Interpenetrating Networks for Delivery Systems

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Abstract

Interpenetrating networks that are composed of gelatin cross-linked with PEG-diacrylate provide a promising solution to decrease healing time for large surface area wounds. However, the current reconstitution and administration methods of this product are clinically undesirable. Our final design of a modified syringe was selected based on the design constraints set forth by our client. This design enables the liquid and solid components of an IPN to be stored separately and offers a simple and ergonomic method for mixing and administration. Prototypes of this design were fabricated and tests were also performed to assess how well the prototype met the design constraints. Furthermore, laboratory research complemented the development of this prototype to ensure full dissolution and proper delivery of the IPN.

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Introduction

Background

Large surface area and chronic non-healing wounds significantly impair the quality of life for millions of people in the United States (Harding et al, 2002). These wounds are characterized by a loss of skin and underlying tissue which do not heal properly with conventional types of treatment (Falanga, V., 2004). Instead, intensive treatment is required that is costly and requires a lengthy recovery period. Hence, solutions have been investigated to aid and advance the wound healing process. Numerous "bioactive dressings" as well as "skin substitutes" have been created, however few are currently operational in a clinical setting (Harding et al, 2002). Our client, Professor John W. Kao, has created a biocompatible interpenetrating network (IPN) that offers a drug delivery mechanism and promotes healing in large surface area wounds.

This particular IPN is a mixture of cross-linked polyethylene glycol-diacrylate (PEG-dA) and dissolved gelatin. PEG-dA, as shown in **Figure 1**, is a polymer which can be synthesized in a variety of molecular weights - of which the three most common are 600 Dalton, 2kD, and 3.4kD. 600D PEG-dA is a liquid, while the others are a powder. When PEG-dA is added to a photoinitiator and exposed to a UV light, the diacrylate groups crosslink via free radical polymerization (Nakayama, 1999). When PEG-dA is mixed with gelatin and cross-linked, the gelatin becomes entrapped in the PEG-dA.

Fig. 1

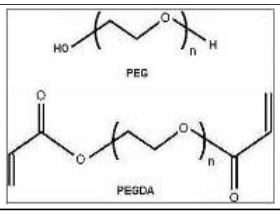

Figure 1: Structure of (top) poly(ethylene glycol) and (bottom) poly(ethylene glycol) diacrylate.

The components from which an IPN is made were carefully chosen for their desired biological properties. First, PEG-dA is bioinert, meaning that it does not elicit a response from a

biological tissue that it may contact (Nakayama, 1999). Additionally, gelatin is derived from collagen, a naturally occurring substance in mammals (Rhee, 1999). For this reason, it is biocompatible in solution and it can biodegrade over time. When an IPN forms, the photo-polymerized PEG-dA provides a matrix that holds the gelatin. The resulting network provides a perfectly-conforming wound dressing that is slowly broken down by the body as the wound heals.

Interpenetrating networks are beneficial for accelerating the healing of large surface area wounds due their physical and chemical properties. First, IPNs are able to cover wounds that are irregularly-shaped. The fluid nature of IPNs allows them to properly conform to these irregularly-shaped wounds, promoting rapid and uniform healing. Also, IPNs are effective barriers against foreign microbial infections, and they can be created to contain therapeutics in either a solvent form or as a covalent attachment to gelatin (Kao et al, 2003). The drugs are then administered to the patient via diffusion or cleavage, respectively, further aiding in the healing process. Professor Kao's laboratory has obtained positive results in a wound treatment study utilizing IPNs (Kao et al, 2003). However, while IPNs offer an exceptional solution to improved healing time and drug delivery, there are many problems associated with the current administration techniques.

Current Methods

Current IPN preparation and administration methods (**Figure 2**) are only suitable for a laboratory setting. Preparation in a clinical setting has been limited by the necessity for gelatin to be mixed with a heated solvent (at 60 degrees Celsius) for five minutes to ensure complete dissolution. In such a setting, a heating element would not be available, so modifications are necessary. Also, administration methods are inadequate because syringes are currently being used, yet IPNs are

intended to treat large surface area wounds. Syringe usage leads to slow and uneven administration of the IPN solution. In order to begin using IPNs in a clinical setting, these issues must be resolved.

