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Buccal iontophoresis: an opportunity for drug delivery and metabolite monitoring

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The development of microelectronics, microsensors and microfluidics is gradually enabling researchers to design artificial glands to deliver drugs or hormones in response to the physiological demands of the host. Such devices are designed to not only replace selected functions of the malfunctioning natural glands, but also to act in new ways, such as serving as an 'electronic nurse', and managing the physiology of the body during normal or abnormal stress conditions, for example, in sportsmen's or soldiers' bodies. Artificial glands will be able to access an external wireless network and will therefore be able to inform about malfunction in the host organism. One of the possible locations for such a device is the human mouth cavity. As we discuss here, the oral mucosa, owing to its unique properties, can serve as both a drug delivery area and a metabolite sampling zone.

Electrical enhancement of drug delivery

The physiological function of human skin or oral mucosa is not to absorb any substance, but rather to prevent this to protect homeostasis. To make drug delivery possible via this route, various chemical drug absorption enhancers or physical methods are used (e.g. electric field, microneedles and sonophoresis). The application of an electric field is particularly beneficial as it can impose an additional driving force on drug ions (iontophoresis), force water (or bodily fluids) to flow with the dissolved drug or metabolites (electroosmosis), or temporarily modify tissue structures to make them more permeable (electroporation).

Iontophoresis is a medical term given to the electrophoretic delivery of active compounds or therapeutics ions into the body. This phenomenon, first described in 1900 [1], occurs when tissue is connected to an electric circuit and a voltage gradient causes the movement of ions. Charged molecules move towards counter-charged electrodes, which are in touch with the tissue surface through conducting solutions that also contain a drug. Owing to the mechanism of iontophoretic delivery, the transfer of cationic, anionic and neutral molecules is possible, and the ionic form of drug determines its location under the correct electrode (cationic and neutral under positive, and anionic under negative electrode). There are two mechanisms of enhanced molecule movement under the influence of an electric field: electromigration and electroosmosis [2,3]. Electromigration is a result of electrostatic interactions and applies to charged species only. Electoosmosis occurs in porous structures (e.g. tissue) with a net charge of one predominant sign (e.g. negative), which causes charge asymmetry between the moving solution and the non-moving porous phase. The mobility and concentration of ions with the same charge as the tissue are reduced and the transfer of counter-charged ions is enhanced. This non-symmetrical ion flux is called 'Donnan exclusion' and induces the movement of solvent and other non-charged molecules by simple momentum transfer. The skin [4,5] and buccal mucosa [6] have a negative net charge and, therefore, a solution flow can be observed that is directed from a negative to a positive electrode. The electroosmotic flux of solvents during iontophoresis was reported for the first time in 1924 by Rein [7]. Owing to this phenomenon, the controlled transfer of neutral drugs accompanied by physiologically inert small positive ions is possible [4]. Negatively charged drug molecules can be delivered by iontophoresis from the anode compartment. However, the electrical efficiency of iontophoretic delivery of anionic drugs is usually lower than that of cationic drugs.

The total iontophoretic flux consists of diffusional, electromigrational and electroosmotical fluxes. The electromigrational flux of X ions can be calculated from Eq. (1) [3]:

$$J_X^{EM} = \left(\frac{1}{z_X F}\right) \frac{z_X u_X c_X}{\sum_{n=0}^{i} z_i u_i c_i} I_D \quad (1)$$

where I_D is the applied current density, F is Faraday's constant and z_X, u_X and c_X refer to the charge, mobility and concentration of the drug ions, respectively. The denominator is the sum of the products of these parameters for each ion in the system contributing to the charge transfer across the membrane. This form of equation explains the reduction in drug transfer efficiency when small ions with the same charge sign as that of the drug are present. If the

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donor solution contains only drug ions, the drug flux is a function of the current density. For small concentrations, this function is linear, whereas, for higher concentrations, it reaches a plateau [8,9].

Another mechanism is the electroosmotic flux of X ions, which is described by Eq. (2) [3]:

$$J_X^{EO} = c_X v \quad (2)$$

where v is the solvent velocity. This flux is directly proportional to the concentration of drug ions. As mentioned above, the current density and drug concentration are the key parameters of iontophoresis, but pH is also important owing to its influence on drug ionization and ionization of the tissue [3]. The former influences the efficiency of electromigration, whereas the latter has an impact on electroosmosis.

