WOUNDCARE MATERIALS: AN OVERVIEW

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INTRODUCTION

Wounds and injuries are not some alien terms affecting someone somewhere far away. As part of our human experience we intuitively understand and almost feel the pain every time these words are mentioned. This unanimity of perception also gives an indication of the potential size of the market and its colossal costs to the healthcare systems around the world. The market value of wound care in US in 2002 was no less than $6 billion and this is to grow at an average rate of 4% per annum[1]. Similarly, combined European market in wound care in 2001 was reported[2] to be in the region of $3 billion. The annual cost of treatment for chronic wounds alone in U.S. has been put at $2.8 billion per year[3]. These figures are also proportionally replicated throughout Europe. The ageing population and increase in life span of individuals in US and Europe, brought about by all round better healthcare provisions, are the prime reasons for these expansions. Most chronic and potentially expensive wound care requirements also tend to occur in the extended latter stages of peoples' lives when they are least mobile and are therefore in greater need of care.

Depending on wound type and stage of reparation wound dressings of one kind or another are usually required. There are, as yet, no universal dressings that can be applied to all types of wounds despite the repeated claims and counter claims by the manufactures. Up to early 1980s there were only few dressings available apart from the traditional cotton wool, gauzes, lint and the paste bandages. The Drug Tariff was strictly observed and each year relatively few products were allowed to enter the market. However, this cautious and well guarded approach seems to have changed from around 1996 onwards where on average 35 new products have been added to the UK Drug Tariff each year[4]. This explosion in product availability is partly related to market competition and partly due to capitalization on now accepted "moist healing concept" intertwined with innovative, but not always necessarily effective, abilities of dressings to deliver drugs, provide scar free rapid healing, antimicrobial protections and many more single or integrated multi-task abilities.

Generally, it is now universally accepted that warm and moist environment promotes healing and prevents tissue dehydration and cell disintegration. Under these conditions growth factor-cell interaction is encouraged and faster healing is achieved [5-7]. An ideal wound dressing must therefore not only be able to maintain these conditions but it should also provide the following functions:

1. free of contaminates and be non-toxic, non-sensitising and non-allergic as well as being sterile
2. allow gaseous exchange whilst remaining impermeable to micro-organisms;
3. manage exudate and excess fluid without causing maceration or irritation;
4. not adhere to the wound and allow easy removal without trauma;
5. require infrequent changes and be acceptable to the patient e.g. comfortable and pain relieving;

6. easily conform to body contours and provide mechanical protection; and be reasonably inexpensive and readily available.

Depending on wound type and severity of malfunction, injury or infection as well as the age of the patient and that of the wound, treatment will depend as much on correct assessment of the wound as to the type of dressing to be applied. Currently there is not enough verified evidence on wound care products to single out effectiveness of a particular brand against another to justify recommendation or discouragement[8]. Lack of evidence on management of wounds and actions to take has reportedly caused confusion and even disagreements between healthcare professionals[9]. However, it is not the intention of this short overview to critically analyse the available dressings for their acclaimed abilities or lack of their effectiveness but merely to introduce the available materials in their most general terms.

Materials available today range from simple cotton gauzes and flints to sophisticated multifunctional systems made from natural or synthetic materials. Origins and fundamental properties of these materials are readily available and adequately discussed in various relevant literatures [10-12]. However, an attempt has been made in Table 1 to summarise the main wound dressings according to their origin, functional ability and form of applications to assist easy access and cross referencing.

Specialized materials and/or additives with predetermined functions can be included in a number of dressings. Activated charcoal, for instance, as in Lyofoam produced by SSL International, Carboflex and Carbopad Vc manufactured by ConvaTec and Vernon Carus respectively are used to absorb offensive odors from bacteria infected wounds. Silver metals or their salts have antibacterial properties and are now included in a series of dressings e.g. Arglaes produced by Maersk, Avance range manufactured by SSL International; claimed to be particularly effective against MRSA, Flamazine and Actisorb 220 are respectively produced by Beiersdorf Smith & Nephew and Johnson & Johnson. Other additives include antiseptics (Inadine, Johnson & Johnson), antibiotics (Bactroban, Beecham) and zinc pastes (Steripaste, SSL International) mainly used to sooth pain and relieve irritation. Sugar pastes[12] are also used as deodorizing agent and as antibacterial constituents. Other non-conventional methods include honey[13-16] and maggot[17-18] therapy.

In recent years, incorporation of biomaterials into cells and tissues for repair and reconstitution of skin or organs has extended the boundaries of reconstruction into what is now commonly referred to as tissue engineering; where living cells are persuaded to grow into specific and pre-determined structures made from natural or synthetic materials. These manufactured structures or scaffolds, when in place, provide mechanical strength and stability in three dimensions whilst allowing cells and tissues to colonize and regenerate the damaged or missing skin/organs. Collagen and hyaluronans extracted from human or animal tissues are often used as natural scaffolding materials for temporary or functional purposes assisting reparation and the healing process, the scaffolds subsequently disintegrate and are absorbed by the body[19]. Synthetic biodegradable materials with similar properties have also been developed although their assessments in *vivo* and *vitro* practices are still limited[20]. Polyglycolic and plylactic acids and their derivatives are amongst the more successful materials used for these applications.

