ELECTRO-OSMOTIC DELIVERY

Proof of Electro-Osmotic Drug Delivery: A Prejudiced Clinical Trial, Delivering From Mouth to Nose

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ABSTRACT

We aligned all vectors and mucocilliary clearance contrary to drug delivery, with the exception of the single electrical vector induced by the dosage form. The electrical vector is considerably larger than the other vectors, which made it possible to perform a clinical trial prejudiced against delivery. It would be strong proof-of-concept if delivery were detected in spite of all the opposing vectors, gravity, and mucocilliary clearance. A buffered lozenge containing Zn^{++} was made to induce a lowering of the pH of the mouth with respect to the nose, and thereby a relative reversal of charge between mouth and nose. This reversal established a favorable gradient similar to a concentration cell, in which Zn^{++} could then move over the membrane of the palate into the nose. The experiment was further prejudiced by the fact that the probe did not lie in apposition to the delivering membrane, but was free in the milieu. This form of delivery is suitable for all dual-compartment and mucous membrane anatomical systems and disturbed membrane systems, such as wounds and burns. It can be combined with other novel or classical delivery modalities. In addition, very thin membranes can be breached directly. Restriction of a medication to a given volume, such as an encapsulated tumor, is a unique property of this system.

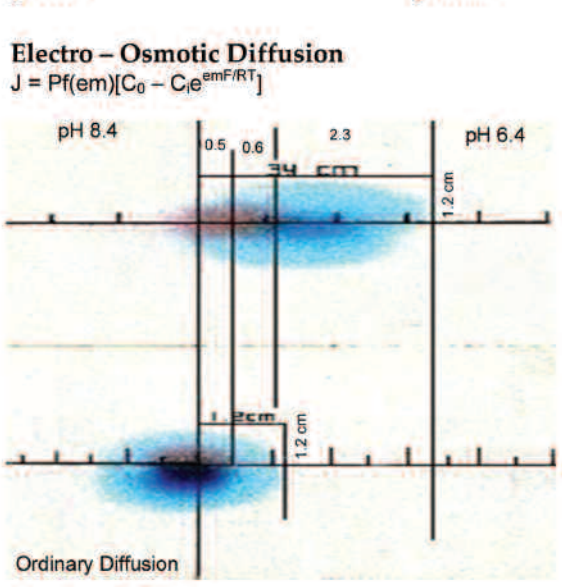
INTRODUCTION

Previously, we have posed the question of electro-osmotic delivery and presented a mathematical model from first principles in its favor.[1,2] We now present the results of an IRB-approved, GCP-compliant, controlled human clinical trial. This trial is submitted as proof-of-concept that electro-osmotic delivery exists and can be induced by the dosage form.

Prejudicing the trial against delivery was achieved by aligning all the delivery vectors, except the electrical vector, contrary to the

FIGURE 1

Vector Forces Graphically Analyzed



0.5 cm = 15% ordinary diffusion vector
0.6 cm = 17% advection of water
2.3 cm = 68% electronic component

Reversal of this vector component overcomes the other vectors. This is a unique property of this system. Dyes: FD&C Blue No. 2 and Red 5 & 40. Blue dye has 2-charges, Red dyes are neutral. pH chosen from the physiological range.

