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Enhancement of Transdermal Delivery of Indomethacin and Tamoxifen by Far-Infrared Ray-Emitting Ceramic Material (BIOCERAMIC): A Pilot Study

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Abstract

BIOCERAMIC have been found to modulate various biological effects. Our earlier published research on various cell lines demonstrated that BIOCERAMIC promoted microcirculation, upregulated calcium-dependent nitric oxide and calmodulin, and exerted an antioxidant effect by increasing hydrogen peroxide scavenging ability. The development of pain relief systems requires most possible minimum doses and methods for effective local control of pain, so as to protect liver and renal function. There is also clinical necessary to develop targeted delivery of estrogen inhibitor in the breast using a local drug release system, to protect the breast from the increased cancer risk associated with the use of estrogen therapy. We compared the viscosity of BIOCERAMIC irradiated water and control water, and found that BIOCERAMIC might weaken the hydrogen bonds. Such breaks are caused by the loss of hydrogen bond covalence resulting from electron rearrangement. The purposes of this study were thus to investigated a transdermal drug delivery model using Franz cell apparatus for Indomethacin and Tamoxifen. The results showed that BIOCERAMIC enhanced the diffusion and permeability of the drugs. Therefore, we suggest that BIOCERAMIC might enhance the penetration performed by hydrogen bond weakening due to physical induction, and may facilitate local drug delivery in transdermal systems.

Keywords: BIOCERAMIC; Hydrogen bond; Transdermal delivery; Indomethacin; Tamoxifen

Introduction

The most widely used analgesics are Non-steroidal Anti-Inflammatory Drugs (NSAID). However, these are known to cause adverse side effects in the gastrointestinal tract, such as ulcerations, strictures, colitis, or exacerbation of inflammatory bowel disease [1]. Another possible consequence of NSAID use is hepatic injury, most likely caused by an idiosyncratic reaction resulting from an immunologic response or altered metabolic pathways [1]. Renal complications have also been reported in cases of frequent abuse of NSAID [2]. Research on minimum doses and effective local pain relief is needed to reduce patients' drug dependence for pain control.

Estrogen Replacement Therapy (ERT) has been shown to reduce the risk of Cardiovascular Disease (CVD) and heart disease in postmenopausal women. Such Hormone Replacement Therapy (HRT) also protects against osteoporosis, a degenerative bone disease, and might provide some protection against Alzheimer diseases and Type II diabetes. HRT can also improve mood and alleviate depression, and enhance short- and long-term memory [3]. On the negative side, major epidemiological data demonstrate an association between HRT and breast cancer risk in menopausal women; specifically, longer duration of recent use of HRT was related to an increased risk of breast cancer [4].

Such research findings have caused fear among many menopausal and post-menopausal women who are using HRT or are considering the therapy, with some women unnecessarily refusing to start HRT or ceasing to use it. The development of a targeted delivery system for estrogen inhibition in the breast, using a local drug release system, would be ideal to protect the breast from the negative side effects of ERT. The transdermal drug delivery system has the potential advantage of local application to concentrate the drug release in regional doses. Transdermal delivery also reduces negative effects in the gastric and bowel mucosa, avoids hepatic first pass metabolism, maintains constant and lower blood levels for a longer time, and decreases side effects in the kidney.

We performed a series of studies on far-infrared ray-emitting ceramic material (BIOCERAMIC). Our earlier published research on various cell lines demonstrated that BIOCERAMIC promoted microcirculation, upregulated calcium-dependent nitric oxide and calmodulin, and exerted an antioxidant effect by increasing hydrogen peroxide scavenging ability [5-15]. We also investigated the potential pain relief mechanism of BIOCERAMIC irradiation on an in vitro cell model, by assessing the intracellular level of iNOS, COX-2, and PGE2 under LPS-induced inflammation [16].