Interdisciplinary interaction between cell biology, polymeric materials, biochemistry and bioengineering for the purpose of repair and recreation of damaged and diseased areas within the human body is an exciting and developing area where a great deal of challenging

Table 1: Summary of available wound dressing according to their origin, functions and applications

Types of wound dressings	Examples	Function	Form of application
Traditional dressings	Cotton wool, gauze &lint	Allow strike through, shed fibers and adhere to the wound + dehydrate the wound	Used on clean, dry wounds or as secondary dressings
Films	Bioclusive C-View OpSite Plus Tegaderm	Vapour-permeable adhesive films, thin, very flexible, easy to mold around difficult shapes. They cool the surface of the wound. Excessive exudate may accumulate	Suitable for relatively shallow wounds. Used to prevent pressure ulcers and retention dressings
Hydrogels	Aqaflo grauGel intrsite Gel Nu-Gel Sterigel	Hydrophilic polymers, partially cross-linked to form 3-dimensional network. They can absorb up to 100% of their weight. They promote moist healing, non-adherent, by cooling of the wound surface they can reduce pain. Amorphous hydrogels are particularly useful for treating cavity wounds.	Most require covering with a secondary dressing, suitable for dry "sloughy" wounds and lightly exuding wounds. They are no good for infected or heavily-exuding wounds. They are also good vehicle for delivering drugs such as placental growth factors and antibiotics.
Hydrocolloids	Aquacel Comfeel Granuflex range Ultec Pro	More complicated than hydrogels, contain constituents such as methylcellulose, pectin, gelatin and polyisobutylene, promote formation of granulation tissue and provide pain relief. Suitable for treatments of acute and chronic wounds, for desloughing ; and for light to medium or medium to heavily exuding wounds.	Not suitable for infected wounds, usually require no secondary dressing, hence patients can bathe or shower
Alginate dressings	Algisite M Comfeel Plus Kaltostat SeaSorb Sorbsan	Natural polysaccharide extracted from brown seaweed. At wound/dressing surface sodium-calcium exchange takes place between the dressing and the exudate respectively hence swelling and formation of gel.	Suitable for use on medium to heavily exuding wounds and cavity. They are not used on infected wounds. Most alginates require a secondary dressing
Foams	Avance Cavi-Care Flexipre Tielle Lyofoam	Polyurethane based. With or without adhesive borders, main applications are to absorb large volumes of exudate reducing the need for dressing changes.	Suitable for use on light to medium exuding wounds
Silicon dressings	Cica-Care Mepiform N-A Ultra Silgel	Consists of silicone gel, used to reduce hypertrophic and keloid scarring, cosmetically acceptable scars.	Gel sheets can be sterilized and they are re-usable
Collagens	Oasis Opraskin Promogran Suprasorb C	Fibre-forming protein of mammalian connective tissue. It contributes to different of wound healing by attracting granulocytes and fibreblasts into wounds and reduces wound contraction etc.	Collagen is used as haemostat, an absorbable suture material, artificial skin, bone filling and wound dressing
De-odoriser dressings	Actisorb Silver 220 Carboflex Denidor Metrotop Gel	Contain activated charcoal responsible for reduction of offensive odour. Suitable for discharging, purulent and contaminated wounds complicated by bacteria infection. Can contain silver to inhibit bacterial growth.	They are used once or twice daily as necessary
Low adherent dressings	Cutilin Melolin Release Setoprime	Suitable for dry wounds or lightly exuding wounds	Need to be secured with bandage or adhesive tape
Non-adherent Dressings		Available nonimpregnated or impregnated and discourage foreign matter from becoming lodged in the wound bed. They can be used on skin tears, donor sites and skin grafts.	Most nonadherent dressings require a cover bandage or tape to hold them in place.

research is currently in progress. Cultivation and subsequent fabrication of skin from animals and human resources for treatment of patients with severe wounds and burns in company of natural and/or synthetics materials are prime examples of these sciences working hand in hand.

Advances made in genctic technology have increased growth factor availability and their potential therapeutic role in wound healing. Engineered growth factors capable of proving speedy and safe healing in all types of injuries including wound-related leg amputations and the like are actively being developed and refined[21]. Main objectives in all wound managements practices however continue to remain fast and effective occlusion of the wound, management of exudate and elimination of bacteria and infections resulting in aesthetically acceptable post recovery scars.

RESEARCH PAPERS

Most research work and subsequent clinical trials in wound care dressings are highly technical and function oriented. Very little work has been reported where patients' health related quality of life (HRQOL) has been taken into consideration. Patients' opinion and expressed experience of the dressings used, however subjective, adds a new dimension to health care provision and treatment efficacy. The first of the proceeding papers by D.V. Praburaj et al[22] in this chapter discusses the current trial methods and their perceived shortcomings and proposes some innovative approaches where patients' perspectives in conducting clinical trials can considerably influence the outcome of such trials.

Burn wounds are probably the most traumatic and most difficult external injuries to treat particularly when skin and its sub-layers have been badly damaged[5] . The use of textiles in Burns from injury to recovery is a journey through a person's life from the moment of injury to full recovery. The second paper in this chapter by J. Edwards[23] highlights the most recent developments that have taken place in patient care, material availability and application practices within the burn treatment units.

Polysaccharide based chitin and chitosan are currently recognized for their collective function of non-toxicity, biodegradability, antibacterial resistance and haemostatic abilities and their safe breakdown by lysozmes, an enzyme secreted within body fluid. Much research is in progress on these materials and their derivatives in the wound care arena and beyond. The proceeding two papers by K.Van de Velde et al[24] and Anna Blasinka et al[25] in this area elaborate on novel methods of synthesizing these polymers with duel purpose of accelerating wound healing and alleviating post recovery scars.

