Design and implementation of a device for skin application of a topical drug solution

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Abstract

Radiation therapy, while a highly effective method of treating cancerous tissue, has the undesired side effect of creating radiation burns. Recently, a topical drug solution has been developed which has the potential to prevent radiation burns from occurring if applied prior to administration of radiotherapy. As clinical trials for this drug solution increase in magnitude and frequency, a more effective and reproducible means of drug application is required. In response to these needs we have designed a disposable device to facilitate the topical application of the drug solution. Repeated testing has shown that this device can consistently apply topical drug solution in various settings. Also, due the simple and effective nature of this device, it is possible that its use could be generalized to apply nearly any drug-containing solution.

Keywords

Radiation, drug application, radiation burns

1. Introduction

1.1 Radiation burns

The goal of this project was to design a disposable applicator for topical, drug-containing solutions. The inspiration for this project came from our client, Dr. Bill Fahl, and his ongoing research on the treatment of radiation burns as a member of the Department of Oncology at UW-Madison. A major concern in the use of radiation therapy is the development of radiation burns to the skin, and a sufficient treatment method does not currently exist (Prat 2008, Lataillade 2007) (See Fig. 1). Some of the symptoms of these radiation burns include dryness, itching, peeling, or blistering of the skin (Corsini 2010). While radiation burns are a common side effect, radiation therapy is often a necessity for cancer patients as there is a significantly reduced recurrence rate for patients who choose to undergo radiation (B. Fahl, personal communication, September, 17, 2010, Corsini 2010). While there are currently several methods for treating radiation-induced burns to the skin, most of these are aimed at treating the burns after the fact (i.e. attempting to treat the burns once they have already occurred). Historically, severe radiation burns have been treated by surgical removal of the necrotic tissue (Lataillade 2007). Also, patients have often used many topical treatments post-radiation exposure—including topical lidocaine, aloe vera gel, and topical corticosteroids—to soothe the burns (Corsini 2010). One particular study examined the use of silver-leaf dressing as a possible treatment for radiation burns (Vavassis 2008). More recently, cellular-based therapies have been combined with standard surgical techniques (Prat 2008, Lataillade 2007). These treatments make use of the regenerative capacity of mesenchymal stem cells (MSCs) and have shown favorable results (Prat 2008, Lataillade 2007). However, none of these treatments are able to prevent the initial occurrence of radiation burns.

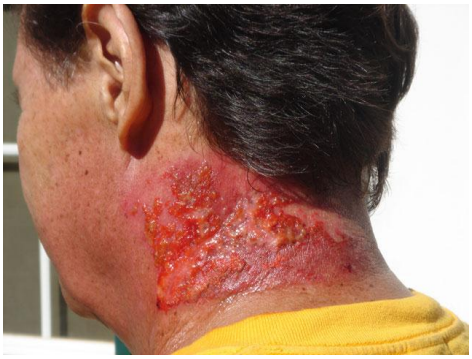

Fig. 1 Severe dermatitis
Source: http://www.cancer-throat.com/index.php?s=lubricate

Radiation burns occur by the same mechanism which destroys cancerous tissues and saves lives. During radiation therapy, a high energy electron beam is focused and directed at the affected tissue (B. Fahl, personal communication, September 17, 2010). The emitted photons and particles destroy the cancerous tumor by disrupting the DNA of the cancerous cells and causing apoptosis, or cell death. The DNA can be damaged by direct ionization of the DNA strands. Also, the DNA can be indirectly damaged by oxygen free radicals which are formed via the interaction of the electron beam with oxygen-rich tissues, such

as blood. While radiation therapy has proven highly effective at reducing the recurrence rates in cancer patients, the side effects are often substantial and painful (B. Fahl, personal communication, September 17, 2010). One of the main side effects of radiation therapy, as mentioned previously, is radiation burns, or dermatitis. These burns occur when the highly charged particles directed at the cancerous tissue interact with the oxygen-rich compounds in the dermal tissues, causing the formation of oxygen-based free radicals (B. Fahl, personal communication, September 17, 2010). The free radicals attack or interact with the DNA of the healthy skin cells in much the same way as they do with the DNA of the cancerous cells, and cell death is a side effect. These radiation burns can range from moderate to severe, and the regenerative capacity of the skin is often damaged as a result. Thus, while radiation therapy remains a necessary treatment of cancerous tissues, radiation burns are a significant side effect causing long-term discomfort and pain to patients.