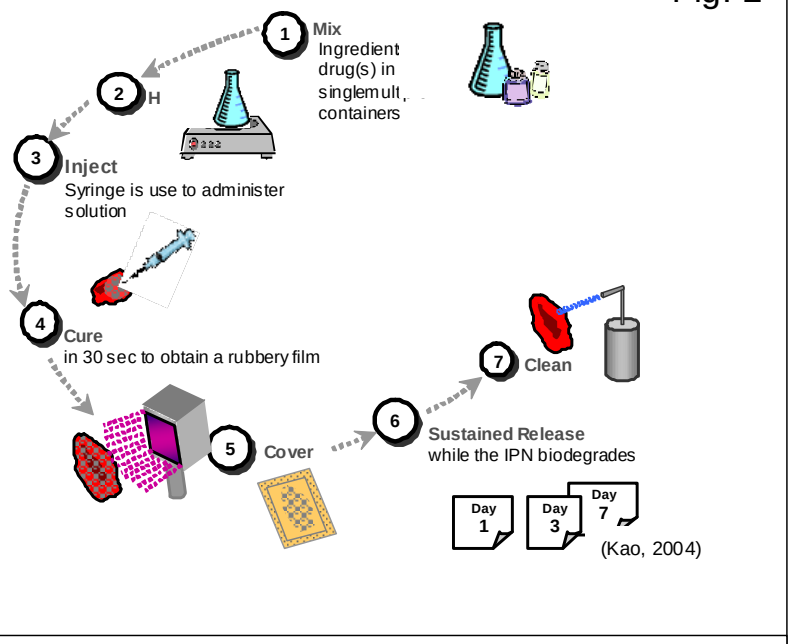

Figure 2 Current method for administering an interpenetrating network to a wound. Main ingredients used include PEG-da, gelatin, and a photoinitiator.

Initial Research

Previous research that commenced in Fall of 2006 focused on eliminating the heating step involved in the aforementioned IPN administration procedure. Since gelatin was deemed the limiting factor in dissolution of the IPN components devoid of heat, we focused on the dissolution of gelatin at room temperature. Experiments involved varying the bloom strength and concentration of the gelatin, as well as the solvent used. In the end, gelatin was found to partially dissolve using 90-110 Bloom gelatin in acetate/citrate buffer at room temperature. The final recipe contained one equivalent of gelatin, one equivalent of PEG-dA, ten equivalents of acetate/citrate buffer, and a 1% solution of I-2959 photoinitiator. Additionally, the spray bottle design was considered to ensure optimal dissolution and spraying capacity. However, at the end of the semester it was evident that further work could be done to streamline and improve upon the administration technique by integrating both mechanical and chemical design modifications.

Problem Statement

Interpenetrating networks are a type of biomaterial that polymerize in situ and have been used in drug delivery, wound healing, and tissue engineering applications. The goal of our project has been to develop a novel delivery mechanism and create a simple reconstitution method for the components of an interpenetrating network. Moreover, the focus of our project has been to develop a novel administration and packaging system to store, reconstitute, and apply IPNs. This design must be suitable for a clinical setting, and the final product must also satisfy the design constraints outlined by the client.

Design Constraints

Our client has delineated several criteria for achieving an optimal product design. In coordination with our objectives last semester, the most important guideline is that the IPN administration mechanism fit seamlessly into a clinical environment. This goal will be achieved by meeting several, more pointed objectives that has led to a product that requires minimal preparation and effort to administer the IPN.

To ensure even application of the IPN, several objectives that incorporate both research and design components must be met. Within the research realm, the final IPN solution prior to curing must be homogenous, with each constituent adequately dissolved. Additionally, dissolution must be able to be achieved by establishing a reliable mixing mechanism within the product that can be actuated efficiently. Finally, the device must safely deliver the IPN solution in an even spray that requires little effort on the part of the user. In short, the product must produce a sustained and uniform spray that can cover a large surface area.

Furthermore, the design of the product must involve some sort of compartmentalization in order to maintain sterility and improve shelf life. Moist gelatin is prone to microbial invasion, so it must be stored separately from the liquid components. Also the solution is not stable if it is exposed to light for an extended period of time, so the product must selectively shield the UV-sensitive photoinitiator while in storage.

In the interest of shelf-life, our client has requested that our equipment be one-time use only. Disposable medical equipment is more practical because, after application, sterilization is not required. In particular, components that can be individually sterilized prior to packaging are necessary. Overall, the capacity for prolonged storage in a sterile environment could lead to increased product applicability.

Finally, the product must be as cost-effective as possible. This, of course, will open up more market potential and help justify the incorporation of high-cost pharmaceuticals into the IPN. The use of minimal parts and prefabricated components would largely aid in this objective, as would parts of varying sizes that could be used to treat different wound sizes. The final price will be reflected in making the final product as simple yet versatile as possible, as will its overall clinical applicability.

In general, the success or failure of this product will ultimately hinge on whether it is accepted by the medical community as an efficient and beneficial treatment for its intended wounds. By taking the above design constraints into consideration, we can greatly increase the probability of it becoming a successfully marketed product.

Ethical Considerations

Ethics are of utmost importance in our design. First and foremost, the product must be safe and effective to minimize patient risk, regardless of any marketing possibilities. Since the design involves administering the IPN by adding pressure, this pressure must be able to be regulated to ensure comfortable and safe application onto the wound. Additionally, biocompatible materials will be utilized for each part of the design and IPN solution to ensure safe contact with the wound. Similarly, it is suggested that consent is given for the application of the IPN, that healthcare professionals are aware of the constituents, and that they have been trained in the methodology for reconstitution. Also, the design must be carefully tested to ensure that when the provided directions are followed all pharmaceuticals are mixed to form a homogenous solution. Moreover the overall administration technique recommended should allow the patient to receive consistently adequate care of his or her wounds. Lastly, ethical considerations will be made during any animal experimentation or clinical trials that may be necessary.