Increasing trend for evasive rather than invasive intervention in surgery where access is often gained by endoscopic means require dressings that are resilient, multi-functional and highly flexible besides possessing the usual non-toxic, antibacterial and compatibility criteria. The fifth paper by John O. Hudson[26] in this chapter discusses one such example where special materials have been developed to improve efficiency and alleviate discomfort in nasal surgery where acute nose bleeding demands far fetched dressing interventions.

Management of exudate from a wound and its treatment with appropriate medication could be a real challenge when there is heavy exudate release. Regular inspection and periodic medication is both time consuming and costly for the health service and inconvenient for the patient. The final paper by D. Kocak et al[27] in this chapter introduces a novel double action dressing capable of transporting exudate away from the wound whilst

delivering medication through different channels. This system reduces or avoids exudate/medication interaction and enables appropriate drug delivery.

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THE USE OF TEXTILES IN BURNS – FROM INJURY TO RECOVERY

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ABSTRACT

The care of burn patients has made steady progress. Until the first half of this century, even moderate burn injuries were usually fatal. The introduction of fluid resuscitation (Settle 1996) and the establishment of burn units have had a major impact on mortality.

Burn patients have subsequently benefited from many developments, including the introduction of systemic and topical antimicrobial agents, progress in intensive care and nutritional support, changes in surgical philosophy, advances in wound care and methods of achieving skin cover, and the concentration of treatment of patients with serious burns in specialist care. Alongside these improvements, the use of textiles in the patient's journey from injury to recovery has been crucial. This paper will explore their role in burn management.

Obviously it is important to assess the depth and extent of the burn and commence fluid resuscitation, which involves catheterisation, siting of intravenous fluids and possibly intubation for smoke inhalation. All of which involve plastics of some sort or another, but this paper will concentrate on the transfer, support surfaces, dressings, splinting, skin substitutes, pressure garments and silicone gels needed to enable a burn patient to travel the road from injury to recovery.

TRANSFER

The problems of hypothermia in burns have long been recognised. Plasticised Polyvinyl Chloride (PVC) is advocated on the Emergency Management of Severe Burns (EMSB) as a means of preventing hypothermia, reducing pain, and preventing desiccation and infection (Allison 2002). The film is very thin and permeable to water vapour, oxygen and carbon dioxide, easy to apply and allows for visual inspection of the wound (Davies 1983).

SUPPORT SURFACES

On admission, severely burned patients need to be nursed on specialised beds. These can either be air-fluidised beds or low air loss beds. Mattress coverings have developed greatly since the mid 80's when regulatory changes were made to the flame retardancy requirements. These new coverings are water/moisture vapour permeable and have the ability to transmit water vapour molecules through itself, whilst at the same time remaining a complete barrier to liquid water (Clubb 1998). There are two main types of materials; microporous materials, these are membranes made from special polymers that have tiny holes in them, e.g. Gore-Tex. Gore-Tex, is vapour permeable, it has pores 700 times larger than water molecules, which let water vapour, pass through. This helps to eliminate moisture, friction, shear, infection, contamination and heat. As burns have copious exudate during the first 24 – 48 hours, this function is important in a bed.

The second types are hydrophilic materials; these fabrics attract water into them and transmit the moisture through the coating by a chemical mechanism. They have no holes in them and are a complete barrier to liquid water. All polyurethane's are hydrophilic to some degree or another, and some can be formed into coatings that are tough, as well as being water vapour permeable. Polyurethane-coated fabrics provide greater patient comfort, are generally resistant to most cleaning agents, and complement carefully engineered support mechanisms.

INITIAL MANAGEMENT

Initially the burns are dressed with Flamazine and a covering called Exu-Dry. Exu-Dry is a one-piece, multilayer, highly absorbent, non-adherent wound dressing. It incorporates a non-adherent wound contact layer, and an antishear layer, which helps to reduce friction. The absorbency of the product comes from the inner layer, which is highly absorbent. The outer layer is permeable and non-occlusive, allowing the wound to breathe (Edwards 2001). These dressings are useful as traditionally dressings were layered using paraffin gauze, gauze and gamgee, which was time consuming and had problems of strike through. They also have a marked tendency to adhere to the surface of drying wounds. This is due in part to the exudate sticking the dressing to the wound as it dries and also if left in place long enough, the in-growth of capillary loops within the granulation tissue into the dressing. This in effect incorporates the dressing into the new tissue, which will inevitably be damaged when the dressing is removed (Thomas 1994). Exudry dressings come in body shapes such as arms, legs and chests, which enable even inexperienced nurses to dress extensive burns efficiently.

A useful alternative is a product called Telfa Clear, this is a non-adherent contact layer made from a Mylar perforated polyester (polyethylene terephthalate) film. The specially designed film is composed of hundreds of minute perforations that act as a selective membrane. The size of these holes allows the passage of wound fluid into the secondary dressing, but blocks the entrance of larger epithelial buds (Edwards 2002). Telfa Clear comes in large sizes and is used a primary contact layer for the application of Flamazine, it enables large awkward areas to be dressed that are not perhaps covered by the use of Exu-Dry.

BANDAGES

Regardless of dressing type used, most dressings for major burns will require bandages to secure them. Bandages perform a number of functions including retention, support and compression. In burns patients the main functions are retention of the underlying dressings, and support to prevent oedema formation and provide joint support (Nelson 1995). The type of bandages used traditionally are crepe, which are made of a cotton fabric of plain weave with a characteristic appearance made from the crepe twisted cotton yarns (e.g. Elastocrepe, Elvic). More recently white knitted bandages have been used, these are made from a white knitted conformable fabric containing 93% viscose, 4% nylon and 3% elastomeric yarn (K Lite). This means that these bandages can give more support than traditional crepe bandages (Edwards 1999).