The constant direct current treatment is the most popular method for delivering drugs using this methodology. However, pulsed direct current and asymmetric alternating current iontophoresis have also been investigated, and were found to cause less irritation to the tissue [10]. Direct current transdermal iontophoresis is a painless technique below a current density of 1 mA cm^{-2} [11].

Electroporation is also an electrical enhancement method, but its mechanism differs from that of iontophoresis. During electroporation, short pulses of constant high voltage current generate pores in the lipid cellular membrane [12]. Owing to the lower dielectric constant of lipids, compared with the surrounding water solution, the membrane is squeezed by an electrostriction force and forms micropores, which then close after a while (miliseconds to seconds [13]). This phenomenon was first applied to single cells, but has since been adopted to enhance drug permeability through the skin [13]. The application of electroporation increases the diffusion rate of drug molecules regardless of their charge by increasing the overall diffusion coefficient through the tissue, creating new paths for diffusion [14]. Electromigrational mechanisms of transport can also occur but only during these very short pulses. The new ducts that are formed are hydrophilic, which makes penetration by ionic drugs easier. However, lipophilic molecules can also be transferred [14]. In the skin, voltages greater than 50 V and pulses of approximately 1 ms are applied and the short pulse duration ensures that the process is painless (voltage higher than 100 V can cause pain) [15]. Application of an electric field that is too strong can lead to permanent damage of the cell membrane and organelles.

The techniques described above are usually used for transdermal drug delivery; however, other options for drug delivery have also been considered (e.g. urinary bladder for bladder pathology treatment [16]). Unfortunately, researchers have focused on iontophoresis and so there are few publications relating to the electroporation of buccal mucosa. Transdermal iontophoresis for drug delivery using a mobile device has already been achieved. An example of successful application of this technology is the E-TRANS® arm patch (ALZA Corporation), which was developed for fentanyl HCl transdermal iontophoretic administration and was the first mobile system on the market [17].

Buccal route

The buccal mucosa is an attractive area for electrical drug delivery. It easily withstands long-term permanent wetting and regenerates quickly. It is not as resistive to damage compared with skin, but is generally more permeable [18]. The oral cavity mucosa is convenient for drug delivery and offers the possibility for the application of many types of drug delivery system. Orotransmucosal varieties of drug delivery systems are popular and available in various forms, including solid and semi-solid forms, gums, lollipops, patches, solutions and suspensions, and micro- and nanoparticles [19,20].

Transdermal drug delivery is currently popular, but has to take into account the presence of the stratum corneum, which is a significant barrier to drug transport. This external skin layer consists of keratinized cells surrounded by lipid lamellae containing cholesterol, free fatty acids and ceramides [21,22]. Although the transfer of a hydrophilic drug through this structure is difficult, the hydrophilic regions of the lipid lamellae enable small ions to migrate through an intracellular pathway [23]. The skin as a drug delivery route has the advantages of easy access and large area. The human buccal mucosa is devoid of a keratinized cell layer and so is more suitable for hydrophilic drug transfer [24]. However, it also acts as a barrier to xenobiotic absorption and some protection is also present. The first prevention barrier is a mucus layer on the tissue surface. The main defence line is positioned within the mucosa and consists of low-molecular-weight polar lipids, which do not aggregate to form filaments and are present in the extracellular matrix [25,26]. Of the disadvantages of the buccal mucosa as a drug administration route are a small absorption area, the presence of a constantly flowing saliva film and drugs that have a strong taste. The main disadvantages of buccal administration (limited dose and clearance of saliva [27]) can be easily overcome by efficient electrical drug delivery. An electric field can also enhance drug transfer through the mucus layer. The application of iontophoresis exploits the advantages of the buccal mucosal route, for example, significant vascularization, which results in a higher drug perfusion rate than for the skin [27,28]. Moreover, owing to its simple, flat shape and small distance from teeth, the cheek is an attractive place for location of electrodes. Positioning the whole medical device in the mouth also provides a discreet therapy, invisible to other people.

