IOPscience iopscience.iop.org

Home Search Collections Journals About Contact us My IOPscience

Photoacoustic evaluation of the penetration of piroxicam gel applied with phonophoresis into human skin

This article has been downloaded from IOPscience. Please scroll down to see the full text article.

2010 J. Phys.: Conf. Ser. 214 012022

(http://iopscience.iop.org/1742-6596/214/1/012022)

View the table of contents for this issue, or go to the journal homepage for more

Download details:
IP Address: 152.84.250.198
The article was downloaded on 12/05/2010 at 20:44

Please note that terms and conditions apply.

Journal of Physics: Conference Series **214** (2010) 012022 doi:10.1088/1742-6596/214/1/012022

Photoacoustic evaluation of the penetration of piroxicam gel applied with phonophoresis into human skin

F.L.F.D.Silveira[a], P.R.Barja[a] and D.Acosta-Avalos[b]

[a]Research and Development Institute, UNIVAP, Av. Shishima Hifumi 2911, São José dos Campos, SP, Brazil, 12209-010

[b]Centro Brasileiro de Pesquisas Fisicas (CBPF), R.Xavier Sigaud 150, Rio de Janeiro, RJ, Brazil, 22290-180

barja@univap.br

Abstract. The photoacoustic (PA) technique has been increasingly employed in biomedical studies, allowing *in vivo* skin measurements not easily performed with other techniques. It is possible to use PA measurements to evaluate transdermal delivery of products topically applied through manual massage or phonophoresis, that is the utilization of ultrasound waves to enhance drug absorption. The aim of this study was to analyze the influence of the period of phonophoresis application in the transdermal penetration of piroxicam gel. *In vivo* PA measurements employed a tungsten lamp as light source and a thin aluminum foil closing the PA chamber. The PA signals of the arm (i) clean; and (ii) after phonophoresis were utilized to estimate the concentration of piroxicam into skin. For all (4) volunteers, drug concentration in skin after phonophoresis application was the same for the different application times employed; in this way, phonophoresis for one minute seemed to be sufficient to enhance piroxicam penetration into skin. The actual amount of drug delivered into tissue depends on the person, suggesting a dependency with the skin type, which affects the PA signal level [2]. We conclude that drug delivery depends not only on the application method, but also on the specific skin type.

1. Introduction

Since 1976, when Rosencwaig and Gersho developed a model [1] that explains the photoacoustic (PA) effect in solids through the diffusion of the heat generated after absorption of radiation by the sample, the PA technique has been successfully employed in different biological and biomedical studies, allowing *in vivo* skin measurements not easily performed with any other technique. The penetration of substances topically applied to skin can be evaluated through PA measurements taken as a function of time [2]. Not only the specific drug (active principle) applied, but also (and mainly) the vehicle substance influences the penetration kinetics of the product under study [3].

Phonophoresis can be defined as the utilization of ultrasound (US) waves to enhance absorption of drugs across the epidermal barrier, and its usefulness in the topic application of anti-inflammatory drugs as diclofenac resinate has been shown by previous studies [4]. However, the mechanism of action for this procedure remains incompletely defined, though cavitation and thermal processes have been strongly implicated [5]. Recently, Barja *et al* employed *in vivo* PA measurements to evaluate transdermal delivery of diclofenac resinate (Cataflan©) topically applied using two different

© 2010 IOP Publishing Ltd

techniques: manual massage and phonophoresis (US in continuous mode) [4]. It was observed that the concentration of Cataflan© was higher after phonophoresis, showing that US therapy did enhance drug delivery through skin.

In the present report, a study of piroxicam gel penetration was performed comparing three different phonophoresis application times (1, 2 and 3 minutes), to analyze if drug delivery enhances with the increase of the phonophoresis application time.

1.1. Theory

The Rosencwaig-Gersho (RG) model [1] states that the PA signal is produced after the transformation of electromagnetic energy in heat, through non-radiative pathways. The heat diffusion through the absorber and environment can be analyzed using the diffusion equation for each media involved. In this way, the RG model produces a complete solution for the PA signal that is, however, a complex mathematical expression. Different thermal and optical regimes are considered, with the samples being optically classified as transparent or opaque and thermally classified as thin or thick, depending on the relation between the thermal diffusion length (μ) and the sample thickness (*l*).