Moreover, we found that the effects of BIOCERAMIC irradiation on water molecules enhanced the volatility of the liquor solution by weakening the hydrogen bonds [17]. We conducted water cluster analysis using Nuclear Magnetic Resonance (NMR) with a VARIANUNITYINOVA 500 instrument, to determine the half-height width of the ^{17}O spectrum of BIOCERAMIC-irradiated tap water and control tap water samples. The variation in half-height width of the ^{17}O spectrum in the chemical shift qualitatively represents changes in water

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cluster size. The NMR results showed that the cluster size of tap water irradiated by BIOCERAMIC was smaller than that of control tap water. We thus deduced that water cluster size was reduced by BIOCERAMIC irradiation by breaking up the O-H-O bonds within the clusters [17].

Transdermal drug delivery is a biophysical model of drug transport through the human skin, with the drug transport relying on the physical properties of the drug such as solubility and permeability. To deliver systematic medication through the skin, skin permeability should be enhanced either by modifying the drug molecules or by applying skin permeation enhancers that reduce the barrier property of the skin. Traditionally, the enhancement of skin permeability is considered to result from the improvement of the skin permeation enhancers [18]. Substances that help promote drug diffusion through the stratum corneum and epidermis are referred to as skin penetration enhancers. Enhancers increase the solubility of the drug in the skin and increase drug diffusivity in the stratum corneum by acting as solvents to dissolve the skin lipids or to denature the skin proteins [18,19].

This study investigated the effect of BIOCERAMIC as a potential non-chemical penetration enhancer of physical induction to help drug loading in a transdermal system [18]. Because the effect of BIOCERAMIC includes weakening the hydrogen bonds in water or liquid, such irradiation may improve the transportation efficiency of drugs passing through the skin [6,15]. We also attempted to develop a transdermal drug delivery system for local drug application of NSAID and antiestrogen (Tamoxifen) using BIOCERAMIC material.

Material and Method

BIOCERAMIC powder

The BIOCERAMIC material used in this study was composed of microparticles produced from several ingredients, mainly elemental compounds including Calcium (Ca), Zirconium (Zr), Sulphur (S), Silicon (Si), Aluminum (Al), Magnesium (Mg), Iron (Fe), oxygen (O), and Carbon (C) [5-17]. However, the application of these material is depends on its physical characteristics. The average emissivity of the ceramic powder was 0.98 at wavelengths of 6 to 14 μm (determined by a CI SR5000 physical, chemical, and bi-spectroradiometer); this value represented an extremely high ratio of FIR intensity. Numerous biological effects can be induced by this ceramic powder at room temperature, without direct contact, employing the method we reported previously [5-9,11-17].

Viscosity test

Effect of the BIOCERAMIC irradiation on intramolecular hydrogen bonding of water was indirectly assayed by a capillary viscometer. BIOCERAMIC irradiaton source is using a silicon rubber mixed with 10% of BIOCERAMIC powder and manufactured as ring (YY Rubber Company, Foshan, Guangdong, PRC), and the control group is plain silicon rubber ring (Figure 1). Samples of 20 ml aliquot dd water were treated by BIOCERAMIC silicon ring and plain silicon rings for 1 min at ambient temperature. The viscometers were placed inside thermostat with a water bath (Lauda, E200, Germany) at 25°C. Data were correlated by using the statistical analysis system (Lauda DR. R. WOBSER GMBH & CO.) package.

The kinematic viscosity (ν) was measured by a calibrated Cannon-Ubbelohde capillary viscosimeter (Schott, 532 03/ 0C, Germany) with control unit (Lauda, PVS1-X02004, Germany).

Kinematic viscometry is defined as the quotients of the dynamic viscosity by the density: and has the unit mm^2/s (or centistokes, cst). Kinematic viscosities ν, expressed in centistokes, were calculated from the measured flow time θ and instrument constant c by using the following equation: $\nu=c\theta$. The values for c are provided by the viscometer manufacturer. The viscometer constants were corrected for effects of temperature.

