An active brace for controlled transdermal drug delivery for adjustable physical therapy

Levent Erol, Ozkan Bebek*, Ayse Karagoz, and Bahar Basim

Abstract— **This study presents an active brace which is a cost efficient precision-controlled advanced therapy medicinal product for time and rate controlled transdermal drug delivery (TDD) through the use of drug containing nanoparticles and electronics. The active brace is designed to adjust the pressure at the contact area where the medication is applied. The drug is contained in the nanoparticles produced and takes effect when the nanoparticles burst under pressure. The brace is designed to be compact and wearable which can be preprogrammed by a specialist to continue treatment sessions outside the medical facilities providing convenience and comfort to the patient.**

I. INTRODUCTION

Transdermal drug delivery (TDD) is a complementary technique in physical therapy that has dramatically improved over the last years. Currently, drug-loaded adhesive patches are used for TDD, which deliver the therapeutic agent to the systemic circulation and to the target tissue through the skin at a controlled rate [1]. These patches have advantages over classical delivery systems, such as oral and intravenous applications. The most important advantage is the ability to skip the liver and the digestive system before the drug takes effect. Also the dose frequency can be reduced. Another advantage is the adjustability of the therapy duration. The patches can be removed to prevent overdosing in the cases where unwanted side effects are observed [1]. Although the skin is a promising route for drug delivery, its selectively permeable nature limits the drug dosage that can be delivered daily through skin patches [2].

Current methods to increase the efficiency of TDD include active (mostly requiring bulky assistive devices) and passive (chemical) enhancements. The use of micro-scale needle arrays is also a promising method to break the skin barrier [3]. Active drug delivery systems use heat, electric current, and sound waves to enhance the delivery of drugs into the systemic circulation. In the passive TDD systems, the drug diffuses through the skin with the help of chemical permeation enhancers. Drugs are delivered through the skin by a driving force that is created by the concentration gradient over the skin and chemical interactions between the adhesive and the skin. A more recent study also shows that hair follicle openings can be a promising route for transdermal delivery since the medication applied on the skin tends to gather in the hair follicle openings [6].

Despite increasing the rate of delivery, current methods for TDD do not allow the dosage or delivery rate to be fine-tuned, neither do they provide time convenience to the patient or the specialist. The active brace prototyped in this paper aims to address these gaps and increase the TDD rate and efficiency by applying pressure to acceleratie diffusion through hair follicle openings as well as the rest of the skin. It allows the drug delivery to be timed and the dosage be adjusted precisely and personally while patient mobility is not compromised. It can be preprogrammed by a specialist and the medicine can continue to be delivered to the patient outside the medical facilities providing convenience and comfort to the patient. All these advantages also make this brace cost efficient. The following sections detail the design specifics of this novel wearable biomedical device covered with sensors and servo motors to enable enhanced and adjustable physical therapy particularly with its sensory-feedback system for precise control of the cure by actively adjusting the applied dose with pressure change.

II. DESIGN REQUIREMENTS

Since mobility is an important advantage this active brace will be providing, being lightweight, portable and compact are important design requirements for its final form. The crucial consideration, however, is the pressure applied and taking the precautions to prevent damage to the body. Our tests show that the higher the pressure the better the diffusion, which serves our purpose of transdermal delivery well. However, in order to prevent damage to the body, the actuators used, i.e. servos, should not exceed a certain torque, which will possibly vary depending on the target area. Sensor selections should also be made accordingly. Constant pressure won't be applied to the target area, but will be varied according to preprogrammed instructions. Based on these necessities and in order to determine the optimum pressure an experiment was conducted to determine the base design requirements of the active brace, which is explained in the following sections.

A. The pressure experiments mimicking drug delivery through the skin

In order to evaluate the skin integrity under the applied pressures of the brace system, a material mimicking the human skin was prepared using a powdered gelatin solution.

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However, since this inorganic texture did not replicate the biological nature of the human skin, the drug diffusion tests were conducted using raw chicken patties and absorbent papers through a multi-step experimental design.

To observe the amount of diffused material, *Silverdin*, an antibiotic cream which is widely used for treating burns and open wounds, and *Olivenol*, pure olive oil, were used to mimick the nanoparticles in the drug delivery. Silverdin is a white, oil-based cream with silver nanoparticle ingredients, which contains 1%wt Silver Sulfadiazine. An oil-soluble blue powder dye was mixed with this cream to observe the diffusion clearly under the optical biological microscope. Olivenol was used along with Silverdin to demonstrate the encapsulation of the oil based medication in the polymer based nanocapsules. It was also colored using the blue dye. Both Silverdin and Olivenol were soaked into the medical padding of band-aid strips which were measured to be $20\times10 \pm 1$ mm in size.