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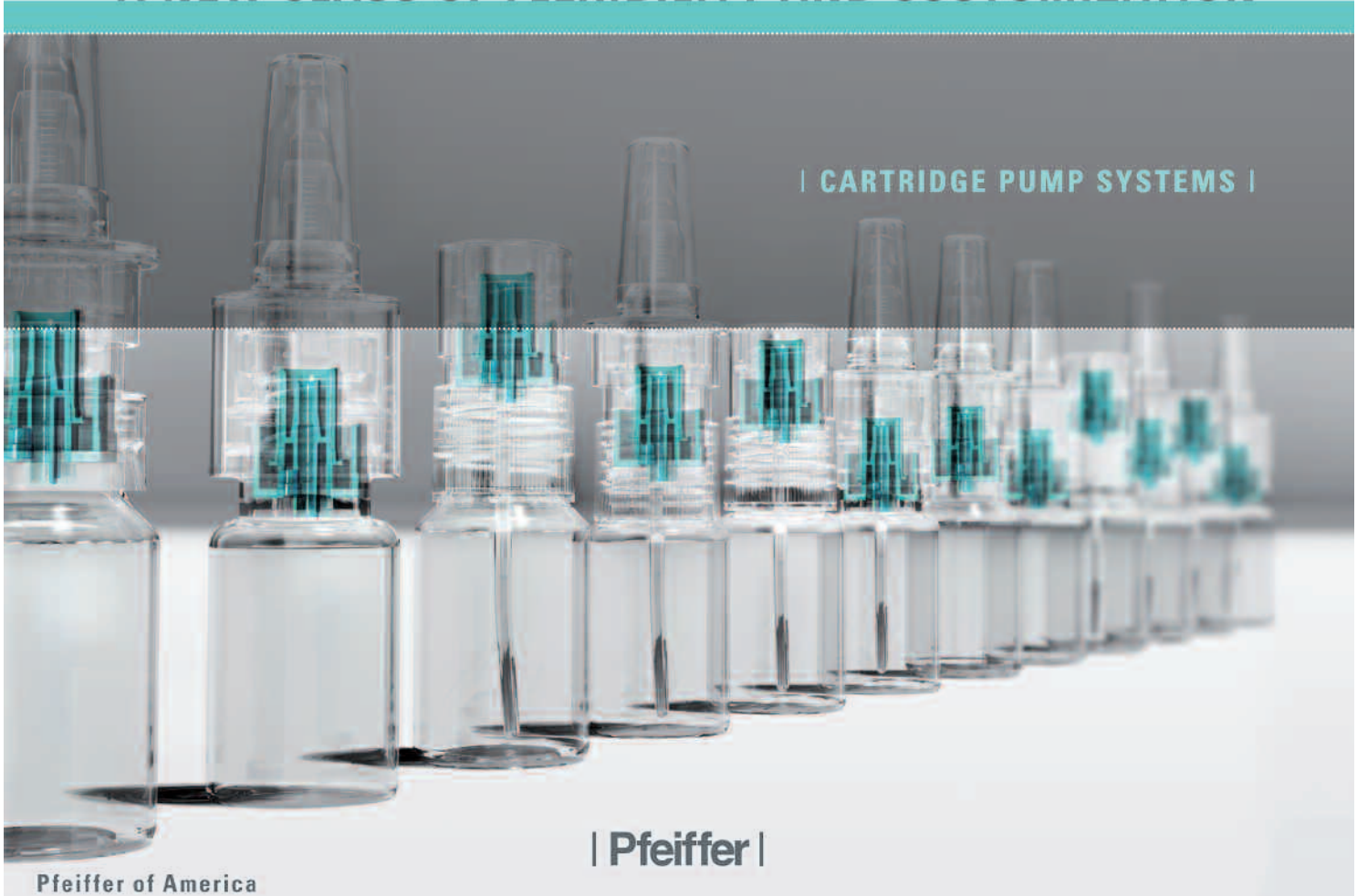

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delivery of the Zinc ion trace.

This was done for two reasons. First, the electro-osmotic vector was larger than all the other vectors combined (Figure 1). Second, if detection occurred against all opposition, it was very convincing evidence. This view was fortified by our mathematical model and known physical chemical principles previously discussed. The point was to take into account the generally ignored electro-motive terms of the governing diffusion equation.