Protocol for experiment on transdermal absorption using artificial skin/membrane

Indomethacin, tamoxifen, methanol (HPLC grade) and phosphoric acid (>99%) were purchased from Sigma-Aldrich (St Louis, MO, USA). Absolute ethanol (99.9%) was obtained from Mallinckrodt Baker B. V. (Deventer, The Netherlands). EMPLURA ® (1,2-Propanediol) was purchased from Merck (Huhenbrunn, Germany). The experimental drugs (Indomethacin and Tamoxifen) were dissolved in a 1:1 mixture of methylene chloride and methanol, and the solution was then precipitated into diethyl ether (1:60). We used 7 g Indomethacin diluted by 993 g Phosphate Buffer Solution (PBS) to form a 0.7 % (w/w) of the solution. We used 0.01 gram of Tamoxifen, mixed with 50% (v/v) Ethanol and 15% (v/v) EMPLURA ® to form 1% (w/w) of the gel.

Artificial skin/membrane treatment

Cellulose acetate membranes disc (Hoefer, USA) were soaked in PBS (pH 7.4) for at least 16 h. Cellulose acetate membranes that contained glycerin were rinsed once with receptor fluid before being placed onto the receptor. Membranes were hydrated and sandwiched between 2 microscope glasses slides and submerged in the receptor fluid in a Petri dish, to prevent creasing or folding when wet. Air bubbles are abandoned trapped within the interface of the membrane and receptor. The donor compartment was covered and closed tightly by a pinch clamp.

Using Franz cell apparatus (Figure 2) covered with or without BIOCERAMIC materials, the donor cell was sealed with parafilm and the apparatus circulation was maintained at 37°C with continuously stirred. Ethanol/phosphate buffer (50:50, v/v) was used as receptor cell buffer for tamoxifen group and phosphate buffer for Indomethacin group. We collected 200 μl from the receptor buffer through the sample port using a pipette and equal volume of buffer was added back. The drug content was then assessed by HPLC methods as described below.

High-performance liquid chromatography (HPLC) analysis

HPLC analysis was performed using a Waters 2487 HPLC UV-Visible Detector (Milford, MA, USA) with a hand injector, two Waters 515 pumps and Waters Millennium 32 software was used for peak data analysis. All samples were analyzed using a reverse phase C18 column

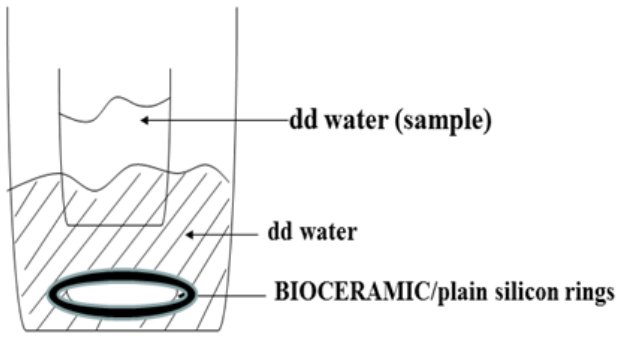

Figure 1: The schematic diagram for water irradiated by a silicon ring containing with or without BIOCERAMIC powders.

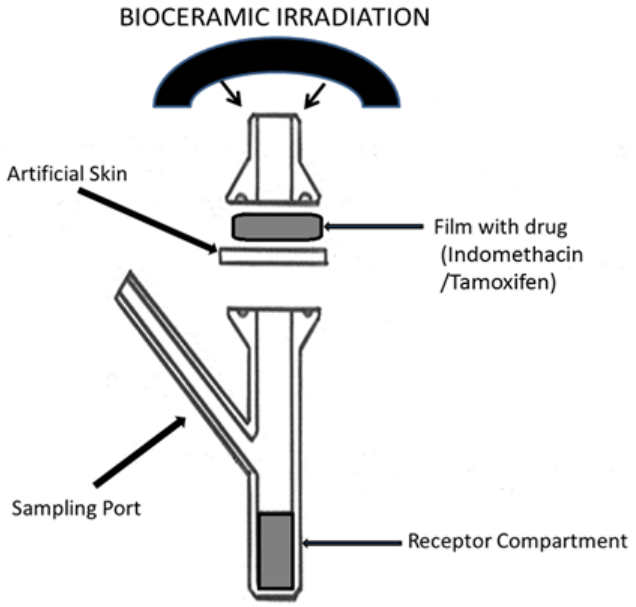

Figure 2: Setup of Franz cell apparatus for transdermal absorption model to test the effect of BIOCERAMIC irradiation on Indomethacin and Tamoxifen

(Inertsil C18 4.6 × 250 mm, 5 µm). Indomethacin was detected at 254 nm, the mobile phase ratio (70:30) of Methanol and phosphoric acid (0.1%, v/v) was membrane filtered (Millipore, 0.45 µm) and the flow rate was 1 ml/min. For Tamoxifen, the mobile phase ratio was 80:20 and was detected at 238 nm [20].