From drug delivery enhancement to a feedback loop system

The number of publications describing electrical transbuccal drug delivery is limited, with the main tissue models being porcine buccal mucosa (which closely resembles human mucosa [29]) and reconstituted human oral epithelium (cell culture TR146) [30]. Porcine buccal mucosa was used in the *in vitro* experiments described in [31–34], whereas *in vivo* experiments using domestic pig are described in [35,36]; by contrast, reconstructed human epithelium was used a model in [37]. The model drugs were monocationic salts with a molecular weight in the range of 303–378: atenolol HCl [31], naltrexone HCl [32,33,35,37] and galantamine HBr [37]. The electrical enhancement was carried out by direct current iontophoresis (pulsed [31] or continuous [32–37]). The influence of current density, initial donor drug concentration and the presence of competitive ions on drug flux were described.

An increase in the delivery of the drug via the iontophoresis transport compared with that of diffusive transport was recorded by all studies except [35,36], which showed comparable delivery of

the drug with and without iontophoresis during *in vivo* experiments. However, because iontophoresis was only conducted for the first 10 min during these animal studies and the plasma profiles were monitored for a few hours, the diffusive and iontophoretic mode of administration showed similar results. The concentrations of the drug in the iontophoretic mode of delivery are initially higher but only over a short period of time (e.g. the first hour); therefore, an enhancing effect is recorded. This advantage can become more so if the flow of saliva hinders diffusive transfer, which is likely to occur if the animal is not under anesthesia, especially because anesthetic protocol might cause a decrease in salivation. During the experiments described in [35,36] the dryness of mucosa was observed (Axel Schumacher, personal communication).

The results of *in vitro* experiments on transbuccal drug delivery reveal dependences similar to those seen in transdermal experiments: for example, the total drug flux was proportional to current density [31,34] and was an exponential function of the initial donor concentration under influence of competitive ions [33]. With a lack of competitive ions, the flux was not a function of donor concentration [33]. In general, the drug flux depended more on electrical factors than on the concentration gradient [31]. However, the donor composition had considerable influence on the electrical efficiency of the transfer process and this efficiency could be optimized [33]. In general, the electrical efficiency was low, approximately 10% for naltrexone HCl administrated from pure water solution at 1 mA cm^{-2} [33], owing to the dominant charge transfer performed by small ions, which naturally occur in the tissue. Small ions display higher electrical mobility and move faster than large ions under the same electric field strength. The application of iontophoresis was found to cause minute cytoarchitectural changes, resulting in cellular disarray. Cytopathic effects, represented by nuclear pyknosis, diffuse signs of abrupt keratinization and loss of cellular alignment, were observed in association with a current density greater than 2 mA cm^{-2} [32]. The drug fluxes achieved in the aforementioned publications could lead to the administration of therapeutic doses of drugs by buccal iontophoresis despite the small absorption area. Additionally, this route is likely to increase drug bioavailability as it bypasses the hepatic effect, which could therefore significantly reduce the desired dose. The results published already concern the transfer of relatively small drug molecules, which can pass the mucosa barrier without enhancement. More significant would be the effects of iontophoretic delivery of larger molecules, such as a peptide drug, that cannot diffuse into the tissue without support.

The research results discussed above can be applied in drug delivery devices such as the IntelliDrug implant (Fig. 1) (http://www.intellidrug.asm-poland.com.pl/). This is a dental implant containing a highly miniaturized computerized system for systemic drug delivery via the buccal mucosa [38]. The device contains a store of the drug in a dry form for a long-term multi-dose operation. To prepare a drug solution, the device absorbs water from saliva via a semi-permeable membrane (reverse osmosis grade) and the osmotic pressure generated by the dissolving drug is the driving force of the microfluidic drug delivery system. Increased hydraulic pressure is accumulated by the polymer-encapsulated gas bubble and consumed during release of the drug solution. The solution is directed via a valve and flow sensor to the buccal side, where it is released in controlled pulses. The device releases the drug solution according to a pre-programmed schedule, which makes chronotherapy possible. The system is easily controlled by the remote control unit; for example, in terms of checking the status of the device and programming the dosing. The device can be inserted in the gum instead of two molar teeth and has denture housing with a drug-releasing iontophoretic port. The ring, coaxial electrodes surrounding the drug nozzle, is in direct contact with the buccal surface.