Competing Products

This semester the focus of the design is primarily on the delivery mechanism of the IPN. As such, products competing with the final design will be those which require separation of liquid and powder until shortly before use. In medicine, many pharmaceuticals are stored in a lyophilized form and must be reconstituted before use. The majority of these drugs are stored in separate vials (one containing liquid, one containing powder). The standard procedure to reconstitute pharmaceuticals is to inject the liquid from its vial to the vial containing the powder,

mix the solution by hand, and then use another syringe to draw up the mixture for delivery. These systems require two syringes and leave room for error in mixing. Pharmaceutical companies overfill the liquid vial by as much as 35% (Renoylds, 2007) to ensure full dissolution.

Since these systems are inadequate, several products have been created. The West Pharmaceuticals Services' Needleless Transfer Device (**Figure 3)** is an adaptor which connects both vials and has a port which allows a syringe to draw up the mixed solution. This system requires only one syringe and is one time use only. A drawback of this system, however, is that it requires the liquid portion be stored under vacuum (Needleless Transfer Device product brochure). The Inter-Vial™ system by Duoject® **(Figure 4)** is a syringe/vial adaptor in which the custom syringe is prefilled with diluent and can draw up the pharmaceutical.

Fig. 3

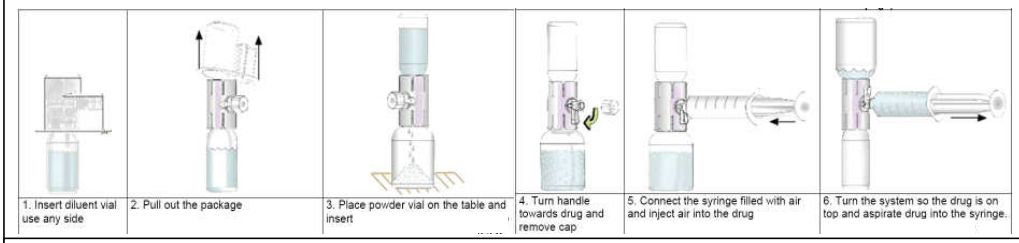

Figure 3 West Pharmaceutical's needleless transfer device

Products which require separation of liquid from powder are not limited to the medical field alone but even include instant baby formula. Because of its short life after reconstitution the UMix™ baby

Fig. 4

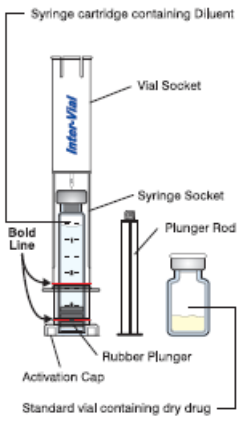

Figure 4 The Inter-Vial System by Duo Ject. The vial is clipped to the activation cap, then the plunger rod is screwed onto the rubber plunger. The diluent is injected from the syringe and into the vial, mixed, then the system is inverted and drawn back into the syringe. The vial is unscrewed and the pharmaceutical may be delivered.

bottle was created. This product, as described in **Figure 5**, stores the powder in the upper chamber and the liquid in the bottom until the product is ready to use. Although there are other products available, the device we develop will improve upon the shortcomings of its competition and fulfill its own niche.

Fig. 5

Figure 5 The U-Mix Baby Bottle and instructions for use

Final Design Concept

After thoroughly considering three different designs, our design matrix (see appendix) indicated that we should pursue our modified syringe design. Following further consideration, we reconsidered the main mechanism of the syringe design. By changing the mechanism, we were able to better meet the design constraints set forth by our client.

Fig. 6

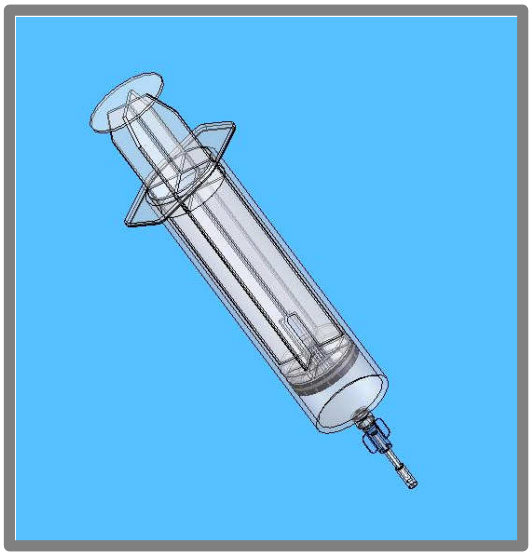

Figure 6 The U-Mix Baby Bottle and instructions for use.

As noted in the design constraints, our client prefers a product that incorporates components that are currently on the market as compared to custom fabricated components. Thus

the main body of our design is a syringe made of polyethylene, which is readily available on the market. In our design we have utilized both the barrel and the dead space between the plunger and the barrel in the syringe to serve as compartments that store the powder and liquid components of an IPN, respectively (**Figure 6**). Other modifications to the syringe included the addition of finely-textured etches to the barrel where the seal is added, incorporation of a one-way valve into the bottom of the plunger, and an atomizer attachment.