To determine the connection between the pressure applied and the area affected by diffusion, absorbent papers and Olivenol were used. A band-aid containing blue Olivenol was placed between two layers of absorbent paper stacked on top of each other and placed between two glass plates. Forces of 5 N and 10 N were aplied to two of the setups by placing weights on it, and a third identical set up received no additional mass on top. After 30 minutes at room temperature, the layers of absorbent paper were separated and the surfaces were scanned for quantifying the spread of Olivenol. The scanned images were cleared and the marks of the blue Olivenol were left in the images. A MATLAB program was used to convert the images to grayscale and calculate the percentage of non-white pixels in the image. The percentage of the non-white pixels in the images corresponded to the measure Olivenol spread.

To determine the effect of pressure and depth, raw chicken patties were used as phantoms. Due to quick decomposition problem at room temperature, the setups were kept in a refrigerator and both Silverdin and Olivenol were used for the drug. Band-aids containing blue Silverdin were placed on two patties. Again 5 N and 10 N forces were exerted on the patties with and a third patty receiving no force. The setup was left to rest at $4°\mathrm{C}$ for 10 hours. After 10 hours, vertical slices were taken from the patties and the samples were viewed under a light microscope. The same procedure was repeated using Olivenol.

B. Results

The result of the experiment with absorbent papers and Olivenol to determine the connection between the pressure and the resulting spread can be seen in Fig. 1. The results of the experiment with chicken patties to determine the effect of pressure and the resulting depth is shown in Fig. 2 shows the chicken patty samples prior to slicing. Note that the Olivenol (small samples on the top row) is less visible in the samples that were under higher pressure. Also, Silverdin has spread over a larger area in the pressurized samples.

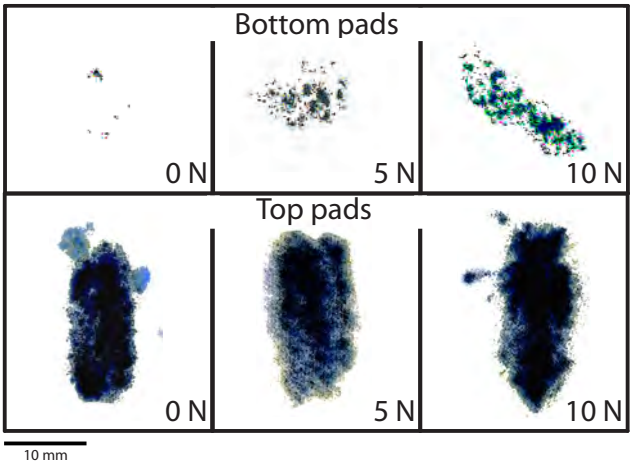

Fig. 1. The scanned layers of absorbent paper. Top row: absorbent paper without the sticky plasters on, the bottom layer. Bottom row: absorbent paper with the sticky plasters on, the top layer.

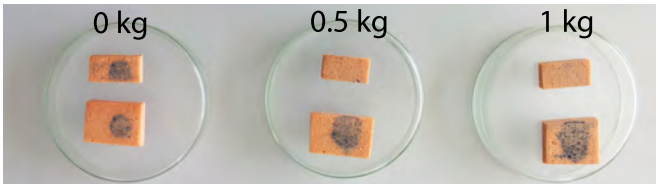

Fig. 2. Olivenol was applied to the smaller samples shown at the top row; Silverdin was applied to the larger ones shown at the bottom row.

The MATLAB analysis revealed that the spread of the Olivenol increased as the pressure increased, as expected. The results from the program are presented in Table I.

TABLE I
PERCENTAGES OF OLIVENOL SPREAD UNDER DIFFERENT WEIGHTS.

	Percentage of colored area		
	No weight	5 N	10 N
Bottom pads	0.48%	4.2%	8.3%
Top pads	21.2%	25.4%	28.7%

The results show an average of 3.88% increase in the surface area covered by Olivenol for each 5 N added onto the bottom pads and an average of 3.74% increase for the top pads. This experiment was conducted using band-aids with a surface area of around 2 cm^2, hence, a 4% increase indicates an area less than 0.1 cm^2. However, as the contact area, i.e. the drug reservoir, on the active brace is much larger, a 4% increase corresponds to a larger increase in the spread area. Eventhough increasing the pressure is expected to increase the efficiency of the product, these parameters need to be taken into consideration for cases where the spreading drug should remain within an area or should not reach certain areas on the skin.