1.2 Drug solution

Dr. Fahl and his associates have developed a drug which, in contrast to previous treatment methods, is aimed at preventing radiation burns. The drug's active compound is the well-known neurotransmitter, norepinephrine (see Fig. 2).

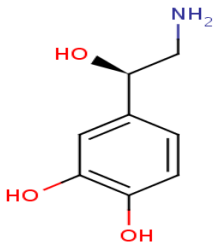

Fig. 2 Norepinephrine
Source: http://www.bmrb.wisc.edu/metabolomics/mol_summary/?molName=Norepinephrine

Most of the oxygen-based free radicals which form in the dermal tissues during radiation therapy and cause radiation burns are derived from the blood stream (B. Fahl, personal communication, September 17, 2010). Norepinephrine interacts with the smooth muscle lining blood vessels to stimulate the smooth muscle to contract and therefore causes the blood vessels to constrict (i.e. it is a vasoconstrictor). Stimulation by norepinephrine thus restricts blood supply to the regions where it is active. The goal of our client's drug is to restrict blood supply to the area of skin immediately prior to radiation treatment and limit oxygen-based free radical formation in the tissue (and thus limit tissue damage). This technique is especially unique in that it has the potential to prevent radiation burns from even occurring and thus has potential widespread applicability and use.

The drug, as currently designed, is supplied to the skin in a 70:30 v/v ethanol: water mixture. Currently our client does not have an efficient and highly reproducible means of applying the drug to patients undergoing treatment. There are devices on the market which are used in the application of topical drug solutions, but due to cost reasons, at the current time do not fulfill our client's demands. Our client therefore gave us the task of designing a device which can apply a fixed amount of drug to the skin of patients about to undergo radiation therapy.

1.3 Device requirements and design

Our client outlined several requirements for the prospective device. The device is required to apply 8.0 mL of the 70:30 ethanol:water mixture (containing the drug, norepinephrine) to a skin surface area of approximately 225 cm^2. This drug solution is to be stored in a glass container, as this is the standard protocol for storage of such drug solutions in the clinical setting. Furthermore, the device needs to be single-use (i.e. disposable). Given the clinical application for which the device is intended, it is imperative that the device be disposable to minimize the potential risk of transmission of infectious agents between patients. Also, our client requires that the device be relatively light-weight and handheld (i.e. similar in size to current devices on the market). Lastly, our client requires that the device deliver the drug solution in a controlled, consistent manner.

In response to our client's requirements, we came up with a device to effectively and reproducibly apply topical drug solutions. After

designing the device in SolidWorks® we had the device rapid prototyped via stereolithography (SLA). It is worth briefly mentioning the key features of this design (see Fig. 3). The design consists of an essentially hollow cylindrical shaft which stores the solution-containing ampoule. Protruding from the shaft is a handle designed to fit the dimensions of the average human hand and provide ergonomic support to the user. Interior to the device is a plate and pin which concentrates the compressive stress applied to the ampoule during drug solution release. At the top of the shaft/handle apparatus is a threaded cap which, when tightened, compresses the ampoule against the pin at the bottom. Attached to the bottom of the device is a reticulated polyurethane foam pad. Ideally, when the cap is threaded and screwed on, the ampoule is compressed against the pin at the bottom, causing the end of the ampoule to fracture and releasing the contents (i.e. the drug solution). The solution then diffuses into the foam pad and may subsequently be applied to a cancer patient immediately prior to the patient receiving radiation therapy.

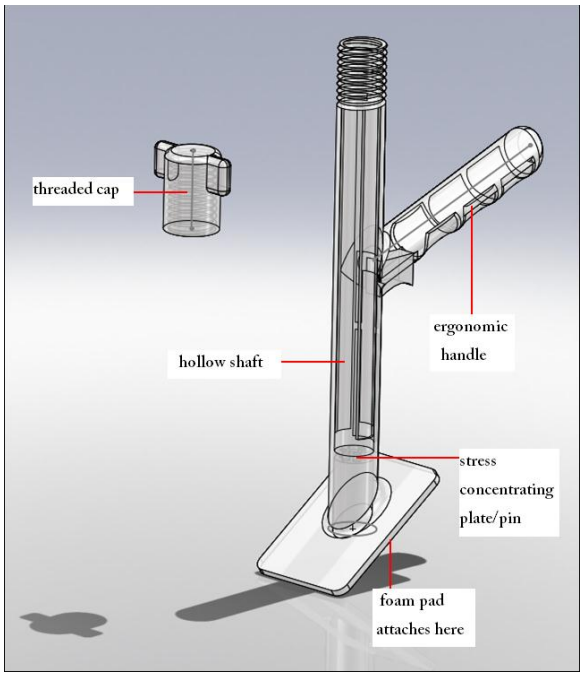

Fig. 3 An image detailing the main components of the device designed and constructed for drug application.