One-Way Valve

The plunger in our design was modified to incorporate a one-way valve. The one way valve we have chosen to use is available from Smartproducts.com. This check valve uses a spring and an O-ring to form a seal which is normally closed. A key advantage of a one-way valve kept closed with a spring is very little backflow compared to other one way mechanisms. Leakage due to the water head is common for most one way valves but with the spring and O-ring, a very tight seal is created without hindering the valve's ability to open but with only minimal effort required on the user's part. To incorporate the valve, a hole must be drilled through both the rubber gasket and hard plastic at the bottom of the plunger (**Figure 7**). This hole is drilled twice the length of the one-way valve to allow the solvent located in the upper chamber to move through the one-way valve (**Figure 7**). Within the

Fig. 7

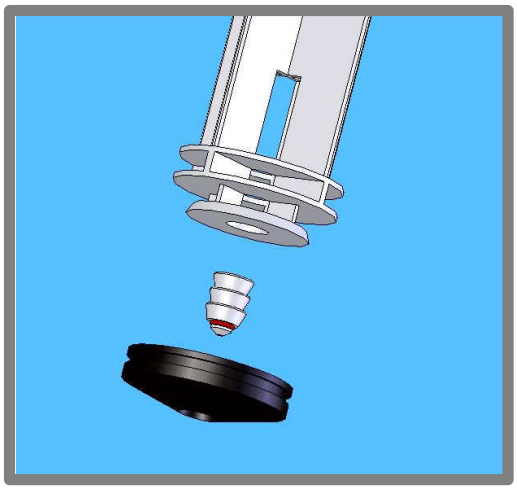

Fig. 7 Exploded view of one way valve, modified plunger stick and rubber gasket.

plunger, the one-way valve is oriented so that the valve will open when the pressure is greater in the top compartment (**Figure 7**). The principal which allows the one-way valve to open is the differential pressure between the upper and lower chambers. Until the time of use the lower chamber is sealed, and drawing back the plunger creates a partial vacuum in the powder chamber. This generates enough of a pressure gradient to overcome the force due to the spring and to open the valve, forcing the liquid to flow into dry compartment where mixing can occur. Lastly, to prevent leakage and maintain the biological integrity of the components, once the valve is inserted into the plunger it is then sealed with a bioinert adhesive.

Seal

In order to create a compartment in the dead space between the plunger and the barrel, it is necessary to have a strong seal at the top of the barrel that is biocompatible. Moreover, this seal must preferentially adhere to the barrel of the syringe, while allowing the plunger to move freely. The seal is a two component apparatus in which a mold of the barrel and plunger was created out of medical grade epoxy (Locite P/N 3981) to fill the large gaps between the barrel and plunger body, as well as wax applied as a liquid to fill in the gaps in the epoxy. When the wax hardens and an airtight seal is created between the diluents chamber and the atmosphere. To ensure that the seal did not move as the plunger was drawn back, finely-textured etches and, consequently, surface area were added to the sides of the barrel to facilitate preferential adhesion to the barrel.

While the one-way valve opens under vacuum pressure created in the dry compartment, for shipping and storage purposes, the compartment which holds the liquid component must also be sealed. The seal not only maintains the integrity of the diluents, but also allows the device to

be stored in any position, and permits the valve to withstand the physical stress of being shipped without breaking the device

Atomizer

The final feature in this design is an atomizing spray-tip. Previously, the syringe which was used for application produced a stream of liquid, which is unsuitable for an even application of the IPN solution. Atomizer tips from Wolf-Tory medical (**Figure 8**) were ordered, and had several desirable qualities for this application. These tips were adequate for this design because they produced an even spray pattern, and attached to a syringe by a luer-lock connector. This quality allows multiple tips to be shipped with each syringe, so they can be easily replaced should one tip become blocked due to an undissolved particle the solution becoming lodged in the tip. However, one drawback of these tips is that they are only capable of atomizing non-viscous solutions. Since we suspect the final consistency of the IPN solution will be somewhat viscous we would either need to work closely with Wolfe Tory Medical to have the atomizers modified or add a different atomizer tip to the top of the syringe, such as the one from a Garnier Frutis bottle, which is capable of atomizing more viscous solutions.

Fig. 8

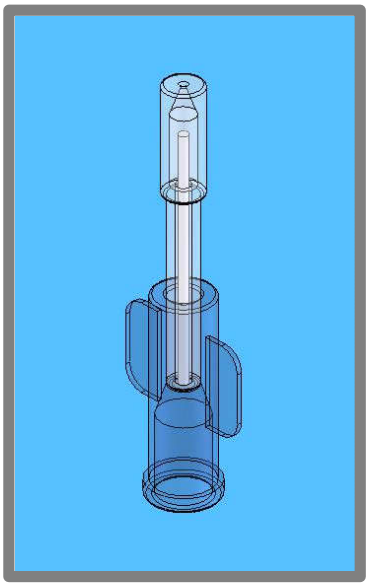

Fig. 8 Luer-lock atomizer tip attachment available from Wolfe Tory Medical

Each of these components plays a vital role in the function of the device. The seal and one-way valve function together to achieve the most complete mixing possible, and the atomizer tip allows the device deliver an evenly coated IPN solution to the wound. This design is elegant in its simplicity, and by having the fewest number

of moving parts, the possibility of mechanical failure is significantly reduced. The design is based off of physical principals which are easily relied upon to deliver consistent results with each device produced.