Equation 1.

$$J = dQ/dt = -DdC/dx = Pf(EmF)[C_0 - C_i e^{(EmF/RT)}]$$

Where P = permeability coefficient of the medium = -D/dx; D = diffusion coefficient, which is temperature dependent; f means *function of* and is part of mathematical notation; Em = -2.303kT Log Keq (Boltzmann Expression for Emf); Em_{37° = -61.5 x 10-3 volts x Log

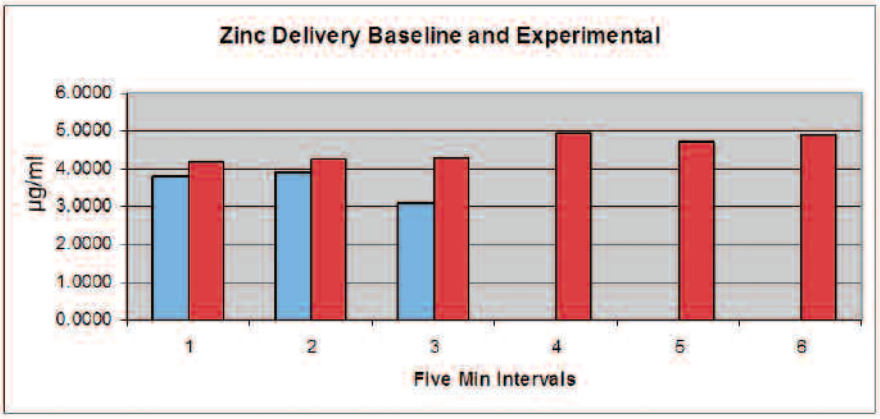
TABLE 1

	Data		
	1.9376	-	2.4520
	4.5950	-	4.7020
	3.3120	3.8300	3.4440
	4.3490	5.2210	
	1.0530	0.7780	0.9600
	1.7310	1.7960	3.2750
	1.6960	1.4700	1.5810
	6.3460	5.0610	3.4140
	5.9610	6.1170	4.0250
	4.9380	2.8240	2.0760
	4.2650	5.0820	3.9670
	3.6110	4.3320	2.8680
	4.6660	6.2450	5.3860
	2.9880	4.9230	2.3080
	5.6920	3.0500	2.4040
Total	**57.1406**	**50.7290**	**42.8620**
N	**15.0000**	**13.0000**	**14.0000**
Average	**3.8094**	**3.9022**	**3.0616**
Grand Average	**3.5911**		

*Blank spaces indicates lost data

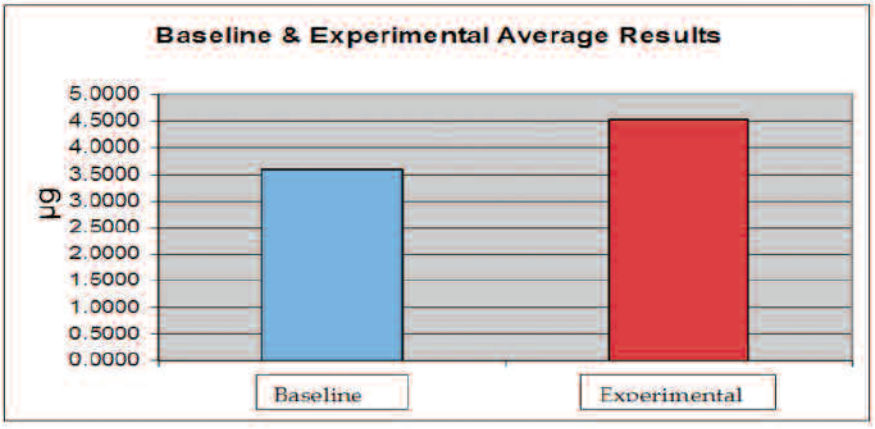
Baseline Mucous Results µg/ml Zinc

FIGURE 2



Baseline & Experimental Results Compared

FIGURE 3



F-Test Two-Sample for Variances		
	Baseline	***Experimental***
Mean	**3.58884851**	**4.532616279**
Variance	**2.48114923**	**4.494796051**
Observations	**42**	**86**
df	**41**	**85**
F	**0.55200485**	
P(F<=f) one-tail	**0.01860757**	
F Critical one-tail	**0.62711969**	

BASELINE & EXPERIMENTAL AVERAGE NASAL ZINC ION RESULTS (µg/ml)

The averaged baseline and averaged experimental values were significant. F-Calculated was less than F-Critical one tail.

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Keq/Z; R = universal gas constant and T = temperature in degrees Kelvin; Keq = [products]/[reactants] = [oxidized]/[reduced] = [pH1]/[pH2]; and Lewis definition: oxidized = loss of electron etc. All positive or negative charges are equal.