1.4 Testing summary

In order to demonstrate the efficacy of our design we developed testing protocols which we subsequently implemented. First, we sought to compare the one-minute solution-application volume (OMSAV) of our device with that of current devices (i.e. the ChloraPrep® applicators) on the market. We then examined the dependence of the OMSAV of our device on the angle of the surface of application. Lastly, we attempted to examine the time-dependence of drug release by our device but were unable to do so due to device failure at the beginning of this testing protocol.

2. Materials and Methods

2.1 Device design and construction

As mentioned previously, we were given the task of designing and testing a drug application device that employed drug solution containing glass ampoules. In designing said prototype we had to consider several factors. First, we had to ensure that our prototype device would fully encapsulate the glass ampoules which store the drug solution. We were able to use a pair of digital calipers to take measurements of several of the drug containing ampoules and determine the average size of the ampoules. We then based on SolidWorks® design around these dimensions, envisioning that subsequent devices could be scaled up or down depending on the size of drug containment vesicle.

Once we had the appropriate dimensions we set about designing our prototype. As mentioned previously, we employed the CAD software SolidWorks® in this design process. After several revisions we came up with our final design, as shown below**.** Once the design process was complete, we submitted our design for rapid prototyping via stereolithography (SLA) (see Fig. 4).

Fig. 4 The final prototype.

While the methodology and science behind rapid prototyping has been previously investigated, it may be worthwhile to briefly cover the process that we employed in manufacturing our device. We hired an outside firm to manufacture our device from two .sldprt (the primary SolidWorks® file extension) files using SLA. We selected SLA for its relatively low cost, short turnaround time, and high resolution when compared to other polymer manufacturing protocols such as selective laser sintering (SLS) and injection molding. Next, as SLA may create devices with varying properties depending on the material used, we had to select an appropriate material for our device. We had previously determined that we would prefer a material similar to polyethylene in physical qualities due to its flexibility, toughness, and translucency. In response to these requirements we chose Somos® 8120 Epoxy Photopolymer, which exhibits physical characteristics similar to polyethylene when used in an SLA process (Somos 1998).

Once we had the device handle and shaft prototyped, we had to construct the foam application surface. We cut out polyurethane foam pads measuring approximately 50 x 70 mm using an x-acto® knife and fastened one of the pads to the application surface of the prototype using an elastic rubber band (see Fig. 5). This foam pad served as the application surface through which the drug diffused to the patient following solution release via ampoule fracture. We disposed of each foam pad after use of the device and replaced with a new pad.

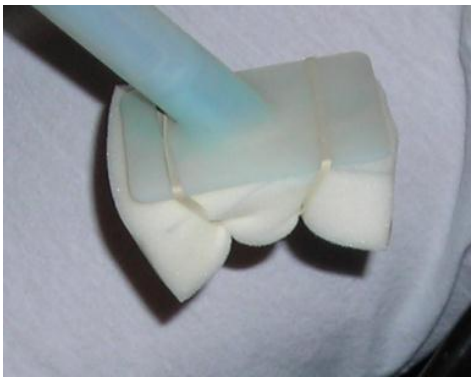

Fig. 5 Foam application surface

2.2 Device testing

After we had designed our device, had it prototyped, and constructed the application pads, we had to complete testing to prove the effectiveness of the device in providing its intended function of drug application to the skin. Specifically, we wanted to show that our device could consistently disperse solution to the patient in a clinical setting. We developed three primary testing protocols to examine this hypothesis.

First, we wanted to show that our device, in a fixed amount of time, could consistently deliver solution in a manner comparable to current devices on the market (i.e. the ChloraPrep® drug applicators). We weighed the applicator using a standard digital scale. We then had a test subject lay their arm out on a horizontal surface. We released a solution (70:30 v/v isopropyl alcohol:water) to the foam application surface via the aforementioned drug release mechanism (1.3) and allowed the foam to saturate for 10.0 seconds. We then applied the solution to the subject's inner forearm for 60.0 seconds. After application we once again weighed the device. We then calculated the difference in weight, and divided this number by the solution density to calculate the one-minute solution-application volume (OMSAV) of solution released to the patient (density = mass/volume and thus mass/density = volume). In this way we were able to quantify fluid delivery in a reproducible manner. We followed this protocol using both our device and the ChloraPrep® 26 mL applicators to establish a comparison between the two devices.