Cost Analysis

A cost analysis was performed for production quantities of 10,000 units, as seen in **Table 1**. This cost analysis was made without taking into account the additional costs associated with the incorporation of the IPN components and pharmaceuticals. These additional costs would likely drive up the price of our product, however we expect the product's final cost would be comparable to that of competing products. According to HealthPricer.com, similar wound dressings without pharmaceuticals incorporated can cost between US**D** $45 (Aquasorb Hydrogel Dressing) - $86 (Cica-Care Silicone Gel Sheets) (HealthPricer Medicine Cabinet)**.** We would expect that if these dressings were made to incorporate pharmaceuticals, their cost would be driven up to a range of USD $200-1000.

Table 1. Cost projection for production of 10,000 units of our final design.

Product	Distributor	Part Number	Price
30 cc Syrince w/ Luer Lock	Excel International Medical	26291	$0.73
Barbed Check Valve	Smart Products	Model 111	$3.00
Atomizer Tip	Wolfe Tory, Inc.	MAD300	$2.25
Sealant	LOCITE	3981	$1.71
Total Cost			$7.69
Projected Retail			**$24.14**

Table 1

Pressure Testing

In order to assure that the spray tip from Wolf-Tory performs adequately, a pressure test was conducted. The syringe was suspended on blocks by the flanges on the barrel and filled with 30cc of water. Varying weights were then placed on the plunger. The pressure in the barrel was then measured by using a Harvard Apparatus (P/N 724496) pressure transducer. Pressure values were based off of a five second average, sampled at 10 kHz. The data were plotted and are shown in **Figure 9**. The relationship between pressure and weight was linear with an R^2 value of 0.9996. Since pressure is force divided by area, the slope of the line should be the area of the

Fig. 9

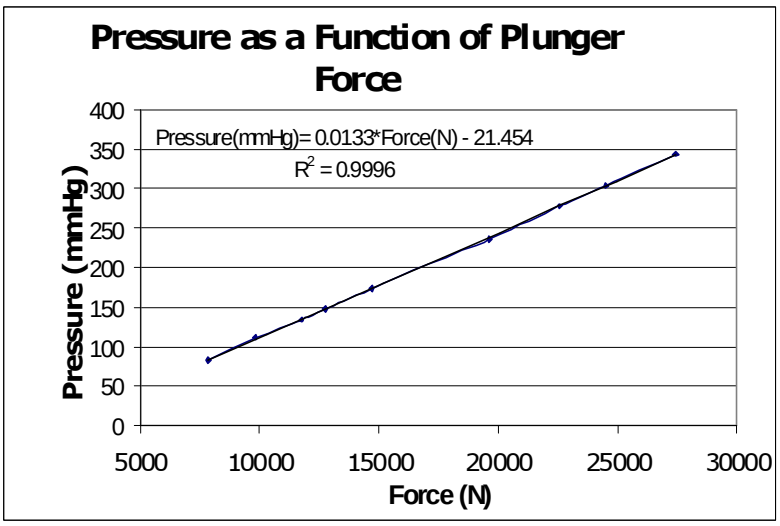

Fig. 9 Pressure tests showing the rigidity of the valve opening, as shown by the linear values on the graph.

plunger. However, it was possible that the plastic from which the tip was made would be compliant and deform under the pressure, changing the area. This test proved that the spray tip had a constant area and, therefore, a constant resistive value. Based off the conclusion that the valve was non-compliant, a test was also performed to quantify the resistive value of the atomizer tip. A 2.2 kg weight was placed on the plunger, and the pressure was measured by the

same means as previously mentioned. Then, the time required for the tip to dispense 30cc of water was used to measure resistance. The final resistive value of the tip was, in fact, constant, at a value of 1132 mmHg/(ml/s). While the results of the pressure tests on the spray tip may seem to reach an obvious conclusion, they were vital to understanding its physical properties.

Surface Area Testing

Another physical property of the atomizer tip of interest to us was the surface area that may be covered. A test (**Figure 10**) was conducted that measured the surface area (in^2) covered when 5mL of water was sprayed from a set height *h* (in). Three clinically reasonable heights were selected: 1, 3, and 5 inches. Five samples were collected for each height, and their areas averaged. Each spray pattern was estimated to be ovular in shape. Major (A) and minor (B) axes were measured, and then the area was estimated using the following equation:

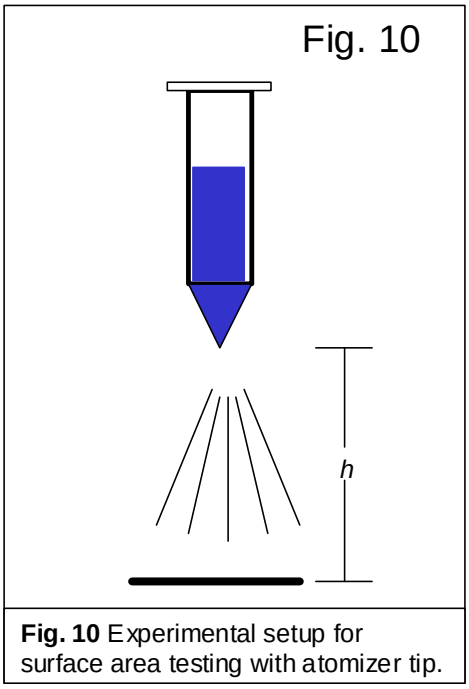

Fig. 10 Experimental setup for surface area testing with atomizer tip.

$$Area = \frac{AB\pi}{4}$$

The results of these tests are seen in **Figure 11**. Theoretically, the spray pattern will produce a cone, so the area should be parabolic in nature. Based on the data, the spray area seems to obey a non-linear pattern, when compared to distance in the observed range. The purpose of this test was to determine the range of areas that the atomizer could reach from a specific distance away. This information would be pertinent when instructing the user how to

apply the IPN, because it would minimize the amount of wasted product as well as promote an even application of the IPN solution.