We then obtain by the aforementioned substitutions the unidirectional flux equation:

Equation 2.

$$J = dQ/dt = \frac{-2.6\ D\ \mathrm{Log}([pH1]/[pH2])[C_0 - C_i e^{(-2.6\ D\ \mathrm{Log}([ph1]/[ph2])}]}{dx}$$

Here, the flux J is now made proportional to pH and is a function of EmF or electromotive force.

MATERIALS & METHODS

The experiment was statistically designed using 15 subjects, emulating the local population of normal male and female subjects between the ages of 18 and 60. The statistical number needed was 13 subjects, and thus there was sufficient power. The trial was conducted in an open fashion without blinding because the values obtained were machine generated and analyzed by outside independent laboratories.

FDA approved for human use probes and fraction collecting equipment were made by CMA-Microdialysis of Chelmsford, Massachusetts. The probe was a CMA 70 catheter, 100-mm flexible shaft, with a 10-mm membrane. The analytical work was done and certified by Dr. Jan Kehr of the Karolinska Institute, Stockholm, Sweden. Blood plasma samples were taken in the usual manner.

Zinc ion (Zn^{++}) was used as the trace. The dosage form was a homeopathically compounded lozenge, or oral tablet, entirely made from food ingredients found in the Generally Regarded as Safe (GRAS) list.[3] All of the lozenge's ingredients were governed exclusively by the Dietary Supplement Health and Education Act of 1994 and the Homeopathic Pharmacopœia of the United States (HPUS).[4,5]

The protocol was conducted in compliance with GCP and all applicable requirements of federal, state, and local authorities. There was no infringement of any proprietary or patented product.[6]

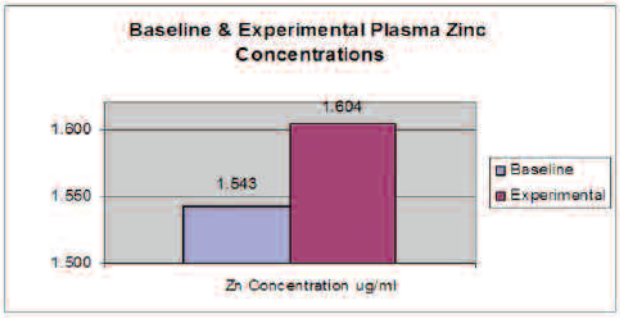
The lozenge was designed to buffer the pH of the mouth at approximately pH 5.4. Our patients' noses had an average nasal pH of 6.35. The electrical potential between compartments as measured by the method of Selimoglu et al using nitrazine pH paper was consistently at Δ= 0.95 pH units in favor of transport to the nose from the mouth.[7] The slight change in expected pH value may have been due to the production of bicarbonate by the sublingual glands.

Inducing the pH change takes control of the corresponding electrical vector, allowing us to manipulate the directions of ionic flow and transport. Because the electrical vector is many times more powerful than the other vectors acting, we may stop or reverse the ionic flow for the time the induced field is present.

The natural electrical gradient lies in the same direction as gravity and the mucocilliary clearance and aids the nose to clean itself. The reversed gradient allows drug delivery to occur over the palate and into the nose from the mouth.

In order to measure delivery, an in situ microdialysis probe was placed in the nostril and introduced past the turbinates to the level of the eustachian tube to freely sample the milieu. The junction of the eustachian tube with the naso-pharynx near the end of the third turbinate was used as a physiological marker for the probe, allowing consistent placement. The probe, which was

FIGURE 4



F-Test Two-Sample for Variances		
	Baseline	Experimental
Mean	1.54372	1.604258157
Variance	0.41817	0.167912146
Observations	49	84
df	48	83
F	2.49038	
P(F<=f) one-tail	0.00013	
F Critical one-tail	1.50885	

BASELINE & EXPERIMENTAL PLASMA ZINC CONCENTRATIONS

A difference of 0.061 between the baseline and experimental plasma values was not significant. The calculated F is larger than F critical one tail.