SPLINTING

Having assessed and dressed the burns, the next most important area of care is splinting. Splinting is used for a number of reasons; to increase function, to prevent deformity, correct deformity, protect healing structures, restrict movement and allow tissue growth or remodeling. A number of splinting materials are used, but the majority are made from polycaprolactones (Polyform, Aquaplast). These are low temperature thermoplastic materials, which provides greater conformability and ease of splint fabrication (Ewing Fess 2002). The introduction of these materials has led to major advances in splinting.

SKIN SUBSTITUTES

Once the patient is stabilised then surgery can be considered. In extensive burns, there is a shortage of skin, and skin substitutes must be considered in order to close the wound as soon as possible, which minimises the risk of burn sepsis. Biobrane has been successfully used as a temporary skin replacement for burn wounds that do not need surgical excision (Tavis et al 1980). It is used as a temporary covering for clean, debrided superficial and partial thickness burns and donor sites (Hansborough 1995). It can also be used as a protective covering over meshed autografts. Biobrane is a knitted nylon mesh that is bonded to a thin silicone membrane. The silicone membrane provides a barrier against bacterial invasion and water vapour transmission.

Following on from this the concept of Biobrane has been taken a step further. TransCyte is a human fibroblast-derived temporary skin substitute consisting of a polymer membrane and newborn human fibroblast cells cultured on a porcine collagen coated nylon mesh. The membrane is biocompatible and protects the burn wound surface from environmental insults. As the fibroblasts proliferate within the nylon mesh, they secrete human dermal collagen, matrix proteins and growth factors (Hasen et al 2001).

Another step forward from this is the development of a product called Integra, which is a permanent skin replacement. Integra is composed of a bilaminate membrane consisting of a bovine collagen based dermal analogue and a temporary epidermal substitute layer of silicone. The dermal replacement of Integra consists of a porous matrix of fibres of bovine type I collagen that is cross-linked with chrondroitin-6-sulfate and glycosaminoglycan (GAG) extracted from shark cartilage. The porous matrix is designed to serve as a template for infiltration of the patient's fibroblasts, macrophages, lymphocytes and capillaries. The outer silicone layer of Integra serves as a temporary epidermis and allows for water flux; protection from microbial invasion and prevention of burn wound desiccation (Sheridan et al 1994).

SKIN GRAFTS AND DONOR SITES

Split thickness skin grafts (SSG's) consist of the epidermis and a partial thickness of the dermis. They are very useful in large burns as the donor site can regenerate quickly and be reused. Wilkinson (1997) contends that SSG's speed up the healing time of large areas of skin loss, whilst protecting the underlying structures and reducing the risk of infection. They can be varying thickness' depending on the age, sex and donor site region, and skin

grafts need a good blood supply, prevention of shear, prevention of haematoma and freedom from infection for them to take (Morgan & Wright 1986).

Donor sites are in reality superficial wounds, consisting of epidermis and dermis and with the correct conditions will heal within 8-14 days depending on the site, depth and general condition of the patient (Wilkinson 1997).

Jelonet has been traditionally used to manage skin grafts and donor sites. This is sterile leno-weave gauze impregnated with yellow soft paraffin. Vloemans (1990) however, argues that tulle Gras type products lack structural integrity and provide insufficient protection for the displacement of the graft, also that disrupture of the graft on removal is unavoidable. Because of this many units are now using Hypafix. Hypafix is an apertured, non-woven polyester fabric, which is coated with a layer of acrylic adhesive. The Hypafix is applied directly to the skin graft or donor site and allowed to dry out. Davey et al (1991), used Hypafix in skin grafts up to 65% Total Body Surface Area (TBSA). They left the dressing in situ for 7 days and noted that failure due to infection or slippage was less than 1%, and that the use of Hypafix gave better cosmetic results.

Another useful dressing for skin grafts is Mepitel. This is a porous, semi-transparent, low-adherent wound contact layer, consisting of a flexible polyamide net coated with a soft silicone. The silicone coating is lightly tacky, which facilitates application and retention of the dressing to the peri-wound area. Platt et al (1996) undertook a study of Mepitel on SSG's, and found no pain or maceration of the graft and 100% graft take in all cases.

DRESSINGS

When the burns, skin grafts and donor sites have commenced healing, the dressings can be greatly reduced, and a number of different dressings are used in the outpatient setting. This is because the patients are more active and mobile and the requirements for the dressings are different. Many of the dressings used are adhesive, to allow for minimal padding and less problems of slippage. Mepilex Border is an absorbent, self-adhesive island dressing. The core consists of 3 components; a thin sheet of polyurethane foam, a piece of non-woven fabric and a layer of superabsorbant polyacrylate fibres. The core is located on a larger piece of polyurethane foam and it is held in place by a perforated silicone adhesive layer that extends to the outer edges of the dressing. This is a very flexible and moldable dressing that is useful for difficult areas such as heels and elbows. Allevyn Adhesive is a soft hydrophilic polyurethane foam, sandwiched between a pink semi-permeable polyurethane film and a perforated polymeric wound contact layer, it comes in large sizes and has good absorbency (Williams & Young 1996). When the wound is almost healed and exudate levels are minimal, then a useful product is Duoderm, this is a semi-permeable polyurethane film, which is impermeable to exudate and microorganisms, which is covered with a thin layer of adhesive (Baxter 2000).

