TECH NOTE

Empi

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Dupel BLUE versus Performa V^{e}
A Scientific Comparison of Drug Delivery Efficiency and Other Performance Factors

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Summary
Empi has performed testing to evaluate ionic solution delivery rates, pH buffering capacity, and current distribution of two iontophoretic electrodes: Empi's Dupel BLUE electrode and Sammons Preston Rolyan's (SPR's) Performa V^{e} electrode. The tests were performed to investigate SPR's claims that the Performa V^{e} delivers 33% more drug and provides more uniform distribution than other buffered electrodes. These claims were found to be without basis. Empi's Dupel BLUE outperformed the Performa V^{e} in delivery of both positive and negative ionic solutions and provided equally uniform current density distribution. Furthermore, the Dupel BLUE electrode more effectively buffered pH for positive delivery.

In Vitro Iontophoretic Delivery of Ionic Solutions

Bench-top testing using a constant current iontophoretic device and an analog of human skin showed that the Dupel BLUE electrode delivered significantly more of the targeted ions than the Performa V^{e}. This was true for both positive and negative ions and for dosages of 40 and 80 mA min.

These tests used the following electrodes:

Dupel BLUE Small	Fill Volume 1.5cc	Active Area 6.67 sq. cm.
Dupel BLUE Butterfly	Fill Volume 2.0cc	Active Area 8.1 sq. cm.
Dupel BLUE Large	Fill Volume 4.0cc	Active Area 15.97 sq. cm.
Performa V^{e} Medium	Fill Volume 2.0cc	Active Area 11.1 sq. cm.
Performa V^{e} Large	Fill Volume 3.0cc	Active Area 18.0 sq. cm.

There were no significant differences in delivery amounts among the different sizes of Dupel BLUE electrodes. The two sizes of Performa V^e electrodes tested were also similar to each other.

The ions targeted for delivery included a negatively charged ionic solution with a molecular weight of 516.4 g/mole and a positively charged ionic solution with a molecular weight of 270.8 g/mole. The negative ion can be monovalent or divalent (-1 or –2) depending on the pH. The positive ion is monovalent (+1).

Method

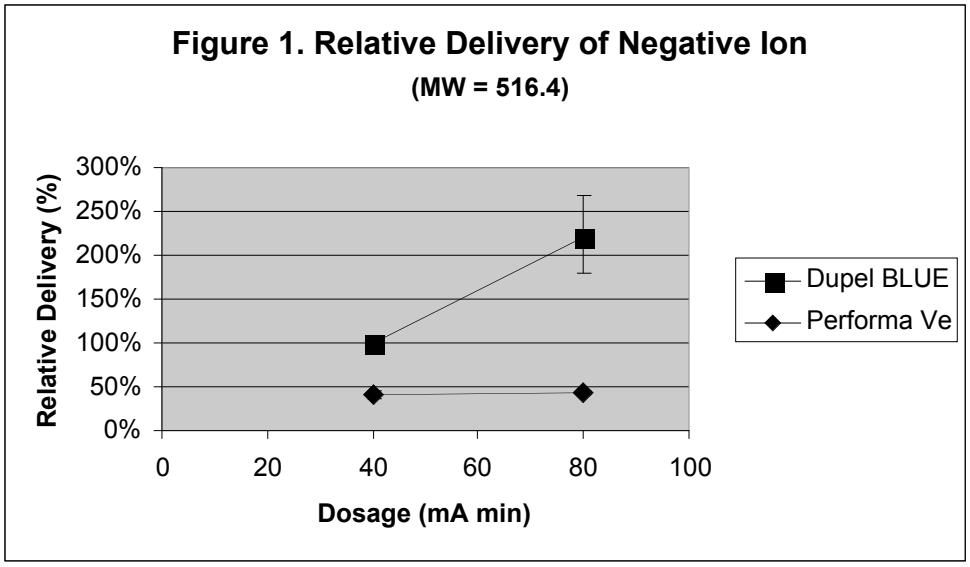
Tests were performed using a hairless mouse skin stretched over agarose (1% in saline) contained in an aluminum pan. Each electrode was filled with the appropriate volume of ionic solution and placed on top of the mouse skin. Empi's Dupel device, a constant current generator, was connected to the electrode, and the aluminum pan was used as the indifferent or return electrode. The Dupel device was set to deliver 4 mA for 10 or 20 minutes in order to achieve dosages of 40 or 80 mA min, respectively.

After the treatment the mouse skin and agarose were extracted with water in separate vials. The samples were analyzed using High Performance Liquid Chromatography (HPLC). The total amount of drug delivered was calculated by the summation of the amount found in both the skin and the agarose. At least three tests were performed for each electrode at each dosage.