At 40X magnification under the light microscope, the images revealed that the Silverdin had diffused deeper by an average of 1.3 mm. The penetration depth on the sample with no additional weight was 2.7 mm, while it was 3.8 mm

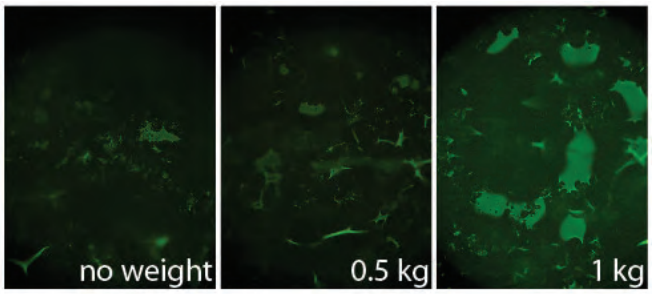

Fig. 3. Cross-sections of the chicken patty samples at 200X magnification under the light microscope. Note the much larger bright green areas indicating a larger and more even spread.

in the sample with 5 N force and 5.3 mm in the sample with 10 N force applied. At 200X magnification, the cross-section images also revealed that increasing pressure resulted in a more even distribution of the drug through the sample. The magnified images can be seen in Fig. 3.

Just like in the samples treated with Silverdin, the Olivenol setups also indicate that increasing pressure contributes to diffusion depth. The maximum depth Olivenol could penetrate with no additional weight was 5.8 mm. The diffusion depth was 6.8 mm in the 5 N and 10 N samples, which is the thickness of the patty itself. However, the width of the Olivenol traces at the bottom of the patties were different in the samples. The diffused Olivenol did not only reach deeper, but also reached a wider area at it's deepest point for increased pressures as tabulated in Table II.

TABLE II
DIFFUSION DEPTHS AND WIDTHS FOR OLIVENOL.

Weight [N]	Diffusion depth [mm]	Width of spread at diffusion depth [mm]
0	5.8	0.7
5	6.8	5.7
10	6.8	5.3

The experiments revealed that pressure is an enhancing factor on diffusion, which is expected to improve TDD. Consequently, the active brace should be built to apply as much pressure as possible as long as it does not harm the patient. The initial experiments conducted using tissue mimicking gelatine phantom indicate that forces up to 20 N will do not deform the human flesh, even if applied for long periods, i.e. 10 hours. However, it might damage the internal tissue depending on the target site, especially considering that the patient's target site is likely to be unhealthy. The brace designed can output even higher torque levels, but can be adjusted by trained medical personnel or the patient to maximize efficiency while avoiding damage.

III. DESIGN AND BUILD OF THE ACTIVE BRACE

A. Mechanical Design

The forearm was chosen as a target site for initial testing for ease of use and development of a wearable brace as well as easy physical modeling of the forearm. For a more specific targeting, a work area of 150 mm length was set and the brace was designed accordingly.

Although the active site of the brace is 150 mm in the current design, it could easily be altered by simple modifications. A Dynamixel AX-12A servo was chosen as an actuator for it's compact size, high and precisely controllable torque, and high reliability. The AX-12A can also be used in continuous rotation mode, which is the case in this prototype. A closed loop proportional controller was implemented to control the applied pressure. A braided steel wire rope with high flexibility was used for gripping the target area. The rope was placed in plastic medical tubing to prevent damage to the skin. A lithium polymer (LiPo) battery was used for supplying power to the unit. The LiPo battery is housed inside a compact container with the rest of the electronic components, which can be worn on a belt or easily carried elsewhere.

The parts and subsystems of the active brace can be seen in Fig. 4. The initial prototype was built out of aluminum alloy for its lightweight and easily machinable nature. The braided steel wire rope goes around the patient's targeted site, i.e. forearm and then through the channels in the shaft, where it is secured by setscrews. The shaft is fixed on the main body with bushings machined from teflon, allowing it to rotate, but not move elsewhere. The servo rotates the shaft, winding the steel rope around it and applying pressure to the area it is attached to. Note that the steel rope is not shown in this figure.

The prototype active brace attached to a person's forearm is shown in Fig. 5. The brace can apply a force to the limits of FSR, which is 20 N. In our experiments, 13 N force measured by the FSR was determined to be the upper limit for a healthy person to start feeling pain. The chicken patty experiments explained in Section II-B revealed that the pressure level required for drugs to penetrate is well below the capability of the designed brace.