Numerical simulations of electrically enhanced drug transport

The discussion above focuses on the ideal drug transport process in the form of an electric field. However, such a situation is not always possible as it is difficult to place counter electrodes outside the cheek. The IntelliDrug implant assumes the form of a coaxial rings electrode that enables the whole device to be located inside the oral cavity. This differs from the usual geometry applied by researchers during *in vitro* experiments. How this system will work? Will it be efficient? Numerical simulations can illustrate how the system works and can be a good starting point for *in vivo* experiments. Nevertheless, there are few publications that focus on the

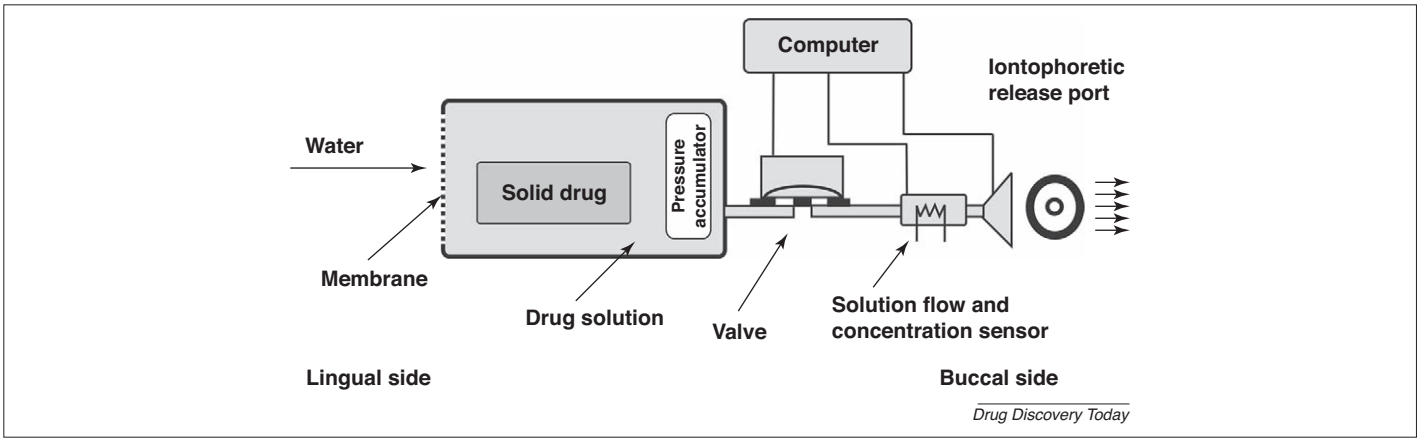

FIGURE 1

A schematic view of the IntelliDrug device showing the principles behind its operation and the coaxial system of iontophoretic electrodes.

modeling of drug transport during electrical enhancement. Some results describing the numerical simulations of the electroporation of skin and subcutaneous tumour have been presented by Pavšelj and Miklavčič [39–42], whereas electrical enhancement of the buccal field has been investigated by Kazmierska and Ciach [43], who carried out numerical simulation of drug transport during iontophoresis using geometry worked out for IntelliDrug. COMSOL Multiphysics software was used that is based on the finite element method: in the elaborated 2D model, the drug is rinsed with saliva film and the top layer of mucus is taken into account. Unfortunately, this model referred to animal tests where dryness of the mucosa was observed. A 3.5-V driving potential difference on electrodes was assumed in the numerical model. The model drug (tracer) was an naltrexone HCl that was released as a dissociated saturated solution from the device reservoir via a nozzle. The extracellular flow of the drug and its diffusive, electrophoretic and convective transfer were assumed. The used balance of mass of the drug cations is expressed in Eq. (3):

$$\frac{\partial c}{\partial t} + \nabla N = 0, \tag{3}$$

where N is the flux vector according to the Nernst–Planck equation, with convection given by Eq. (4):

$$N = -D\nabla c - zu_m c\nabla\phi + cu, \tag{4}$$

where D is the diffusivity, z is the charge (+1 for the assumed tracer), u_m is the mobility of the tracer, c is its concentration, Φ is the potential and u *is* the velocity vector. The balance of current comes from Ohm's law for electrolytes and is given by Eq. (5):

$$\nabla \cdot (-\kappa\nabla\phi) = 0, \tag{5}$$

where κ is the conductivity of the electrolyte. The model geometry, electrodes and model mucosa compartments of various diffusion coefficients and dielectric constants are shown in Fig. 2.