Statistical analysis

Statistical evaluations of data from BIOCERAMIC and control groups were performed using the paired Student's *t* test (SPSS Inc, IBM, Chicago, IL, USA). A *p*-value of less than 0.05 was considered significant.

Results

BIOCERMIC's effect on viscosity of distilled water

The viscosity of water samples determined by the viscosimeter for BIOCERAMIC-irradiated water and control water was 0.90 ± 0.00 cts and 0.92 ± 0.01 cts, respectively (Figure 3). These findings indicated that the resistance of BIOCERAMIC-irradiated water was significantly compliance to deform by either shear or tensile stress. Thus, BIOCERAMIC-irradiated water showed a decreased "internal friction" compared with the control water.

BIOCERAMIC's effect on transdermal skin absorption of indomethacin and tamoxifen

This study examined the effect of BIOCERAMIC on the permeability of drugs in transdermal drug delivery, using the Franz cell experimental model. The results showed that BIOCERAMIC irradiation significantly facilitated the passage of Indomethacin solution through an artificial skin membrane (Figure 4a; 395612 ± 274609 vs. 927991 ± 656247; P<0.05). Similar results were found for the Tamoxifen solution (Figure 4b; 2820730 ± 1491947 vs. 3152850 ± 1561996; P<0.001).

Discussion

The results of this experiment indicated that BIOCERAMIC irradiation on 'dd' water caused a decrease in viscosity compared with the control sample (Figure 3). A previous study had already shown that distilled water under various conditions that treating with magnetic field and ultrasound. It was found that difference in sound signal absorption in distilled water under unequal conditions is due to different viscosity with various sizes of water cluster formation [21]. A similar phenomenon is noted for BIOCERAMIC at room temperature, without necessity of external supply of power, electrical instruments, ultrasound or strong magnetic field. The reduced viscosity of BIOCERAMIC irradiated water in this study respond our earlier reports that BIOCERAMIC weakens the hydrogen bonds in water [5-17,22]. BIOCERAMIC irradiation also significantly facilitated the passage of either Indomethacin or Tamoxifen through synthetic skin in our transdermal absorption experiment (Figure 4). The better transdermal rate of Tamoxifen than indomethacin without the BIOCERAMIC irradiated treatment (Figures 4) may due to the gel-like preparation of Tamoxifen by adding EMPLURA® solvent in this study. But the breaking of hydrogen bonding by irradiated with BIOCERAMIC powders and formation of activated water molecules [5-17,22] will significantly improve the transdemal rate of Indomethacin or Tamoxifen as shown in (Figure 4). We propose a Schematic representation (Figure 5) of the potential mechanism behind BIOCERAMIC irradiation mediated weakening of hydrogen bonds and enhanced diffusion and permeability of Indomethacin and Tamoxifen passing through skin layers. To increase the drug delivery performance of a hydrophobic drug, one of the common approaches used for controlling the rate of drug release is to incorporate a drug in the amphiphlic micellar systems [23]. In this study we demonstrate the moderate hydrophobic drug, as Indomethacin or Tamoxifen, could be significantly increased transdermal rate by the possible activated water molecules surrounding the hydrophobic drug molecules, and resulted in the easier penetration of dermal structure.