Next, we wanted to see how well our device released solution to the skin when the surface of application was at varying angles with respect to the horizontal. We used the method of difference in weight described previously to quantify fluid release and as before, allowed the solution to saturate the sponge for 10.0 s prior to application. We tested the solution application by our device on the inner forearm at angles of 0°, 45°, and 90° from horizontal (see Fig. 6).

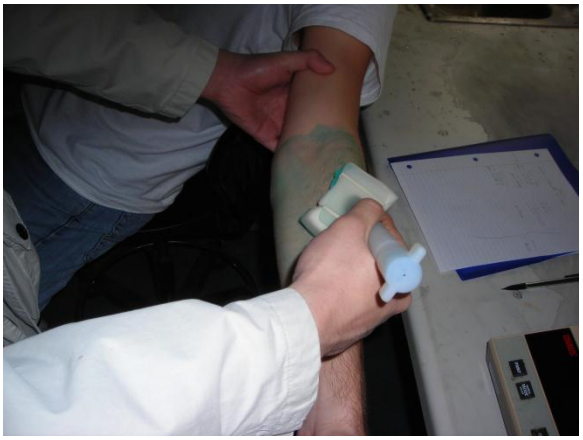

Fig. 6 Testing the one-minute solution-application volume (OMSAV) at different angles.

Lastly, we wanted to quantify solution release via our device over an extended period of time. We had planned on employing a method similar to that used in the protocols above for quantifying solution release, with before and after weight readings taken at various time points (1.0, 1.5, and 2.0 minutes). However, unfortunately, the stress concentrating plate present in our design failed due to fatigue after the first two testing protocols and we could not complete this last test.

3. Results

3.1 Comparison of one-minute solution-application volume (OMSAV)

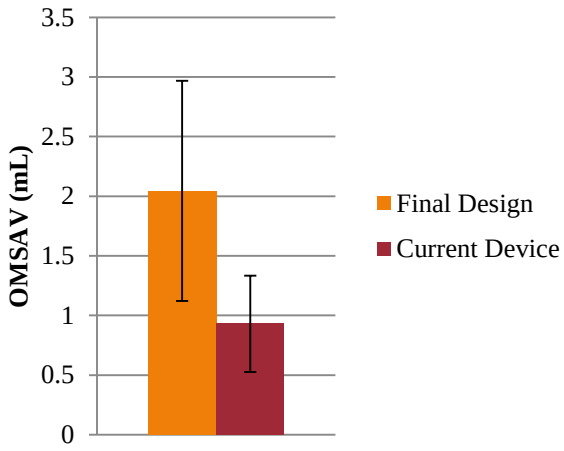

Fig. 7 A comparison of the one-minute solution-application volume (OMSAV) between our applicator device ("Final Design") and the ChloraPrep® applicator ("Current Device"). The OMSAVs obtained in the test (n = 3 for each group) were as follows: 0.930±0.404 mL for the ChloraPrep® applicator and 2.04±0.923 mL for our device.

Fig. 7 shows a comparison between our applicator device and the ChloraPrep® 26 mL applicator for the one-minute solution-application volume (OMSAV). Both devices were tested three times (i.e., n = 3) following the aforementioned protocol. The results yielded OMSAVs of 0.930±0.404 mL for the ChloraPrep® applicator and 2.04±0.923 mL for our device. Based on a paired two-sample student's t-test, this result suggests a statistically insignificant difference between the two applicator devices (p = 0.161).

3.2 Positional dependence of drug release

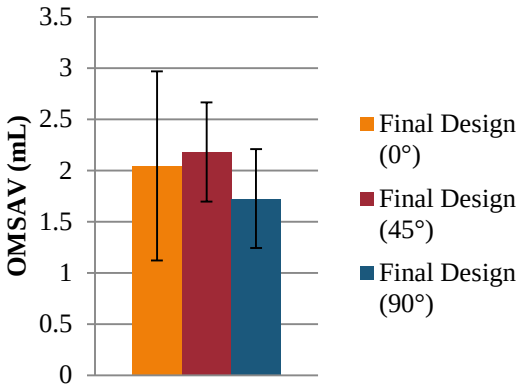

Fig. 8 A comparison of the one-minute solution-application volume (OMSAV) with variable angles (0°, 45°, and 90°) with respect to the application surface for our applicator device. The OMSAVs obtained in our test (n = 3 for each group) were as follows: 2.04±0.923 mL for the 0° orientation, 2.18±0.484 mL for the 45° orientation, and 1.73±0.482 mL for the 90° orientation.

