the circuit. While applying a low-level electric current, charged analytes move toward the microneedle electrodes due to the RI. They can be detected and quantified using electrochemical or optical detection methods[21].

5.2. Iontophoresis Assisted microneedles used in transdermal drug delivery

Iontophoresis-assisted microneedles offer a cutting-edge approach to transdermal drug delivery, combining the benefits of minimally invasive MNs with the enhanced transport efficiency of IP[22]. IP delivers drugs into the skin in the opposite flow direction. In two-step drug delivery, MNs are first employed to pierce the skin, and IP is then applied to drive the drug into the skin through the holes. However, in the one-step method, MNs are usually preloaded with drugs and injected into the skin, and electrodes are placed on the backside of MNs. Having controlled and localized drug administration, IP-assisted MNs have a significant potential for treating various conditions, from diseases to medical needs, further improving therapeutic efficacy and lowering systemic side effects.

5.3. Electroporation (EP)

An electrical technique that disrupts cellular membranes, creating transient pores in the skin within milliseconds. Which generates aqueous pores in the stratum corneum's lipid bilayers. While effective for enhancing transdermal drug delivery, EP can cause discomfort, pain, and muscle contractions. Side effects occur due to changes in the stratum corneum's electrical resistance, which can stimulate underlying nerves and motor neurons [23,24]. Various drugs with different molecular weights have been administered through EP, including Fentanyl, Timolol, calcitonin, and heparin, with molecular weights reaching up to 40 kDa[25].

6. Advantages, limitations, and future perspectives

In modern dentistry, Iontophoresis, being a non-invasive drug delivery system combining physical and chemical methods, has demonstrated significant advantages in pain management.

Firstly, it is considered a safe and effective alternative to traditional local anesthesia in pediatric dentistry[26]. It can also be combined with traditional injections to prolong the effective concentration of anesthetics significantly[10,27]. This reduces pain and anxiety during invasive treatments, especially in patients with dental phobia, and increases willingness and satisfaction with treatment [13,28]. In addition, it is successful in the management of early postoperative pain after mild to moderate mandibular surgery[29].

Iontophoresis has also demonstrated its effectiveness in root canal treatment. When sodium hypochlorite rinses are used in conjunction with Iontophoresis, the depth of diffusion of the medicine into the root canal wall and the duration of its maintenance are significantly enhanced[13], thus contributing to the removal of microorganisms from the root canal and smear layer[28]. In addition, through the development and refinement of the Iontophoresis apex-phoresis technique, the drug and the metal ions can be delivered via DC to the deeper regions of the root canal system, especially in complex root canal branches that are difficult to clean thoroughly with conventional instrumentation technique, effectively solving the problem of disinfecting the deeper layers of the root canals while promoting remineralization and enhancing antimicrobial capacity[30]. This approach has a promising future in the field of root canal therapy.

Iontophoresis has also shown potential in promoting tooth remineralization. For example, combining the classical remineralization drugs casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) or tricalcium phosphate with iontophoresis has resulted in significant savings in chairside treatment time, thereby increasing work efficiency and improving clinic economics, although the difference in efficacy compared to traditional topical delivery is not significant[31]. The savings in chairside treatment time have led to increased efficiency, fewer patient visits, and improved clinic economics. Its efficient remineralization effect also makes it widely used for treating hypersensitivity, combining it with nano-hydroxyapatite or pro-argin, which not only achieves a rapid drug concentration but also prolongs the maintenance of therapeutic efficacy[1].

In the field of targeted drug delivery, Iontophoresis has been used in the delivery of anti-cancer drugs, significantly improving the efficacy of anti-drug delivery. Specifically, iontophoresis has enhanced the efficacy of 5-FU in the treatment of SCC and Bowen's disease [32,33]. By combining the advantages of selective delivery with immunoliposomes, iontophoresis not only effectively inhibits the growth and proliferation of tumors and reduces the invasiveness of the cells but also significantly improves the precision of the targeted therapy. While increasing the local drug concentration, the systemic drug concentration is kept low, thus reducing the side effects of medication on systemic tissues[34].

Although iontophoresis has shown good therapeutic promise in several areas, there remains scope for further exploration in the future due to certain limitations in existing studies. Future research areas are expected to expand. This review focuses mainly on using iontophoresis in dentinal hypersensitivity and remineralization, local anesthesia, endodontic treatments, and targeted drug delivery, whereas its potential in periodontal therapy, oral pathology, and systemic applications has been less explored. In addition, due to time constraints, this review did not include the most recent relevant research developments and may have omitted some important literature.

Improving study quality and expanding sample sizes could be essential. There is a paucity of available literature and insufficient data from clinical trial studies on the application of Iontophoresis in treating periodontal disease, oral bacterial control, viral and fungal diseases, and oral squamous cell carcinoma. Therefore, only a brief overview of these areas can be provided in the review. Additionally, some of the cited literature has a small sample size, and the conclusions may lack generalizability.

The development of objective efficacy assessment tools merits greater attention. Most studies have focused only on the immediate efficacy and duration of a single treatment and lack statistical data on the reduction in recurrence rates or shorter treatment cycles. Especially in studies involving anesthetic drugs, the subjects' perception of pain is subjective and lacks a uniform method of quantitative assessment. Currently, only subjective questionnaires are relied upon. In the future, objective assessment tools could be incorporated, such as electroencephalography (EEG) or functional MRI (fMRI), to monitor pain-related changes in brain activity and physiological indicators, such as changes in heart rate, blood pressure, and respiratory rate, which can indirectly reflect the degree of pain.

Optimization of technical parameters and dosage might need to be emphasized. Iontophoresis may cause skin erythema and epidermal burns, limiting the depth of drug delivery and the potential for wide-area application. Further research and optimization are needed regarding the ideal current intensity, treatment duration, and drug concentration to maximize the drug effect while controlling the side effects in various application scenarios. In addition, the review did not discuss whether iontophoresis may trigger contact allergy, which needs to be verified by more case statistics and studies in the future.

In conclusion, while iontophoresis shows promise in dental treatments and targeted drug delivery, additional high-quality clinical studies and technological optimizations are necessary to further validate its efficacy and expand its applications.

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