PRESSURE GARMENTS

Pressure garments were developed by Larson et al (1971) at the Shriners Burns Institute, Galveston, Texas. They have 4 main functions, these are; restoration of function, relief of symptoms, prevention of scar recurrence and promotion of optima aesthetic appearance. Pressure results in the reduction of the cohesivencss of the intercollagen fibres, increased vesicular fibroblasts and decreased mast cells. Most useful when the scar is still immature,

and is used on burns that, have not healed within 14 days or have been grafted, and should be applied as soon as the wound has healed or has been surgically closed (Monro 1995).

Pressures should be 24mmHg or above and must be maintained for a minimum of 12 months, during which time the garments should be worn 23 hours per day. Although mechanism of action is not validated, over 24mmhg is a level that exceeds the inherent capillary pressure and therefore ensures occlusion (Rockwell, Cohen & Erlich 1988). Tailor made pressure garments are used to apply pressure and must be changed regularly, they are available commercially from Kendall Camp, Gilbert & Mellish, Second Skin or Jobskin.

The materials used for the garments are either Lycra or Elastane based. Lycra is a manmade premium stretch fabric, which was invented and manufactured by Du Pont, it is a continuous filament elastic yarn, which can be combined with other yarns such as cotton or nylon. Elastane (Spandex), which is a manufactured fibre in which the fibre forming substance is a long chain synthetic polymer comprising of at least 85%of a segmented polyurethane. Initially patients may start with cotton Lycra and progress to Powernet, as the graft becomes more stable. However, one company is now taking the development of pressure garment materials forward (Second Skin). They are now using suede and leather to make garments more hardwearing, hydrophobic fabrics, which are elastic and have a wick-like action and shimmer fabrics, which are softer and more comfortable to wear.

SILICONE GELS

Effective pressure is sometimes impossible to achieve in scars located in anatomical depressions, over flexures or during movement. Also patients may not tolerate pressure therapy. A useful adjunct is silicone gel, it can be used prophylactively or as a sole treatment or in conjunction with pressure therapy. The mechanism of action is not really understood, pressure, temperature and oxygen tension have all been investigated, but the most common theory is that softening and flattening of the scar occurs due to hydration of the scar (Quinn, Evans, Courtney and Gaylor 1985). Silicon is the second abundant element in the earth's crust, comprising about 20%. It is formed in sand, minerals, ??/ and rocks. Silicone is a manmade material; the raw materials include silicon, water and oil.

Silicone gels are said to soften and reduce scars, they are comfortable, durable, and easy to apply and remove, non-antigenic and non-toxic. They can be removed for bathing and can be washed in warm water and reapplied. Patients are advised to build up wear time until patients can tolerate 8 hours or more, and ensure good hygiene of the product. Many gels now exist and can be used for different areas of the body, and are available on FP10. Cica-care, is a cured silicone gel laminated to an elastomeric silicone membrane (Carney et al 1994). Mepiform is made of thin, pliable polyurethane, viscous, non-woven backing covered with a soft silicone Safetac layer, and a polyolefin release film protects the Safetac layer. Silgel, is a high molecular weight silicone gel made of polysilaxone and Novagel, a product based on glycerine can be used when silicone reactions occur (Morgan 2002). The gels are self-adhesive or can be held in place by bandages, tape, silicone adhesive or pressure garments.

In conclusion, the use of textiles in burn is essential to the burn patient's recovery, new developments in textiles impact directly on advances in burn management. From initial injury through a lengthy recovery and into rehabilitation, textiles are inherent in all aspects of patient care and particularly in rehabilitation the quality of those textiles impacts directly

on patient compliance. If textiles are patient friendly, comfortable and easy to apply and wear, then patients will be more inclined to wear them. Designers and manufacturers must continue to develop textiles in conjunction with clinicians to improve the overall quality of care delivered to the patients.

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WOUNDCARE DRESSINGS FROM CHITIN

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ABSTRACT

Chitin, a ubiquitous biopolymer found in the exoskeleton of insects and marine invertebrates, shows the extraordinary capability to promote the ordered healing of tissues and is well suitable to use in wound dressings. However, chitin is insoluble in common organic solvents, therefore direct industrial applications of chitin are very difficult. Recently the method of the synthesis of dibutyrylchitin (DBC), an ester of chitin, was elaborated. DBC is easily soluble in common organic solvents and has film and fibres forming properties. This invention opens the way for production of a wide assortment of novel functional biomaterials made from DBC and pure chitin regenerated (CR) from DBC, which would promote the wound healing process and can find other medical applications.

INTRODUCTION

Most of the wound dressings, which are at present on the European market, do not provide any aid in the reconstruction of wound tissues, and as a result retractive scars are produced upon healing. Chitin, a ubiquitous biopolymer found in the exoskeleton of insects and marine invertebrates, shows the extraordinary capability of promoting the ordered healing of tissues and activating of macrophages. Chitin is active as antibacterial, antimetastatic, antiosteroporotic, and immunoadjuvant agent. It is found that chitin is biodegradable in the presence of human enzymes and is non-toxic and beneficial to the human body. When used to heal wounded tissues, following properties are manifested:

- the healing process is facilitated,
- absence of allergies and undesirable reactions,
- desired reactions with antiseptic agents.

However, due to its hydrogen bonding and highly crystalline structure chitin (poly N-acetylglucosamine) is insoluble in common organic solvents, therefore direct industrial applications of this polysaccharide are very difficult.