Fig. 8 shows the variation in OMSAV with the angle between the applicator surface (i.e., reticulated polyurethane foam sponge) and the horizontal for our device. The results of this test yielded OMSAVs of 2.04±0.923 mL for the 0° orientation (repeated from previous test), 2.18±0.484 mL for the 45° orientation, and 1.73±0.482 mL for the 90° orientation. Based on a one-way analysis of variance (ANOVA) statistical test, the difference between the orientations was not statistically significant (p = 0.788).

4. Discussion

4.1 Summary of testing protocols

Through the course of our testing, we attempted to address two important considerations: how our device compares with a similar, competitive device on the market, and how our device's performance is affected by the application angle. Based on the first test which we performed we did not find a statistically significant difference in the OMSAV between our device and the ChloraPrep® applicator. This indicates that the performance of our device is comparable to that of the ChloraPrep® applicator, a leading competitive device, in delivering a similar ampoule-contained solution (13 mL 70% v/v isopropyl alcohol in water). Furthermore, our second test resulted in a statistically insignificant difference in the OMSAV for various application angles (i.e., of the polyurethane foam pad with respect to the horizontal). This result is indicative of a uniform solution delivery by the device in various configurations. Such a result has important implications for using our device in a clinical setting, wherein a radiotherapy patient may be oriented variably prior to receiving treatment. It is worth mentioning that, in addition to the efficacious solution delivery demonstrated by our test results, our device consistently broke the glass ampoule near the bottom as desired, thereby promoting very efficient expulsion of the drug solution from the shaft (see Fig. 9).

Fig. 9 The fracture pattern of the glass ampoules broken using our final prototype

4.2 Device failure

As mentioned previously, the device failed upon completion of the second testing protocol (i.e., variable angle). While this unfortunate occurrence prematurely ceased further possible testing protocols to assess the device's efficacy, this failure does not negate the potential of our device for clinical applications. Indeed, the device is intended to be a single-use, disposable product, and thus the failure which occurred after several (i.e., approximately thirty) uses is not necessarily an egregiously alarming result. Conceivably, repetitive use of our single prototype through the course of our testing

would invariably lead to plastic deformation and eventual failure of the polymer-based device. Also, it is worth mentioning that the final product which results from our efforts will likely be injection-molded and composed of polyethylene, as rapid prototyping is not a cost-effective method of construction for the several hundred or thousand devices which our client requires for large-scale testing of the drug solution. Such a final prototype would lack the brittleness and weakness of a device manufactured via SLA.

4.3 Project future

In the future, as mentioned previously, the manufacturing method will need to be scaled up as upcoming clinical testing will require at least several hundred devices. As these devices will likely be injection-molded, a negative mold machined from aluminum and composed of two halves will need to be constructed. Injection molding, while initially an expensive undertaking, will greatly diminish the per-unit cost of the device. Also, as mentioned before, a somewhat unnecessary though potentially useful result of fabricating these devices via injection molding with polyethylene is that the final product will be substantially more durable than the rapid-prototyped device which we tested. Ultimately, it appears that our device has great potential for meeting our client's specific needs. This device could also be of use for many similar drug application needs due to the simple, ergonomic, and cost-effective method of drug solution application which it provides.

Acknowledgements:

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References:

1. Prat, M., Bey, E., Brachet, M., Trompier, F., Ernou, I., et al. (2008). New therapeutic approach in the treatment of severe radiation burn: Surgery and local stem cell therapy. *Wound Repair and Regeneration*, *16*(6), A78.
2. Lataillade, J., Doucet, C., Bey, E., Carsin, H., Huet, C., et al. (2007). New approach to radiation burn treatment by dosimetry-guided surgery combined with autologous mesenchymal stem cell therapy. *Regenerative Medicine*, *2*(5), 785-794.
3. Vavassis, P., Gelinas, M., Chabot Tr, J., & Nguyen-Tan, P. (2008). Phase 2 study of silver leaf dressing for treatment of radiation-induced dermatitis in patients receiving radiotherapy to the head and neck. *Journal of Otolaryngology -- Head & Neck Surgery*, *37*(1), 124-129.
4. Corsini, L. (2010). Potential treatments for radiation dermatitis. *International Journal of Pharmaceutical Compounding*, *14*(3), 210.
5. Somos® 8120 (1998). Retrieved May 2, 2011 from the Realize, inc. website at http://www.realizeinc.com/ProductSheets/Product%20Data%20Sheet%20-%20Somos%208120.pdf