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not in apposition to the membrane, induced the production of mucous, which leads us to suspect that the delivery may be higher than actually measured because of the extra production of mucous the probe induced.

At 5-minute intervals, 20-microliter dialysis samples were taken from each subject: three controls of deionized water, three from the nasal mucous for baseline, and six from the nasal mucous with the lozenge in place. Simultaneous blood plasma samples were taken at baseline and experimental intervals. The control samples were taken to determine the level of zinc in the lines and probes due to manufacturing.

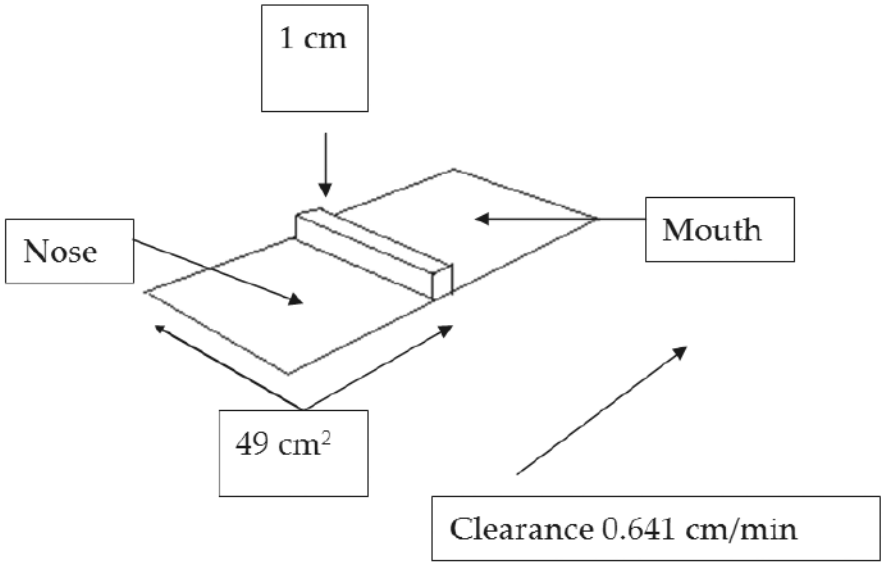
RESULTS

There was less than 2.60 µg/ml of zinc in the line and probes. The baseline nasal zinc was 3.59 µg/ml, and 4.54 µg/ml in the experimental. The differences between experimental and baseline (0.95 µg/ml) were the same with or without subtraction of the controls. The subtraction of the controls from the baseline and experimental values did not affect the results. The unsubtracted results are presented in Figures 2 &3 and Tables 1 & 2. The difference between Baseline and Experimental was 0.95 µg/ml, and this was significant by F-Test ($p = 0.019$). The difference in the two plasma zinc concentrations was 0.061 µg/ml and was not statistically significant by F-test. It is presented in Table 3 and Figure 4.

DISCUSSION

The nasal mucous samples showed a statistically significant difference between baseline and experimental values, while the plasma samples did not. This result demonstrates that systemic

FIGURE 5



Sheet Model of the Naso Pharynx

TABLE 2

	2.9420	3.0980	2.5800	-	2.5300	3.3650
	5.4890	5.7870	5.8580	5.8160	5.9040	8.2800
	3.0870	3.0440	5.8330	5.5060	-	-
	3.9950	4.6460	3.0910	4.5920	5.0460	4.6230
	0.9580	2.0860	1.6820	1.8350	1.9020	2.1450
	2.0220	1.6350	2.1550	3.5720	4.1960	3.0890
	2.4100	2.7150	2.4020	2.6160	2.6910	2.7230
	4.5760	4.4900	4.4100	5.4700	4.3960	5.1840
	2.7070	5.6590	5.5930	5.1170	5.7150	5.8170
	3.4350	4.3380	7.1760	5.6510	3.4940	3.4740
	5.2820	2.2010	4.9880	4.9380	4.8970	4.1160
		3.7280	4.3300	5.4710	5.2140	5.9680
	4.4950	5.7490	1.9870	6.7090	3.9830	4.3250
	6.8750	3.2390	3.5580	2.7490	4.3100	6.3430
	10.4680	11.1150	8.4570	9.1710	11.3870	9.1040
Total	**58.7410**	**63.5300**	**64.1000**	**69.2130**	**65.6650**	**68.5560**
N	**14.0000**	**15.0000**	**15.0000**	**14.0000**	**14.0000**	**14.0000**
Average	**4.1958**	**4.2353**	**4.2733**	**4.9438**	**4.6904**	**4.8969**