The analysis of the electric field distribution as a driving force of the iontophoresis revealed the focusing effect of the geometry of the concentric electrodes on the evolution of the drug concentration profile. A comparison of this drug concentration profile with that of solely diffusive transport is presented in Fig. 3. In the conditions described above, diffusion does not enable the drug to reach the vascularized domain (connective tissue). The presence of a flowing saliva film causes asymmetric movement of the drug cloud. By contrast, the application of iontophoresis, under experimental conditions, guarantees drug transfer to the vascularized tissue region.

Reverse iontophoresis

As mentioned above, the transfer of cations through skin or mucosa is preferential and induces a net movement of body fluids. This phenomenon (iontophoresis) can be used in the sampling of body fluids to measure the concentration of certain metabolites, such as glucose [44]. Taking into account the recent development of microsensors, it is possible to design a miniature, mobile system for body condition and metabolite concentration monitoring. Several clinical sensors are already available, for example, for monitoring glucose, urea, lactate, cholesterol, choline, uric acid, creatine, creatinine [45], blood pressure [46], and oxygen and carbon dioxide saturation [47]. Additionally, these types of monitoring device for use with the skin are already established; for example, the GlucoWatch is used for non-invasive and continuous glucose measurement [48] (http://www.glucowatch.com). The application of this device highlights the disadvantage of using human skin, which is not resistant to the long-term wetting necessary to sample body fluids; by contrast, the buccal mucosa withstands such wetting without any side effects. Unfortunately, there are no similar solutions for glucose extraction through mucosa, although there appear to be no objections to the development of this type of device, especially as the electroosmotic flux of fluid through buccal mucosa is 1.4 times greater than through the skin [6].

The liquid extraction rate as a function of electric current for porcine mucosa is illustrated in Fig. 4 and shows that the electric current can efficiently sample extracellular liquids. For feedback