Recently the method of the synthesis of dibutyrylchitin (DBC), an ester of chitin, was elaborated.[1] DBC is easily soluble in common organic solvents and has film and fibres forming properties.[2,3] First investigations of biological properties of DBC showed its biocompatibility, bacteriostatic characteristics and sensibility to enzymatic degradation.[4,5,6,7] This invention opens the way for production of a wide assortment of novel functional biomaterials made from DBC and pure chitin regenerated (CR) from DBC, which would promote the wound healing process and can find other applications with much more reduced price (by as much as 30%) in comparison to Japanese products manufactured from chitin filaments.

A consortium of chemical, textile and medical companies, universities and hospitals was set up to do a systematic study around the topic. The main aim within the European RTD project CHITOMED 'Biomedical Textiles from dibutyrylchitin and chitin' (2003-2005) is the development of novel biomaterials and medical items, which accelerate the wound healing with no scar formation and undesirable effects. The wound care dressings have to be easy in handling and would reduce the pain and suffering of patients. The first step in the work programme is the analyses of different chitins, for which a few will be selected according to quality criteria and suitable for modification to dibutyrylchitin. Technologies for the production of DBC and their fibres and films will be developed. High-performance textiles will be designed and developed for which the biochemical, biological and medical properties will be assessed. Finally the optimal forms of a new generation biomaterials will be elaborated.

MATERIALS AND METHODS

Materials and methods

Materials

Two kinds of chitin samples were delivered: α-chitin from shrimp shells and β-chitin that originate from squid pens.

DBC (dibutyrylchitin) was made on laboratory scale from α-chitin and β-chitin. The first synthesis was done under heterogeneous conditions using reagents molar ratio chitin: butyric anhydride (100%): perchloric acid (100%) = 1:4:1.[1]

Polypropylene non-woven material with surface mass of ca 30 g/m^2 (PP) was coated with DBC prepared as above from α-chitin of krill shell origin. DBC content was ca 40%. Obtained dressing materials covered with DBC were tested on biological properties.

Dressing material containing regenerated chitin (RC) was obtained in the process of alkaline hydrolysis of DBC film covering PP.[8] RC content was a ca 30%. Obtained dressing materials covered with RC were also tested on biological properties.

Methods

Viscosity measurements were carried out in DMAc+5%LiCl at 25°C using an Ubbelohde viscometer. Concentrations of α-chitin used for intrinsic viscosity value determination were in the range of 0.03 to 0.009g/100 ml, for β-chitin they were in the range of 0.015 to 0.005 g/100 ml.

Viscosity measurements of DBC were carried out in DMAc at 25°C using an Ubbelohde viscometer. Concentrations of DBC used for intrinsic viscosity value determination were in the range of 0.5 to 0.15 g/100 ml.

Particle sizes and distribution were measured with optical microscopy (Olympus microscope BX 51) combined with an image analyses system.

Moisture content and regain was determined through conditioning and weighing of the samples.

IR (infra red) spectroscopic measurements of chitin in KBr (1/100) pellets were carried out on a Perkin Elmer Spectrum GX (FT-IR System). Measurements on films of chitin cast from their solutions in DMAc+5%LiCl (ca 0.1%, g/v) and DBC films cast from acetone solutions were done with Perkin Elmer FTIR 2000.

TGA (thermo-gravimetric analyses) were carried out with a TGA 1000 from Stanton Redcroft (PL Therma Sciences). A 3-3.5 mg sample was heated in the range 10°C - 800°C at 10°C/min under air and nitrogen atmosphere.

Wound healing was evaluated with polypropylene non-wovens coated with dibutyrylchitin and regenerated chitin on skin wounds of albino rats. Dressings were changed every 24 hours.

RESULTS AND DISCUSSION

Viscosity measurements

The viscosity results are given in following table 1.

1. Viscosity measurements of chitin and DBC

	[η] (dl/g)	g/mol
	Method 2	
α-chitin	26.0	613000*
β-chitin	46.5	1187000*
DBC from α-chitin	2.50	172550**
DBC from β-chitin	1.22	74640**

* Molecular weight values calculated using parameters K and a from reference[9].

** Molecular weight values measured using size exclusion chromatography (SEC) method

Optical Microscopy

Using optical microscopy in combination with an image analysis system, the particle size distribution of both samples was determined. Following conditions were investigated: dry – unconditioned – conditioned (@ 20±1°C and 65±2% RH) – wet (in water) – wet+DMF (water removed by DMF).

Sufficient particles were measured in order to obtain a stable average value. The measured parameters were: particle area and –perimeter. Other derived parameters were: particle equivalent diameter, -volume of equivalent sphere, -length, -width, and -circularity. And following statistical parameters were determined: mode, (number and volume) average, and (25%, 50%, 75%) percentile values (50% percentile equals the median). Since (falsely detected) small particles dominated, the (50% and 75%) percentile values were considered to be the most meaningful with regard to swelling assessment.

Moreover, the particle area is considered one of the most relevant parameters. Results are given in table 2.

2. Particle size distribution of α-chitin and β-chitin

Area (in µm²)	α-chitin		β-chitin	
	median	75% percentile	median	75% percentile
Dry	203	3812	12551	39922
Unconditioned	797	4744	10231	62651
Conditioned	710	4543	14661	62299
Wet	472	4122	23099	85486
Wet+DMF	2329	7960	22782	90285

It can be seen that β-chitin contains much bigger particles than α–chitin. In fact, using the measured particle width distribution, one could conclude that the former virtually did not contain particles wider than 500µm, while the latter virtually did not contain particles wider than 250 µm. Regarding the swelling, α–chitin is clearly less swellable than β-chitin, the latter being already swollen by water (this swelling is maintained after water removal by rinsing with DMF and visible as a gel) and the former needing DMF in order to swell to some degree.
These findings are in agreement with the information found in literature.
α-chitin (mainly found in crabs, lobsters and shrimps) has an orthorhombic structure and antiparallel orientation of the polymer chains, resulting in a very dense structure. β-chitin has a monoclinic structure and parallel orientation of the polymer chains, resulting in the ability to accept small molecules as intercalcates within its structure to yield a series of crystallosolvates. So, a higher degree of swelling (and solubility) may be expected for β-chitin.