*** Blank spaces indicate lost data**

Experimental Nasal Mucous Results µg/ml Zinc

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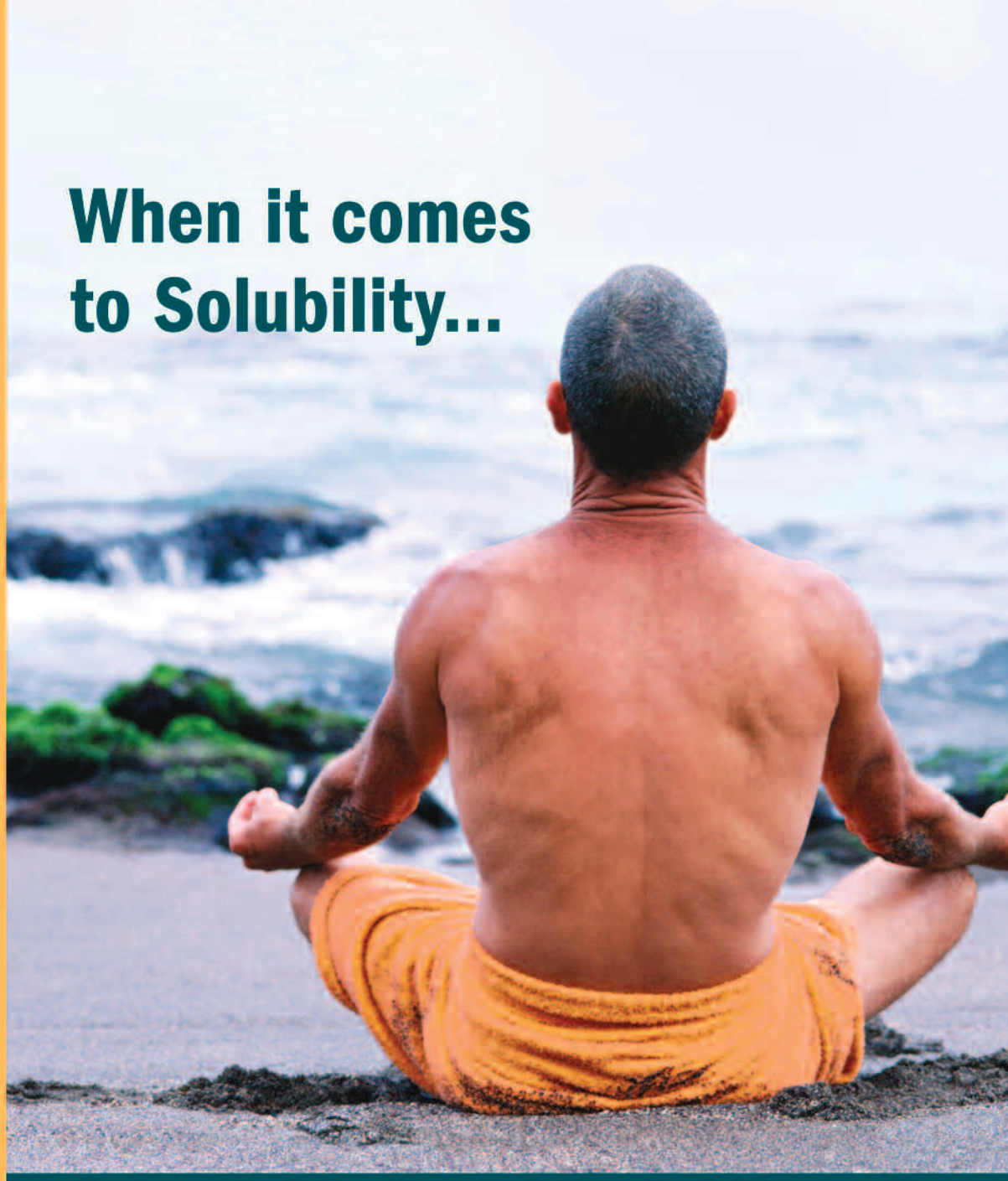