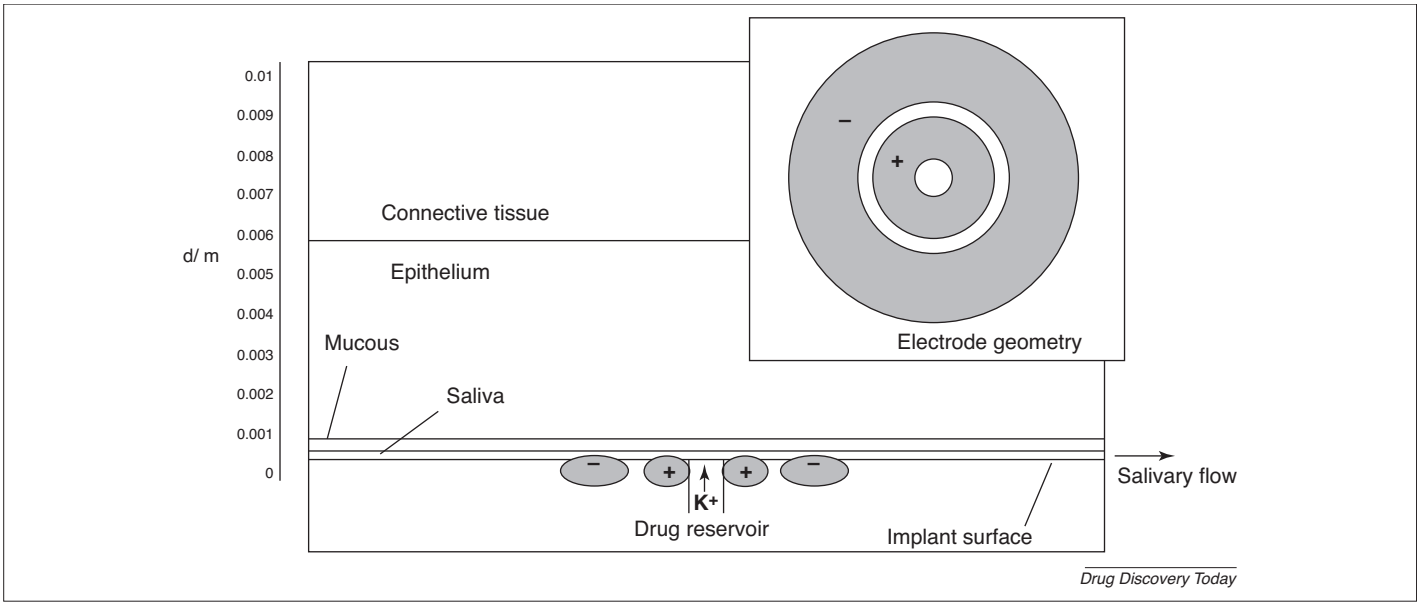

FIGURE 2

The computational model of the coaxial electrodes with drug source (K^+) applied for numerical simulation [43]. Reprinted, with permission, from [43].

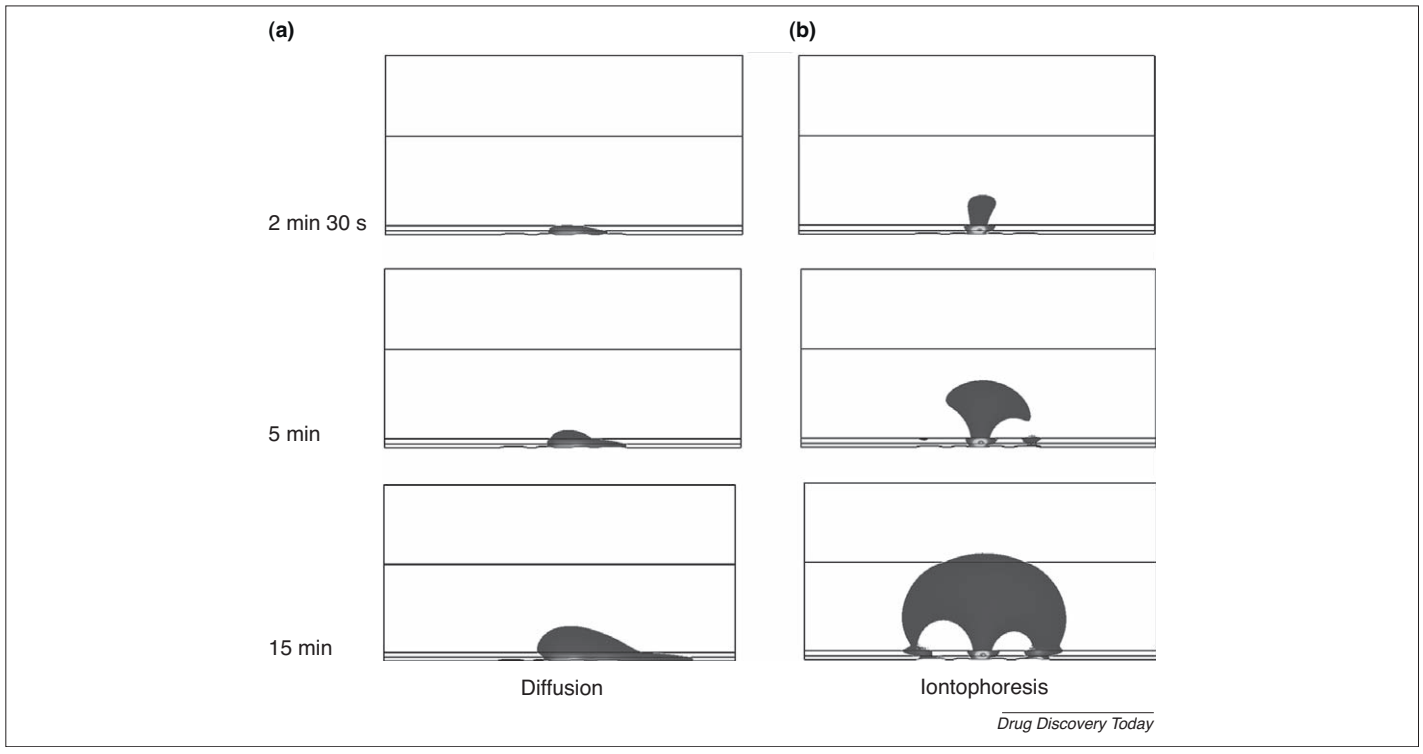

FIGURE 3

Diffusion (a) versus iontophoresis (b) with an assumed salivary film flow. The drug concentration contour = 10 mol m^{-3} [43] and saliva film flow = 8.3×10^{-6} m s^{-1}.Reprinted, with permission, from [43].

application, the liquids can be sampled via a semipermeable ion exchange membrane, thus avoiding mixing and rinsing by the saliva film.

