

DOCTOR'S REPORT

New Trends in Drug Delivery Systems: Mesoporation, a Novel Technique

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RATIONALE

Transdermal drug delivery is based on the absorption of drug into the skin after topical application. This route of drug administration has a long history and the advantages have been well documented. In contrast to orally delivered drugs, compounds entering the body through the skin escape first-pass metabolism in the liver, often resulting in higher bioavailability. In addition, transdermal delivery can be used in nauseous patients, is little affected by intake of food, and can be easily interrupted. In contrast to intravenous drug delivery, transdermal administration is noninvasive and poses little risk of infection. Because transdermal drug delivery allows continuous delivery of drugs, frequent bolus dosing of drugs with short half-lives is avoided. As a result, side effects or variability in therapeutic effect due to peaks and troughs in plasma concentration that are seen with bolus administration are minimized.

However, the excellent barrier function of the skin and the lipophilic nature of the stratum corneum in particular mean that the useful transport of charged and/or highly polar drugs requires an effective enhancement strategy. In fact, skin protects the body from the environment very effectively and generally is permeable only to small, lipophilic drugs.

Transdermal delivery systems, therefore, not only have to provide drug to the skin under stable conditions and in a form convenient to the patient, but also serve to locally increase the permeability of skin to larger, charged, or hydrophilic drug molecules while minimizing irritation.

Iontophoresis, of course, represents one such approach, and its application to the delivery of pharmacologically active peptides has attracted significant attention. Peptides also serve as models for other classes of new biotechnology drugs, such as small proteins and oligonucleotides.

The objectives of this study, therefore, are to review the current state of the art in peptide iontophoresis, examine

the mechanistic implications of the results obtained, and identify the experimental variables that affect the efficiency of peptide delivery.

Iontophoresis enhances the transdermal delivery of substances by 3 different mechanisms: electrorepulsion, electro-osmosis, and electrically induced skin permeability changes. These 3 mechanisms are operative for iontophoresis of peptides, and their relative importance has been studied. With an alternative medical device developed by Microlab Biomedical Srl, Italy, the transport observed is higher than with iontophoresis. This device seems to enhance transdermal delivery by using a combination of iontophoresis, mechanical pressure, and electroporation. The mechanism of this new technique, called *mesoporation*, appears to be completely different from iontophoresis. In iontophoresis the flux is related to the total charge transported through the system; electroporative voltage pulses produce transient permeabilization of the stratum corneum, and transport cannot be related to the amount of charge passed across the skin.

In this study, observation was limited specifically to iontophoresis versus mesoporation.

MATERIALS AND METHODS

A labeled peptide solution was dissolved and homogenized via a centrifuge into the carrier gel. A total of 6 volunteers, all overweight women between ages 30-45 years, were selected from patients waiting for liposuction operations. They underwent a light micro-dermoabrasion treatment in the abdominal area. An 8% solution of glycolic acid was spread on the same area to lower the pH of the skin. Radioactivity was measured with an automatic digital detector. The 6 volunteers were divided into 3 groups. The first 2 groups were treated with mesoporation with labeled peptide. The last group was treated with iontophoresis and labeled peptide. Samples of fat were extracted using a syringe with a 14-gauge needle. After 20 minutes of treatment, samples from each volunteer were extracted at 1 cm, 2 cm, 4 cm, and 6 cm depth. Fat tissues were homogenized and dissolved in 3 mL NaOH 1 N solution, and radioactivity of the solutions were measured.