The thermal diffusion length is defined as:

$$\mu = \sqrt{\frac{\alpha}{\pi f}} \tag{1}$$

where α is the thermal diffusivity and *f* is the modulation frequency of the incident radiation; thus, an increase in *f* produces a decrease in μ. If $\mu > l$, the material is considered thermally thin; if $\mu < l$, it is considered thermally thick. The continuous increase in *f* produces a transition from the thermally thin to the thermally thick regimes. The complete mathematical expression for the PA signal can be simplified in the different optical and thermal regimes. For the case of optically opaque and thermally thin samples, the PA signal [4] can be written as:

$$\text{PA signal} \approx \frac{Y\mu_b\mu_g}{2k_b} \tag{2}$$

where *Y* is a constant, μ_b is the thermal diffusion length for the base material (material over the sample, in the opposite face to that illuminated by the electromagnetic radiation), k_b is the thermal conductivity of the base material and μ_g is the thermal diffusion length for the gas (generally, air) facing the sample on the side illuminated by the electromagnetic radiation. Eq.(2) can be rewritten using the definition for the thermal effusivity $\varepsilon = k/\sqrt{\alpha}$, a parameter related with the capacity of a material to interchange heat with the environment. Eq. (2) can then be rewritten as:

$$\text{PA signal} \approx \frac{Y\sqrt{\alpha_g}}{\varepsilon_b \pi f} \tag{3}$$

In this case, the PA signal depends on the thermal parameters of the gas and the base, being influenced by changes in themal parameters of both materials.

In the double-faced PA cell employed, the modulated light impinges first on a glass window that closes one face of the PA chamber, and the opposite face is closed with an aluminum foil. *In vivo*, human skin is behind this aluminum layer. In such a scheme, the "sample" corresponds to the aluminum foil, the "gas" is the air and the human skin plays the role of the "base". To apply eq.(3) the Al foil must be not only optically opaque, but also in the thermally thin regime, obtained by low modulation frequencies; the PA signal then depends on the thermal effusivity of the human skin.

Gutierrez-Juarez *et al* [6] also studied the drug penetration through human skin using PA techniques. They evaluated the thermal effusivity of a mixture of substances (ε_{MIX}) and proposed the following expression for ε_{MIX}:

$$\varepsilon_{MIX} = \varepsilon_1 (\varepsilon_2 / \varepsilon_1)^X \tag{4}$$

where X is the relative concentration of substance 2 on substance 1. As we are interested in evaluating the penetration of drug into the human skin through the estimation of X, in eq.(4) the subscripts are identified as follows: MIX for the complex skin plus drug, 1 for the clean skin and 2 for the drug. In this way, X can be written as follows:

$$X = \frac{\log(\varepsilon_{MIX}/\varepsilon_{SKIN})}{\log(\varepsilon_{DRUG}/\varepsilon_{SKIN})} \tag{5}$$

As $\varepsilon_{\mathrm{DRUG}}$ and $\varepsilon_{\mathrm{SKIN}}$ are constants and ε is inversely proportional to the PA signal, we obtain for the concentration:

$$X_{\mathrm{Re}l} \approx \log\left(\frac{PA\ Signal_{SKIN}}{PA\ Signal_{MIX}}\right) \tag{6}$$

where X_{Rel} is an approximate estimation of the concentration X of the applied product inside the skin; it can be used for comparison among different treatments (this value is approximate because of the multiplicative constant factor $\log(\varepsilon_{DRUG}/\varepsilon_{SKIN})$ that does not depend on the phonophoresis treatment). According to this definition, one can see that $X_{Rel\ \mathrm{m}}$ must be zero for untreated skin.

In this way, the measurement of the PA signal of the clean skin and of the skin plus drug after phonophoresis application is sufficient to compare the concentration of the drug inside the skin for diverse treatments.

2. Materials and Methods

Four young (21 to 32 years old), female volunteers took part in the study. Volunteers should not present neither allergy to the drug employed nor injury or metallic implant in the region of the skin chosen for the experiment.

PA measurements employed a tungsten lamp (24V, 250W) as light source, modulated at 17Hz by a mechanical chopper (Stanford Research Systems, mod.SR540). Light was directed to a double-faced PA cell closed by a glass window in one side and, in the other, by a thin aluminum foil (about 65μm thickness). Under these conditions, μ=0.13cm and the thermally thin requirement is satisfied.

The PA signal was detected by an electret microphone (inside the PA cell) connected to a lock-in amplifier (Stanford Research Systems, mod.SR530). A computer was interfaced to the lock-in through the RS232 port to control the data acquisition process.

Initial PA measurements were performed in the clean skin, gently pressed against the external face of the Al foil. After that, Piroxicam gel (3g) was applied to the right arm through phonophoresis. Three different regions of the same arm were chosen to apply the drug with different phonophoresis application times (1, 2 and 3 minutes). The experimental procedure was repeated after 24h, because this period corresponds to the half life time of the drug in the body. Ten repetitions were done in all volunteers. The US equipment utilized in the phonophoresis was operated in the continuous mode, at 3MHz, with an intensity of 0.5W/cm^2. After phonophoresis, the volunteer pressed the skin against the Al foil on the PA cell and the PA signal was registered at three second intervals, up to a total of 100 points, from which the average value was taken as the PA signal value. For each phonophoresis application period (1, 2 and 3 minutes), this procedure was repeated subsequently 10 times and a statistical analysis was done on the total set of average values.