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TABLE 3

Baseline	Baseline	Experimental	Experimental
1.275	1.001	1.426	1.367
1.249	1.066	1.184	1.609
1.145	1.648	1.302	1.642
2.643	1.354	1.446	1.557
1.766	1.426	1.171	1.249
1.779	1.328	1.275	1.374
1.603	1.374	1.851	1.367
1.452	**Average 1.543**	2.113	1.609
1.158		1.524	1.642
1.773		2.734	1.557
1.400		2.937	1.243
1.485		1.746	1.452
2.394		1.439	1.622
1.243		1.622	1.426
1.341		1.347	1.498
1.491		1.452	1.831
1.302		1.792	2.714
2.407		1.537	1.962
1.361		1.485	1.374
1.491		1.001	1.164
1.498		1.164	1.701
1.596		1.354	1.459
1.374		2.080	1.380
1.328		1.321	1.472
1.432		1.583	1.308
1.570		2.021	1.511
1.426		1.406	1.616
1.524		1.347	1.334
1.217		2.093	2.165
1.426		1.295	1.073
1.524		1.504	1.387
1.217		1.845	1.517
1.341		1.426	1.413
1.190		1.544	1.642
1.544		1.648	1.544
1.596		1.171	3.663
1.308		1.786	1.642
1.491		1.877	1.661
1.328		1.962	1.511
1.616		1.786	1.596
5.409		1.936	1.603
1.033		1.249	1.740
1.223		1.374	**Average 1.604**

Plasma Baseline & Experimental Values µg/ml Zinc

delivery of zinc can be ruled out, and delivery of zinc must occur from the mouth to the nose. How much is delivered and what are the characteristics of the delivery? We may be able to answer these questions by using the geometric model developed in our previous work. The placement of the probe was at the end of the third turbinate near the eustachian tube junction with the pharynx. This anatomical placement corresponds to a uniform position just anterior to the midpoint of our flat sheet model. We estimate that the probe was about 1 cm above the surface of the membrane by direct observation. By estimating the volume of liquid in this domain and multiplying by the concentration, we can estimate the amount of zinc delivered by using the approximate velocity of the mucocilliary clearance.

Referring to our model, the length and width of the path is 7 x 7 cm, with an estimated height of 1 cm. Thus, the nasal half of the sheet holds 49 cc of fluid. This fluid is considered to result from all sources and includes flow from the turbinates and sinuses as well as probe-induced mucous. The average mucocilliary clearance (Table 4) is considered to be 0.641 cm/minute. To travel a distance of 7 cm clearing the nasal half of the sheet and its volume of 49 cc of fluid requires 10.92 minutes.

Because the lozenge dissolves over 30 minutes, mucocilliary clearance clears this 49-cc volume of mucous 2.75 times. This becomes 134.75 cc of fluid cleared over 30 minutes. The approximate steady state concentration detected by probe is nearly 1 µg/ml of zinc. This translates into approximately 0.135 mg of zinc ion delivered (Figure 5). This calculation does not take into account the other turbinates, sinuses, or the mucous induction due to the probe, but assumes them to be contributory to the milieu. Thus, delivery

TABLE 4

Source	Range	Average Speed
Ann Otol Rhinol Laryngol. 2002;111(1):779	2.9 to 5.66 mm/min	4.28 mm/min
Rhinol. 1986;24(4):241-247	3.3 to 8.2 mm/min	5.3 mm/min
Arch Otolaryngol. 1982;108(2):99-101	5.8 to 13.5 mm/min	9.65 mm/min
Grand Average Velocity		**6.41 mm/min**

Mucocilliary Transport Velocity

may be greater than is estimated here.