Latimer and Rodebush (1920) were the first authors to describe hydrogen bonding. This bonding occurs when an atom of hydrogen is attracted by strong forces to 2 atoms instead of one as would be expected from its single valence electron. The hydrogen atom thus forms a divalent bond with 2 other atoms [24]. Such hydrogen bonds explain many of the unique characteristics and properties of water. Water contains far denser hydrogen bonding than solvents that have almost as many hydrogen bonds as covalent bonds. Hydrogen bonds can rapidly rearrange in response to changing conditions and environments (e.g., the presence of solutes). Each water molecule, in liquid form, is surrounded by approximately 4 randomly configured hydrogen bonds. The molecules tend to clump together, forming clusters for both statistical and energetic reasons [22-25]. Also important is the possibility of the hydrogen bond breaking, which can be measured by physical techniques such as NMR. Such breaks are caused by the loss of hydrogen bond covalence resulting from electron rearrangement. The hydrogen bonds present in water, together with its tendency to form open tetrahedral networks at low temperatures, gives rise to the characteristic properties of water, which differ from those of other liquids.

An important feature of the hydrogen bond is that it possesses directionality. When hydrogen bonding is strong, the water network expands to accommodate these directed bonds; where hydrogen bonding is weak, the water molecules collapse into the spaces between neighboring molecules of other types. This clustering of water molecules (resulting from the directional characteristics of hydrogen

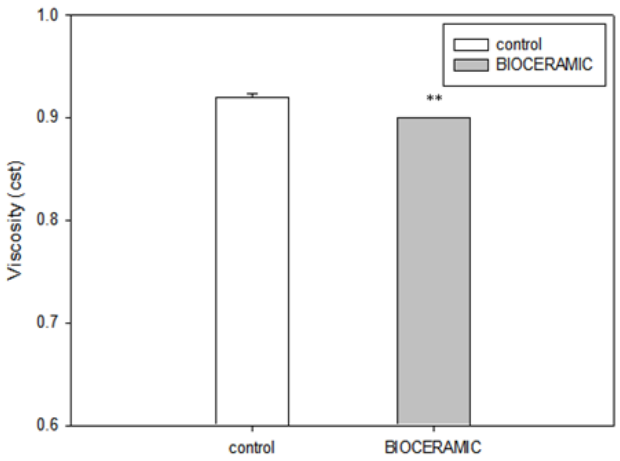

Figure 3: A significant decrease of viscosity (p value <0.05**) was observed in the water sample irradiated by BIOCERAMIC, compared with the control water sample (centistokes, cst).

bonding) is responsible for the special properties of water that allow it to act in diverse ways under different conditions [22,24]. For example, stronger hydrogen bonds increase water or liquid's viscosity because they increase the water or liquid's intermolecular forces, making it more resistant to flow. Higher hydrogen bonds decrease the viscosity because they decrease the liquid's interactions between molecules [26-29]. Numerous additional properties and characteristics changes in the hydrogen bonds weakening are include decreased of adhesion, decreased if cohesion, decreased of compressibility, decreased of surface tension, and decreased of viscosity; conversely, increased of density, increased of diffusion coefficient and increased solubility of solid [22]. Diffusion is related to a drug's molecular volume; the ability of a drug to pass through human skin depends almost entirely on the physical properties of the drug [30,31]. The permeation of compounds from an aqueous solution through the human stratum corneum is affected by the overall hydrogen-bond acidity and basicity [32]. Previous research has shown that the molecular properties of drugs with relatively low numbers of hydrogen bond donors and acceptors are associated with a higher permeability and bioavailability of the drug [33].