Moisture content and regain

Before determining the moisture content, the required samples (3 per type) first had to be conditioned (until constant mass was achieved) in a standard atmosphere (@ 20±1°C and 65±2% RH). The actual drying was performed at 105°C (during 16h). By comparing the masses before and after drying, following values (see table 3) could be obtained.

3. Moisture content of chitin

		Moisture content (%)*	Max. resorbable moisture (%) for dry chitin
α-chitin	**Average**	**9,57**	**10,58**
	stand. dev.	*0,08*	*0,09*
	C. V. (%)	0,8	0,9
β-chitin	**Average**	**15,60**	**18,48**
	stand. dev.	*0,04*	*0,06*
	C. V. (%)	0,3	0,3

*related to conditioned chitin

These findings are in agreement with consulted literature that suggests that the moisture resorption of β-chitin is about 1.8 times higher than for α-chitin.[10,11] This difference in moisture (re)-uptake can be explained by the earlier mentioned difference in structure between α-chitin and β-chitin. Whether or not the followed method removed all the water is not certain but TGA study may shed more light on these findings.

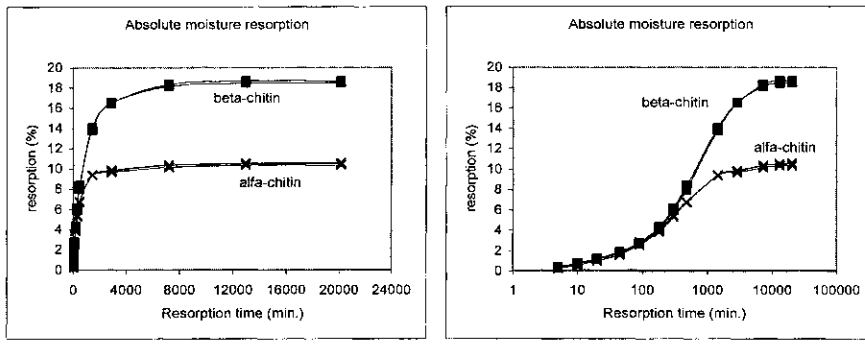


Fig1. Moisture resorption of chitin.

Following the drying, the samples were put back into the conditioned atmosphere and the moisture (mass) regain was periodically measured. These results are shown in (Figure 1).

Both chitin types virtually returned to their original moisture content, although α-chitin might not do so completely. The moisture resorption speed during the first two hours is similar for both chitin types. After that, the speed seems to be determined by the maximum possible resorption.

α-chitin seems to reach its maximum resorption somewhat later than β-chitin. This could possibly be due to its smaller particle size, resulting in a more densely packed sample (reduced diffusion).

Infra red spectroscopy

FT-IR spectra on chitin in KBr pellets and in films are presented in Figure 2a-2b. In the spectra of the pellets a more detailed structure in the O-H, N-H and C=O stretching regions (3000-3500 cm^{-1}) was observed for α-chitin, compared to β-chitin (where a broader band dominates). The latter is in accordance with literature and thought to be caused by increased hydrogen bridge formation. The spectra of the films contain no such difference in this region, probably because of recrystallisation to the most stable crystal structure during film forming.

The degree of acetylation is being investigated with different methods and these results will be published at a later stage.

FT-IR spectra of DBC samples (obtained from α-chitin and β-chitin) in form of films are presented in Figure 2b. In both spectra there is no band of absorption at 3500 cm^{-1} due to hydroxyl groups present in chitin and there are new bands of strong absorption at 1740 and around 1450 cm^{-1} characteristic for the ester of fatty acid. No difference in chemical structure of DBC samples is seen.