Calculation Summary

- 7 x 7 cm x 1 cm = 49 cc fluid
- 7 cm/0.641 cm/min = 10.92 minutes to clear nasal end of sheet once
- 30 min lozenge dissolution time/10.92 minutes per clearance = 2.75/clearances per 30 minutes
- 49 cc fluid x 2.75 = Volume cleared in 30 minutes = 134.6 cc
- 134.6 cc x 1 µg/cc detected = 134.6 µg Zn^{++} = 0.1346 mg Zn^{++} delivered

This amount of drug is well within the range of the minimal effective concentration of most drugs, when directly delivered, and corresponds to delivery at nearly 1 pH unit difference. This increases exponentially by increasing the difference between compartments (pH), according to Equation 2.

CONCLUSION

Electro-osmotic delivery exists and is potentially a very useful modality in drug delivery. Since the governing flux equation is responsive to the ratio of the pHs in an exponential manner, a small difference in this ratio makes a large difference in delivery. By reversing this ratio, a charged medication can be forced to remain in one place, within a solid tumor, for example. This can sensitize the tumor to radiation and chemotherapy, resulting in a reduction of these agents, and localization of therapy. This modality predicts new forms and new activity for old forms. Particularly, extremely thin skin patches, lozenges, bandages, and wound staunching pastes are foreseen.

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BIOGRAPHIES

Dr. Nicholas A. Sceusa was born and privately educated in New York City. He graduated from Syracuse University with a BS in Biology and a minor in Chemistry. During the learning phase of his career, he studied at the Sorbonne in Paris and the University of Clermont-Ferrand in France. Familiar with European methods of administrations and scientific development, he paid particular attention to the medical sciences and the development of the national cultures of Spain, Italy, and France. Dr. Sceusa earned his BS in Pharmacy at the Arnold and Marie Schwartz School of Pharmacy and Allied Health Sciences. He practiced pharmacy for several years before joining the drug development team of Revlon Health Care Group, Inc. His research interests were furthered by courses at New York University in Physical, Organic, and Inorganic Chemistry and Statistics. Dr. Sceusa earned his PharmD from the University of Illinois at Chicago, specializing in the scientific and drug development aspects of the field. He is experienced in Clinical Trials Project Management & Monitoring, Clinical Trials Coordination and Drug Information, various aspects of Informatics and Safety Evaluation, and has practical experience in Drug Safety, Adverse Events Reporting, and Regulatory Affairs. Medical research interests include cardiovascular disease (particualrly hypertension), infectious and pulmonary disease, viral attachments sites, adhesion molecules, allergy, endocrinology, and obesity. He holds patents in biofiltration and on the unique Teorell-Meyer Dosage Forms.

Dr. Paul M. Ehrlich was born and privately educated in the New York Metropolitan Area. He prepped at the prestigious Taft School in Watertown, CT. He is an alumnus of Columbia University and a graduate of New York University Medical School. His post-doctoral education was extensive. From 1977, he has maintained a private practice in Allergy and Immunology and has been regarded as one of New York's Best Doctors since this publication was first published. Dr. Ehrlich completed his pediatric clerkship at the Hospital for Sick Children, in London, UK, was a member of the Department of Allergy and Immunology at the Walter Reed Army Hospital in Washington, DC, and served as a Lt. Commander in the United States Navy during the Vietnam era. He is a Diplomate of the National Board of Medical Examiners, the American Board of Pediatrics, and the American Board of Allergy and Immunology. Dr. Ehrlich is a Fellow of the American Academy of Pediatrics, The American Academy of Allergy, Asthma and Immunology, The American Thoracic Society, and takes an active part in many professional societies too numerous to mention. To add to the list of his accomplishments, Dr. Ehrlich is the Medical Editor of the MA Report and a member of the Editorial Advisory Board of *Asthma Management*. He is the author of *What Your Doctor May Not Tell You About Your Children's Allergies or Asthma*. He is presently Clinical Assistant Professor of Medicine in the Department of Pediatrics at NYU Medical Center in Manhattan.