Several factors determine the rate at which a molecule diffuses

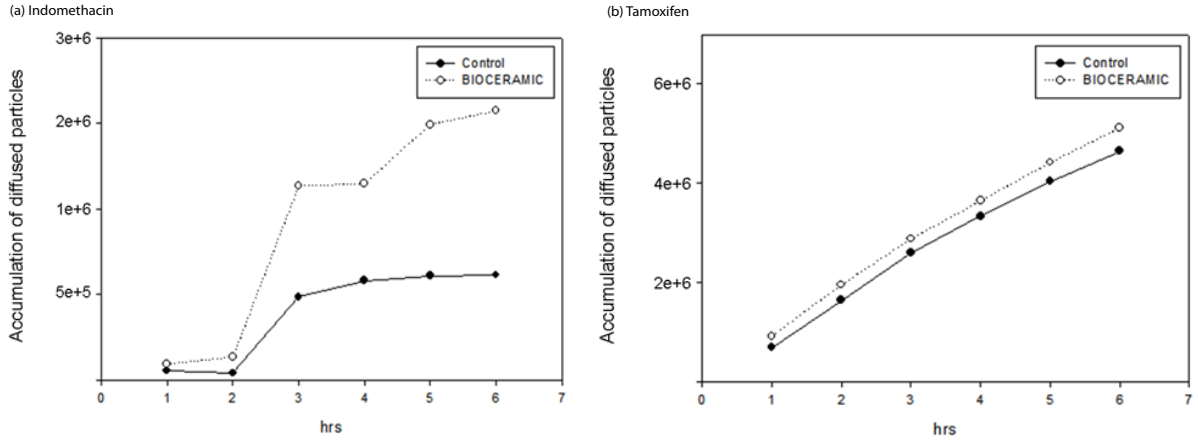

Figure 4: Significant increased transdermal diffusion of Indomethacin and Tamoxifen was observed under BIOCERAMIC irradiation, than control group in the Franz cell experimental model.

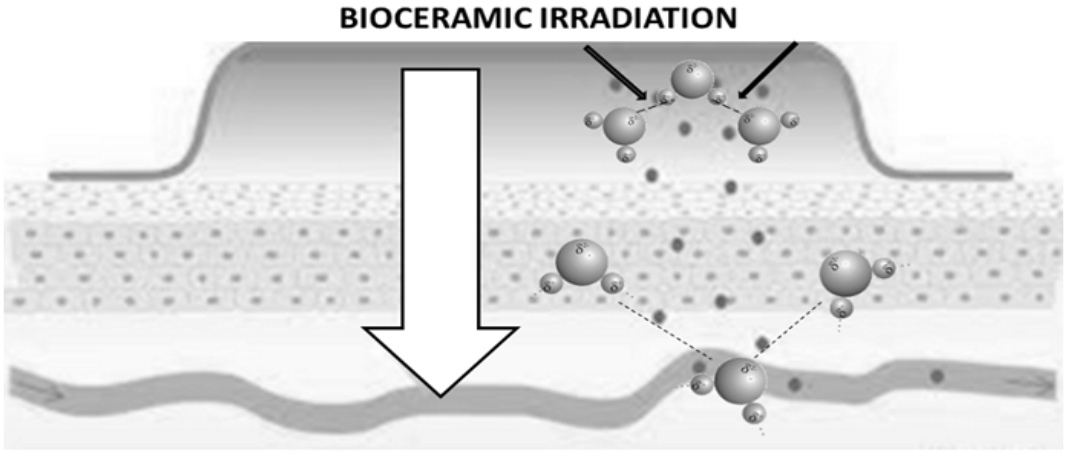

Figure 5: Schematic representation of the potential mechanism behind BIOCERAMIC irradiation (solid arrows) mediated weakening of hydrogen bonds and enhanced diffusion and permeability of Indomethacin and Tamoxifen (small dots) passing through skin layers.

across a membrane, including the size, polarity, charge of the molecule, decrease in agglomeration of particles, increase of wet ability, and decrease in crystallinity of the molecule [34]. If an uncharged (polar) molecule is to leave the aqueous phase and enter the lipid phase, it must first break its hydrogen bonds with water; this requires activation energy at a rate of 5 kcal per hydrogen bond to be broken. Thereafter, the molecule may also dissolve beyond the lipid phase. The number of hydrogen bonds a molecule forms with water is determined by the number of polar groups on the molecule, as well as the strength of the hydrogen bonds formed. Each additional hydrogen bond formed between a polar group and water results in a 40-fold decrease in the partition coefficient, and a resulting decrease in the molecular permeability through the cell membrane [34,35].

Conclusion

The results of this study suggested that the experimental method can successfully predict the BIOCERAMIC facilitation of the diffusion and transdermal absorption of Indomethacin and Tamoxifen. This facilitation evidently occurs through a weakening of the hydrogen bonds.

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