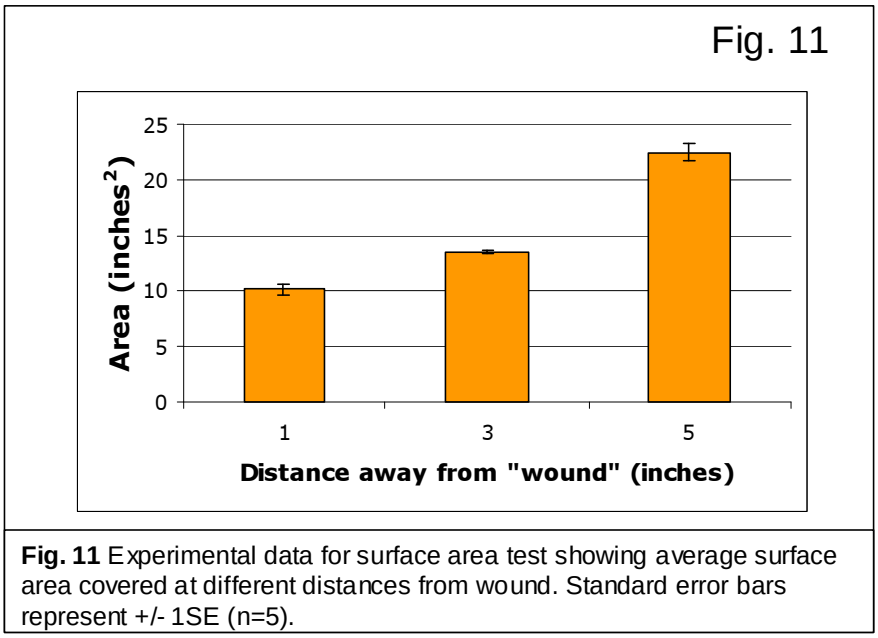

Fig. 11 Experimental data for surface area test showing average surface area covered at different distances from wound. Standard error bars represent +/- 1SE (n=5).

Continued Laboratory Research

The end utility of the IPN product is limited by the effectiveness of the IPN solution, so an additional facet of our work this semester was to continue to investigate gelatin dissolution under varying conditions. Last semester, we concluded that acetate/citrate buffer provided the best possible dissolution of standard Bloom Type-A porcine gelatin at room temperature, based on qualitative observation and quantitative analysis of dissolution using UV-Vis. spectrophotometry. However, when gelatin in acetate/citrate buffer was observed on a microscope slide relative to a gelatin in 60°C water solution, the characteristics were drastically different (**Figure 12**), suggesting that gelatin did not fully dissolve in acetate/citrate buffer. Without full dissolution, gelatin loses its bioactivity, and it would compromise its functionality in the final IPN.

In order to promote optimal efficacy of the final IPN cold-set gelatin was considered as a viable alternative to a heated gel. Cold-set, instant gels are considered amorphous; contrary to standard gels, which exhibit crystalline properties (Dick, 1999). These instant gels demonstrate the same rheological properties as gels obtained by dissolving normal gelatin in hot water, so the final viscosity of the solution should remain consistent with standard gels. However, the rates of gel formation are different, since instant gelatin attains 90% of its hardness after 30 minutes, while standard gelatin hardens only after 15 hours (Dick, 1999). Variability in the properties of cold-set gelatin comes from how it is prepared. Most of this gelatin utilizes a spray or drum-dried method (Cole, 2000) but there is a chemical approach to preparing this gelatin as well (USPTO #2834683). These gelatin solutions would have a more flexible range of application without affecting the composition of the final IPN.

Fig. 12

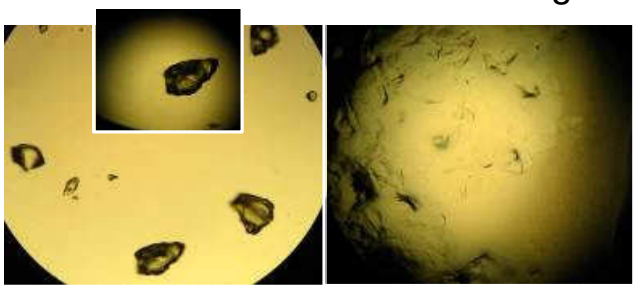

Fig. 12 On left: Solid 90-125 Bloom gelatin particles under 20X magnification (inset shows 40X magnified view). On right: Gelatin dissolved in acetate/citrate buffer under 20X magnification. Gelatin dissolved in 60℃ water sho wed no irregularities, but rather, the solution appeared homogenous and translucent.