Percentage of Radioactivity Detected Versus Depth of Penetration

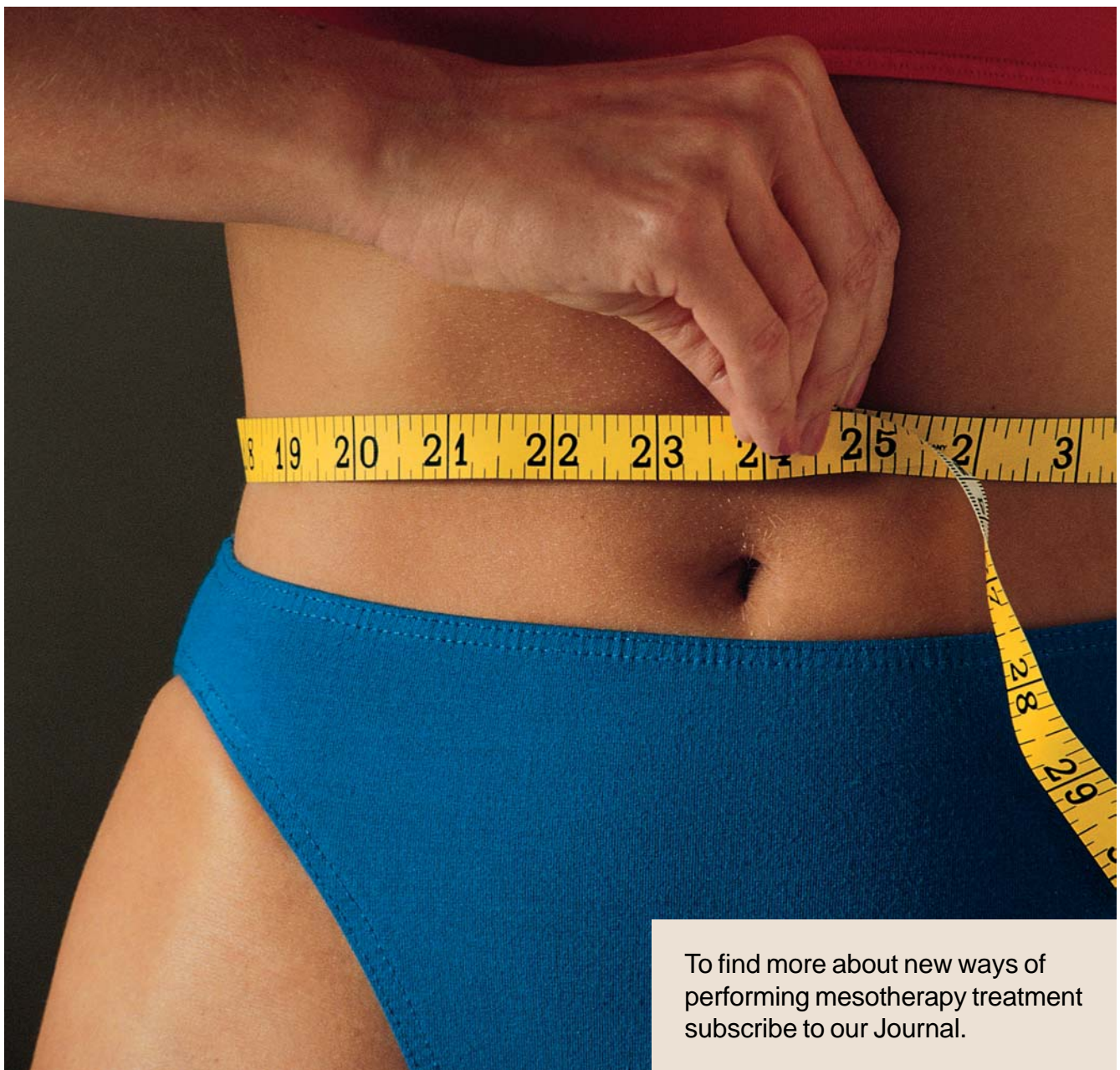
Depth, cm	6	4	2	1
Frequency, Hz	900	1300	1650	1800
Radioactivity, %				
Mesoporation	65%	82%	94%	99%
Iontophoresis	3%	3%	5%	10%

After 20 minutes of treatment with iontophoresis in the abdominal area, the radioactivity detected at 6 cm was 3% of the total. The activity, measured at 6 cm depth and at a frequency of 900 Hz, was 65% after mesoporation.

CONCLUSIONS

Measurement of radioactivity indicates that iontophoresis is minimally efficient in transdermal transportation of the marked substance administered. This result may be related to the lipophilic nature of the stratum corneum, which is an electrical impedance.

Mesoporation improves migration of the radioactive compound under the effect of the electrical field and the electric roll-on creates an ideal driving force that favors the transdermal passage of the marked peptide. We conclude that mesoporation is an innovative, effective method for the transdermal transportation of both ionized and neutral drugs.



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