The reverse iontophoresis through mucosa enables the creation of a needleless metabolite monitoring system. Taking into account that the same electrophoretical mass transport phenomenon is involved in fluid sampling and in drug administration, one set of electrodes can be used for these two functions. Coupling the monitoring and drug release with a feedback loop with microprocessor control results in a feedback loop system. This provides a unique opportunity to create low-invasive and painless medical devices for online monitoring and reactions to a stimulus that mirror almost precisely the functioning of natural glands.

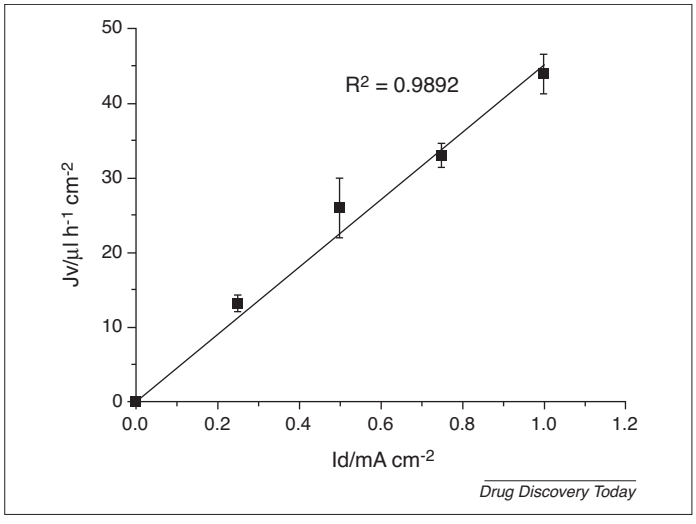

FIGURE 4

Body fluid extraction by the electroosmotic flow of solvent the influence of current density (Id) on electroosmotic flow of the solvent(Jv), using a porcine buccal mucosa model, with the anodal and cathodal chambers filled with phosphate-buffered saline [6].Reprinted, with permission, from [6].

Perspectives

In this review, we have described the properties of buccal mucosa as a target for electrically enhanced drug delivery. We have also shown that the same area can serve as a site for body fluids sampling by reverse iontophoresis. The combination of drug delivery and metabolite sampling in one device, and the use of the same driving force, is very promising. Such a device can sample body fluids and detect metabolite concentration with a proper sensor placed behind the sampling membrane. Placing a drug delivery system in the oral cavity is easier and safer than surgical implantation. Additionally, this location provides easy access if it is necessary to replace elements of the system or to fill the drug reservoir. At the same time, this type of solution is also discreet and invisible to other people.

The potential of electrically enhanced and electronically controlled drug delivery from a device placed in the tooth or other part of the body provides a unique opportunity to develop a drug delivery system to treat chronic disease. Equipping this device with an electrophoretic bodily fluid sampling system and proper sensor array combined with a microcomputer creates a feedback loop for drug delivery. This can result in the design of artificial glands to replace selected functions of malfunctioning natural glands. Artificial glands will be able to release drugs or hormones in response to the changes in concentrations of specific metabo-

lites. The device can, for example, monitor glucose concentration and, using a proper numerical procedure, release an appropriate dose of insulin, replacing this function of the pancreas. Such a device can monitor various host metabolites and body functions, such as glucose, pH, partial pressures of oxygen and carbon dioxide, rennin, urea, creatinine, sex hormones, blood pressure, temperature, body position, and so on. Further development and application of wireless information exchange systems could result in an 'electronic nurse system', which would actively control the physiology of the host and be able to inform the nearest hospital about any malfunction. In the future, such a device placed in the oral cavity or elsewhere inside the body might also be able to perform initial emergency treatment responding to the acute failure of an organ, therefore saving the life of its host.

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