B. Controller Board

The active brace prototype is controlled by an Arduino Uno board that uses an Atmel atmega328-p processor running at a clock speed of 16 MHz [8]. A 3-way buffer was used for communicating with the Dynamixel servo. The atmega chip has 6 8-bit analog inputs, 4 of which was used for connecting the sensors. The Arduino Uno was chosen as

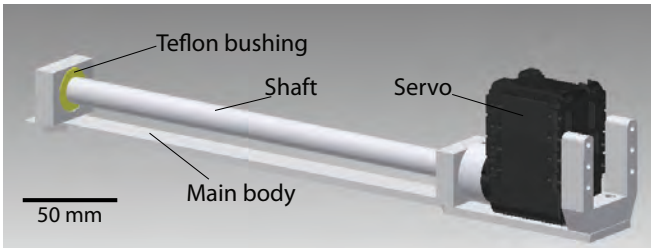

Fig. 4. A simplified 3D rendering of the active brace. The electrical components and the steel wire rope are not shown.

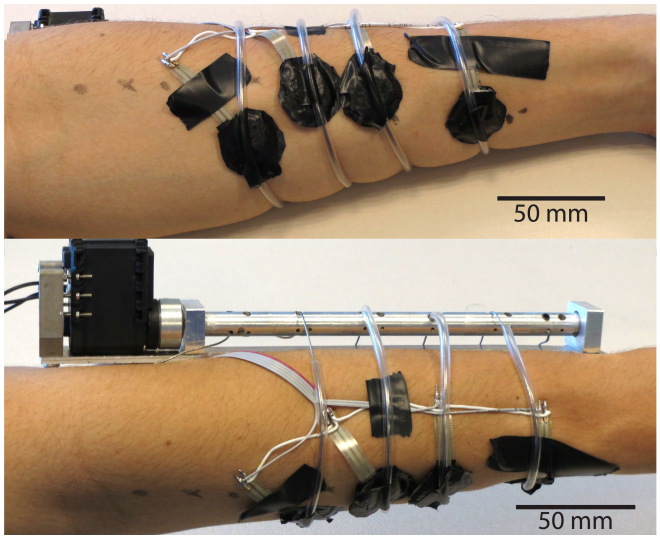

Fig. 5. The active brace prototype, mounted on a patient's forearm for demonstration. (Top: side view; Bottom: bottom view)

a controller for it's simple, C-like programming language and easy configuration. A more compact controller can be built for shrinking the overall size of the brace. A more compact design will also help in making the active brace more mobile and patient friendly.

C. Sensors

An array of force sensing resistors (FSRs) were used for measuring the pressure applied on the target area. The FSRs used in the prototype were *Interlink Electronics* 400 series, part of the *single zone Force Sensing Resistor family*. The FSR's provide a suitable solution for the active brace with their wide availability and reasonable price range and their simple build. However, the sensors are prone to output noisy data due to their simple structure. A low-pass filter was used to filter the unwanted noise and improve stability of the pressure applied.

The sensor array used in the initial prototype consisted of 4 FSRs, each with a diameter of 18 mm and an active area of 14.7 mm. In order to protect the sensors and minimize the damage that could be done by the cable to the skin, foam padding was applied on the sensors, which increased the diameter to 26 mm. Considering a work area that is 150 mm in length, 4 sensors are sufficient to cover the whole work area. As with the brace itself, a number of sensors can be added or removed depending on the size of the targeted area. The FSRs used can measure up to 20 N [9]. The 8-bit analog inputs of the controller unit allow a resolution of 0.078 N, which is sufficient for the adjustments that would be needed for the active brace.

IV. FURTHER DEVELOPMENTS

Although only at an early prototyping stage, the active brace appears as a solution that can improve the current applications of TDD. The prototype revealed some issues with the design, as follows.

Aluminum alloy was used as the main building material for the initial prototype of the active brace. Despite being a strong, lightweight and conventional structural material; aluminum is not very suitable for the final form of the product. Due to the naturally corrosive composition of bodily fluids and the possibility of unwanted side effects, i.e. allergies, perspiration or irritation, aluminum should not be in direct contact with the patient's skin. For commercial and more personalized applications, the aluminum body can be replaced by or mounted onto a skin-compatible and easily formable material, i.e. medical polymers, whose structures could also be altered function as the drug reservoir to house the nano particles. As 3D printing techniques advance and become more affordable, patient specific braces could be printed at local facilities on demand. Such customization is also expected to increase the positive effects of the active brace on healing.

A different issue with the prototype was the time required for mounting it to the patient. However, customized bodies would also help overcome this problem. The prototype can be minimized and its weight distribution can be optimized for comfort by using more compact actuators and an increased number of smaller sensors. This would also help balance the overall weight distribution of the device. The electronic components used could also be redesigned to fit into a smaller enclosure.

V. CONCLUSIONS

Despite being at an early development stage, the Active Brace offers solutions to some of the problems transdermal delivery currently faces. Development of the active brace and similar devices, along with nanotechnology can significantly improve the efficiency of TDD and patient comfort.

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