Results: Negative Ions

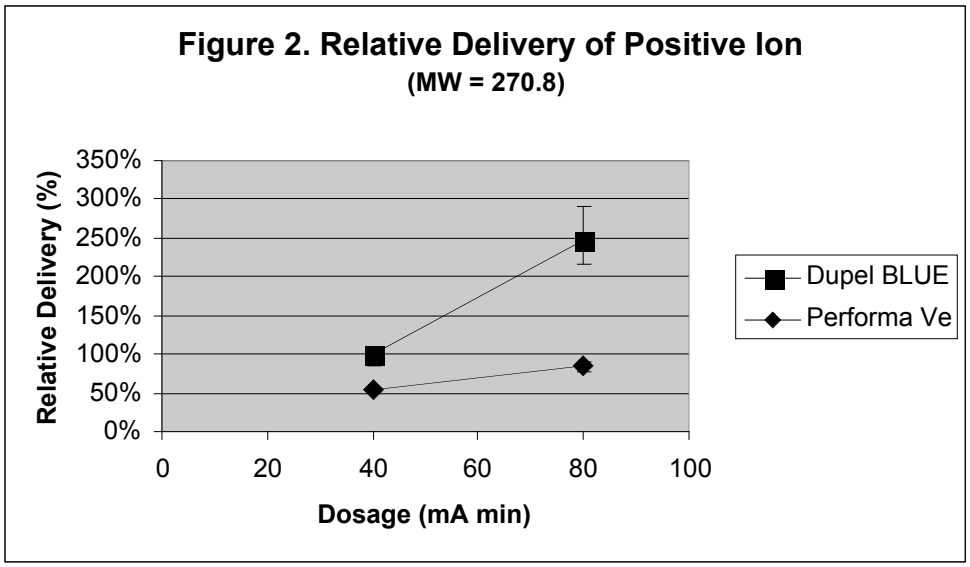
The results for negative ion delivery are shown in Figure 1. At 40 mAmin, Dupel BLUE electrodes deliver more than twice as much of the targeted negative ion as the Performa V^e electrodes. The difference between the two electrodes is even more pronounced at 80 mAmin. **The Dupel BLUE electrodes deliver more target ions at 40 mAmin than the Performa V^e electrodes deliver at 80 mAmin.** Furthermore, for Dupel BLUE electrodes, the amount delivered continues to increase as the dosage is doubled from 40 to 80 mA min. The Performa V^e delivers only 10% more for the same increase in electrical dosage.

The Dupel BLUE electrodes buffer the ionic solutions to a neutral pH near 7. The Performa V^e electrodes buffer to an acidic pH near 4.5. At pH 7, most of the target ions are doubly charged, but at pH 4.5 they are singly charged. Although singly charged ions can deliver more efficiently than doubly charged ones because they require only half of the current, there are many other factors that affect the total amount of ionic delivery. As shown in Figure 1, the Empi electrode at pH 7 delivered substantially more of the targeted negative ion than did the Performa V^e buffered at pH 4.5. Empi conducted additional tests in which the Dupel BLUE buffer was adjusted to a lower pH to make 90% of the target ions singly charged. There was no significant difference in delivery between these electrodes and the pH 7 electrodes.



Results: Positive Ions

The results for positive ion delivery are shown in Figure 2. At 40 mAmin, the Dupel BLUE electrode delivers nearly twice as much of the targeted positive ion as the Performa V^{e}, and nearly three times as much at 80 mA min. Again, the Dupel BLUE at 40 mAmin outperforms the Performa V^{e} at 80 mAmin.



pH Buffering

Empi electrodes use a patented immobilized buffer to maintain a safe solution pH between 4 and 8 during treatment. The composition and amount of the buffer is closely monitored during electrode production. Empi electrodes are capable of maintaining the pH between 4 and 8 for more than 160 mAmin (twice the maximum recommended dosage). For negative delivery, the Performa V^{e} electrode is also capable of keeping the

pH below 8 for more than 160 mAmin. However, for positive delivery, the pH of the Performa V^{e} electrode falls below 4 almost immediately.

All buffers contain ions or charged molecules. These buffer ions will compete with the target ions for iontophoretic delivery across the skin if they are not immobilized. Only Empi electrodes contain a patented immobilized buffer, which keeps the buffer molecules in the electrode. Dupel BLUE electrodes also incorporate a patented bi-layer design that separates the buffering layer from the ionic solution reservoir. In this design, the granular buffer is intentionally placed next to the conductor in the electrode to neutralize the acid or base molecules as soon as they are generated. The ions targeted for delivery are concentrated in the electrode layer nearest the skin.

Viscosity

Performa V^{e} electrodes are claimed to contain a Viscosity Enhancing Agent that "creates uniform distribution of ingredients ensuring superior drug transport." (from SPR web site) The more viscous a substance is, the more it resembles molasses or grease. The progress of molecules through a more viscous substance is slower than its progress through a less viscous substance. The Performa V^{e}'s Viscosity Enhancing Agent may improve the uniformity of delivery, but it is likely that it decreases the delivery rate.

Uniform Current Distribution

SPR claims that the immobilized buffer in Empi's electrodes causes air pockets and uneven current distribution. In reality, the Empi buffer is hydroscopic, meaning that it readily absorbs water or aqueous solutions. The recommended fill volumes for each electrode were chosen to ensure complete wetting of the electrode from the skin to the conductor. Current density distribution can be easily checked by running an electrode filled with saline on a silver plate. The process is similar to the photographic process, and Dupel BLUE electrodes have consistently demonstrated very uniform current distributions.

Conclusion

Testing has shown that Empi's Dupel BLUE electrode performs better than Sammons Preston Rolyan's Performa V^{e} electrode in iontophoretic delivery of both positive and negative ions. The Dupel BLUE electrode delivered two and a half to five times more of the targeted negative ions used in this study than the Performa V^{e} electrode did. BLUE electrodes also delivered 2 to 3 times more positive ion than Performa electrodes.

Dupel BLUE electrodes provide significantly better buffering for positive delivery treatments than Performa V^{e} electrodes. The Dupel BLUE's patented bi-layer design separates the pH buffer from the drug reservoir, thereby reducing the effect of the buffer on drug delivery. Also, Empi uses a patented immobilized buffer that is less likely to compete with the drug ions. The Dupel BLUE electrode materials ensure adequate wetting of the electrode and provide a uniform current density distribution.