Thus, cold set gelatin was initially created according to the chemical approach found in Patent 2,834,683. Since the creation of IPNs typically use a high bloom strength of gelatin, sugar was used in the procedure to infiltrate the gelatin matrix during the solubilizing process to help break it apart. The sugar also serves as a lyophilizing agent, since it readily binds water. Based on recent testing on the role of sugar in this procedure, it seems to make the final product less of an aggregate and more of a powder.

Preliminary testing of the gelatin product has revealed that it is a suitable alternative to a heated solution. After observing the dissolved solution under a light microscope, no residual gelatin particles remained, so full dissolution appears to have occurred. Also, the properties of the modified gelatin do not appear to have been altered, since solutions of this gelatin in water develop a sol-gel consistency, indicating that the gel properties have not been compromised through the solubilizing process. Furthermore, the cold water-soluble gelatin-based IPNs are able to cure in 5-10 minutes under UV light. Isopropanol was used as a solvent in the procedure, since it acts as a dehydrating medium with a high affinity for water and a low affinity for gelatin.

Future Work

Now that a proposed prototype has been created, there is still a large amount of work that would need to be completed in order to make this design a commercially available product. These considerations are described below.

Packaging

Two aspects of our design require attention when considering packaging. Firstly, the final design requires that the syringe plunger remain stationary until its use. Secondly, the solid must be protected from light to avoid unintentional cross-linking between the PEG-dA and the gelatin. Our proposed packaging involves encasing the syringe inside of a firm polystyrene foam molded to fit the syringe's contours. This is then to be inserted into a cardboard box (**Figure 13**). The polystyrene foam provides both protection and support for the syringe, which is crucial in

Fig. 13

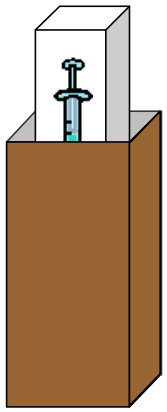

Fig. 13 Packaging for Syringe.

preventing unintentional movement of the plunger. Both the cardboard box and the foam ensure that the product will not be exposed to light that could initiate cross-linkage before use.

Testing and FDA approval

Future testing includes ergonomics and consistency testing. To minimize potential errors that may occur at the place of administration, a clear, easy to follow method for using the device should be drafted. By conducting ergonomic and consistency testing, this procedure can be drafted. One area of major concern is making sure that the IPN solution is completely dissolved. All of these things must be considered and proven in order to obtain FDA approval. This is an area of future work and testing that must be done.

Manufacturing

Currently, the method for making the design requires someone to physically assemble the pieces, create an epoxy seal, and then put a wax layer on by hand. This is a tedious method, and a streamlined manufacturing process is needed. The main hurdle to overcome is sealing the upper compartment after putting the diluents into the syringe. One more manufacturing concept to consider would be that sterilization should be incorporated to ensure the safety of the patient.

Continued Research

The cold –set gelatin will continue to be investigated as a feature of the final product through testing that will seek to streamline the solubilizing process. The final process must optimize the gelatin's yield, by using the least amount of sugar to ensure the incorporation of the most gelatin into the IPN matrix. However, reduced amounts of sugar should not compromise the amount of gelatin that can be dissolved in 1 mL of water, nor its ability to cure in an IPN. This data will be

analyzed by using high-performance liquid chromatography (HPLC) to quantify the ratios of sugar to gelatin in several samples of gelatin that are produced under varied reaction conditions.

Appendix

Design Matrix

The final design was determined by the drafting of a design matrix (**Table 2)**, which evaluated characteristics of multiple designs. Categories were based on design constraints and were weighted with respect to their importance in the final design. Mixing procedure was determined to be the most important category. Without a successful mixing procedure, the design is likely to fail, regardless of how well the remaining requirements are met. Other criteria that are important include scalability and application ergonomics. Scalability refers to the design's ability to be manufactured in different sizes. Application ergonomics refers

Table 2 Design matrix used to determine the final prototype design.

Criteria	Weight	Design 1 Syringe	Design 2 Pressurize	Design 3 Spray
Mixing Procedure	15	10	9	12
Uniform Solution	10	6	7	7
Compartmentalization	10	9	5	8
Parts Availability	10	7	9	6
Application Ergonomics	10	8	6	4
Safety	10	8	6	8
Cost	10	5	3	7
Sterility	5	5	3	4
Scalability	5	5	2	4
Spray Pattern	5	4	5	2
Client Preference	5	5	5	3
Photo-initiator Protection	5	3	5	4
TOTAL	**100**	**75**	**65**	**69**

Table 2

to the work required by the user to apply the product as well as the efficiency of application. Photoinitiator protection was evaluated based on how effectively the design could incorporate adequate protection. After each design was rated, the matrix suggested that the syringe design (**Figure 14)** would be the most effective design. Several modifications were made to this design once tangible device components were acquired and tested.