The software Microcal Origin™ was utilized to analyze the obtained data. Statistical analysis (ANOVA or Student's t tests) was performed using GraphPad InStat v.3.0 (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

3. Results and discussion

With the experimental setup and conditions employed, the PA signal level for the clean skin was equivalent for all volunteers. For the modulation frequency employed the skin layer under study has a thickness between 30 and 40μm [4]. Penetration and storage of the drug in the skin decrease the PA signal when compared to the signal of the clean skin (see eq.6). Accordingly, for all volunteers, it was

observed that the PA signal for the clean skin was indeed significantly higher than the PA signal of skin plus Piroxicam (paired Student's t test, $p<0.05$ for all the analyzed times, in all volunteers).

The averaged values for the PA signals of clean skin and skin plus Piroxicam were used to estimate the value of the relative concentration X_{Rel}, for each volunteer and for each phonophoresis application time. Table I shows the results for X_{Rel}.

Table I: Average value ($X_{Rel\ m}$) and standard deviation (SD) calculated for the approximate values of the relative concentration X_{Rel}, for each volunteer and for each phonophoresis application time.

Volunteer	1 min	2 min	3 min
1	0,082 ± 0,045	0,092 ± 0,052	0,125 ± 0,044
2	0,076 ± 0,049	0,064 ± 0,036	0,041 ± 0,029
3	0,067 ± 0,053	0,062 ± 0,023	0,083 ± 0,046
4	0,086 ± 0,048	0,035 ± 0,026	0,077 ± 0,058

For each volunteer, an ANOVA test was done to compare the X_{Rel} values obtained for the three different application times. For all volunteers, the ANOVA test showed that all the obtained X_{Rel} values are statistically similar in the different times analyzed ($p>0.05$). This suggests that higher phonophoresis application times do not increase the quantity of drug that penetrates the skin; in this case, phonophoresis for one minute seems to be already enough to enhance transdermal drug penetration. It was also observed that the actual amount of drug delivered into tissue depends on the person, suggesting a dependency with the skin type, which affects the PA signal level [7].

Considering the skin as a barrier that cumulates the drug to a later (and slower) diffusion to deeper tissues, the result obtained indicates that the drug does not penetrate increasing its concentration with the increase in phonophoresis time, but its concentration maintains approximately the same value and perhaps the phonophoresis promotes lateral drug diffusion when the vertical drug penetration saturates. However, another interpretation is possible if we think that the skin behaves as a dynamical barrier when phonophoresis is used, allowing continuous drug delivery to deeper tissues without drug accumulation in the stratum corneum (which is the layer actually responsible for the photoacoustic signal in our experiment). More experiments must be done to elucidate which interpretation is more correct.

4. Conclusion and perspectives

The results obtained in this work support that the PA technique can be successfully employed to study *in vivo*, transdermal drug delivery. In all evaluated cases, drug concentration in skin after phonophoresis application was equivalent for the different application times employed, indicating that the application of phonophoresis for one minute suffices to enhance piroxicam absorption up to a saturation concentration. Preliminary experiments already performed at our laboratory indicate that this saturation value depends on: i) skin parameters; ii) US parameters (US in pulsed wave mode seems to promote higher concentration values than US in continuous mode). Additionally, drug delivery depends not only on the application method, but also on the specific skin type. We emphasize that different topically applied formulations may present different responses to phonophoresis application.

References

[1] A.Rosencwaig, A.Gersho. J Appl Phys 47, 64-69 (1976).
[2] P.R.Barja, C.A.Lobato, R.F.Paiva, R.C.P.Rossi. 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, cd-rom (2008).
[3] R.C.P.Rossi, R.F.Paiva, M.D.Silva, P.R.Barja. Eur. Phys. J. ST 153, 479-482 (2008).
[4] P.R.Barja, D.Acosta-Avalos, P.C.B.Rompe, F.H. dos Anjos, F.R.Marciano, M.D. da Silva. J.

Phys. IV 125, 789-791 (2005).
[5] G.Merigno, Y.N.Kalia, R.H.Guy. J Pharm Sci 92, 1125-1137 (2003).
[6] G.Gutierrez-Juarez, M.Vargas-Luna, T.Cordova, J.B.Varela, J.J.Bernal-Alvarado, M.Sosa. Phys Meas 23, 521-532 (2002).
[7] J.P.Mota, P.R.Barja. 14th ICPPP - International Conference on Photoacoustic and Photothermal Phenomena, Cairo, 14th ICPPP Abstracts, 216 (2007).