Fig. 14

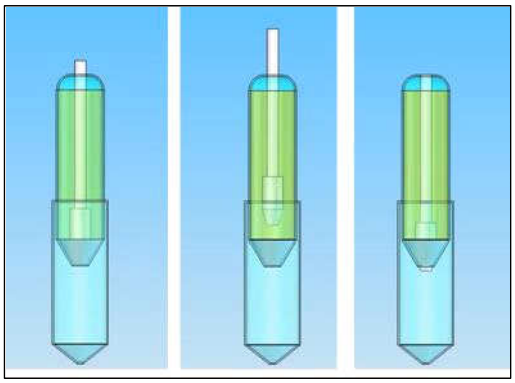

Fig. 14 The liquid portion of the IPN would be stored in a custom chamber housed in the plunger, and the powder in the barrel. A retractable ball-point pen-like release mechanism allows the liquid to fall through a hole into the barrel, where mixing will occur. The user can control whether the hole is plugged or open to accommodate effective liquid release, mixing, and solution delivery. To achieve a fine mist during delivery, an atomizer is attached to the luer lock connection on the tip of the syringe. Manual pressure applied to the plunger of the syringe effects spraying.

Cold Water-Soluble Gelatin Protocol

To prepare the gelatin, a sample of 90-125 Bloom gelatin was added to room temperature water at a concentration of 0.2 g/mL. Sucrose was also added in a 10:1 weight ratio with the gelatin. The gelatin, sugar, and water mixture was heated to 60°C until full dissolution occurred and then added to a beaker containing a heated solution of isopropanol. At this point, the isopropanol to water ratio was 6:1. The resulting solution was heated and stirred for 30 minutes, after which the liquid portion was decanted and replaced with fresh 60°C isopropanol. The decanting/isopropanol addition steps were repeated three more times, and then the solid portion was dried under vacuum in an oven at 60°C. Once dry, the product was crushed using a mortar

and pestle and could dissolve within 5 minutes in a 20% solution of product and room temperature water.

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Product Design Specifications

May 6, 2007

Product Design Specifications

Title: Interpenetrating Networks for Delivery Systems

Team:
Ashley Huth- Team Leader
Claire Flanagan- Communicator
Adam Rieves- BWIG
Jon Sass- BSAC

Function : Interpenetrating networks (IPNs) are a type of biomaterials that polymerize *in situ* and have been used in drug delivery, wound healing, and tissue engineering applications. This design project involves the development of novel delivery mechanisms that should be clinically easy to use with improved storage life. Our device should safely, efficiently, and accurately aid in the administration of IPNs to a specific wound region.

Client requirements: Our client, Dr. John Kao, would like us to build on our research from last semester by further exploring the delivery mechanism for IPNs. This has involved both mechanical and chemical components, so throughout the semester our team has integrated both to streamline the mixing and application of the final solution. Compartmentalization, delivery vessel design, homogeneity of the mixed IPN solution, spraying ergonomics, and shelf life were several critical concepts that we focused on in establishing a working prototype for our design.

Design requirements:

1. Physical and Operational Characteristics

a. *Performance requirements*

Isolating liquid and powder components will be desired. Mixing procedures should be relatively straightforward and produce a uniform spray pattern, resulting in a uniformly cured IPN. Final solution should readily cure under UV light after application.

b.*Safety*

Chemical properties of the original IPN should not be compromised. The final solution or any of the initial chemical components should not inflict any harm on the patient or medical personnel making or applying the IPN. Sterilization of all components should be possible. Delivery should be straightforward to execute to minimize injury during administration of the IPN.

c. *Accuracy and Reliability*

Mixing procedures should be relatively straightforward to minimize human error. Composition should be standardized between bottles. Final solution should have a uniform consistency and an even spray.

d. *Life in Service*

Each package will be single use.

e. *Shelf Life*

The useful life of the reconstituted product will be explored, with a goal of two hours. Prior to reconstitution, components should be separated to ensure a theoretical shelf life of several years.

f. *Operating Environment*

Product will only be used in a sterile environment such as hospital operating rooms and emergency rooms.

g. *Size*

The product's volume will be standardized to accommodate variable wound sizes. Possible sizes might be 10 mL, 30 mL, and 60 mL.

j. *Materials*

Components of the formula will include gelatin, PEG-dA, solvent, photoinitiator, and pharmaceuticals. Materials for vessel fabrication should be biocompatible, easily sterilized by the manufacturer, and of low-cost. Pieces that are currently commercially-available are also favored.

k. *Aesthetics, Appearance, and Finish*

Possibly color-coded for varied applications. Product must be well-labeled. A capacity to shield the photoinitiator from UV light is essential.

l. *Ergonomics*

Application must minimize fatigue and work required from the user. Final delivery system must be comfortable to use. User should be able to control the rate of application.

2. Production Characteristics

a. *Quantity*

Only one unit is desired per IPN delivery. Units may be packaged in varying quantities, however.

b. *Target Product Cost*

Pharmaceutical components should be the largest percentage of the total product's cost.

3. Miscellaneous

a. *Standards and Specifications*

FDA approval will be necessary.

b. *Customer*

Various medical institutions.

c. *Patient-related concerns*

Proper wound debridement will be necessary prior to application. Sterile packaging is essential.

d.*Competition*

Inter-Vial, Clip'n'ject, U-Mix travel bottle, and Hasplast.