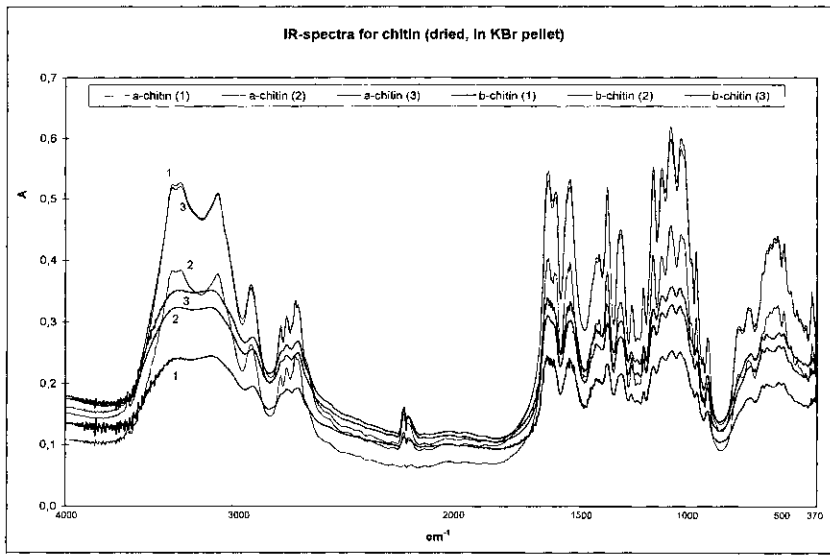


Fig 2a

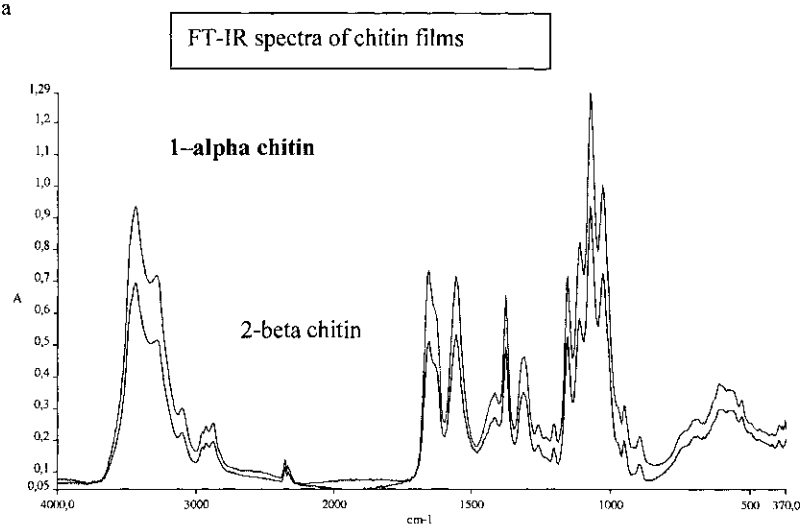
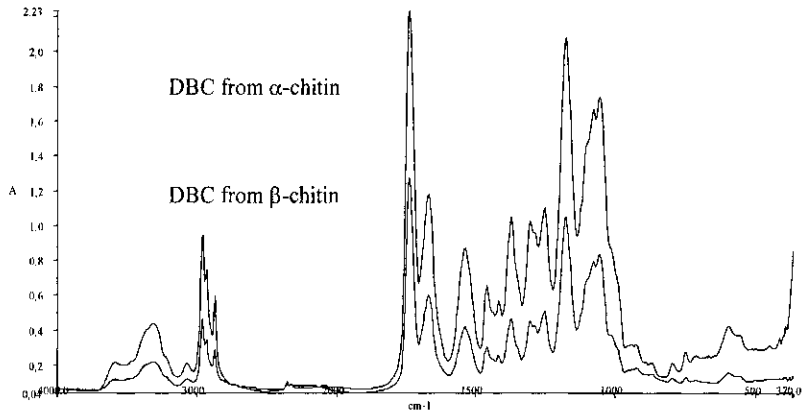


Fig 2b. FT-IR Spectra of chitin in KBr pellets and in films



Thermo-gravimetric analyses

A TGA curve of α-chitin under nitrogen atmosphere is given in Figure 3. Further research is in progress.

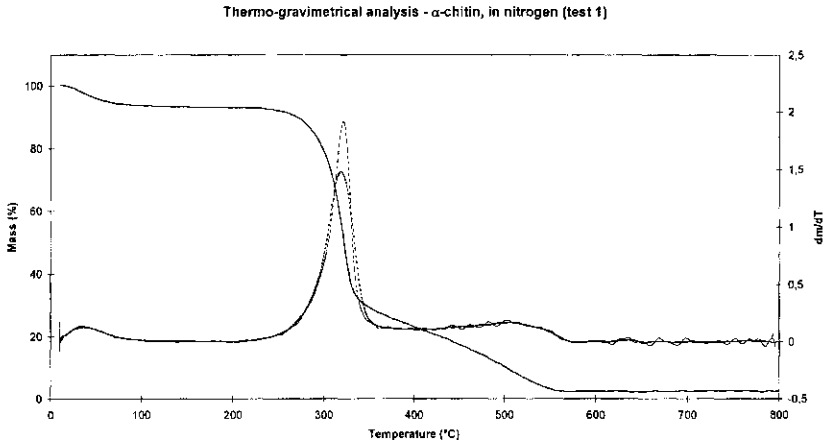


Fig 3. TGA curve of α-chitin under nitrogen atmosphere

Wound healing tests

The evaluation of the influence of the polypropylene non-woven materials coated with DBC and regenerated chitin on the healing process of skin wounds was conducted on 16 albino rabbits of New Zealand breed of nearly body mass equal of 3,2-3,5 kg. Before these tests cytotoxicity and immunology was evaluated, results are published elsewhere.[12]

The surgery was carried out under the general anaesthesia and in fully aseptic conditions. Four oval wounds (ca 12 mm in diameter) across the entire skin thickness were incised with the scalpel on the back of each rabbit. The wounds to the left of the backbone were covered with aseptic swaps as the controls. On the right side, the anterior wound was covered with the polypropylene non-woven material coated with

regenerated chitin, while the posterior wound was covered with the polypropylene non-woven material coated with DBC. Additionally all dressings were protected by gauze band. The wound healing was observed and the dressings were changed every 24h until the wounds were covered with scabs. Later on, the wounds with scabs were protected only by gauze band.

During the macroscopic observations no significant differences were noted in the healing of full thickness skin lesions covered with dressings containing either DBC or regenerated chitin. The wound edges were flat and the neighbouring skin was without any signs of inflammation. All the full thickness skin lesions dressed with the tested materials were filled with the white-yellowish, elastic tissue and all appeared to be more contracted, more wet and more elastic as compared to the control wounds covered only by gauze. The edges of control wounds were thickened and with the significant area of redness, while the skin was congested. By the sixth day after the surgery massive scabs covered the skin lesions. The photographs of the wounds taken in 14^{th} day after the surgery are shown in Figure 4.

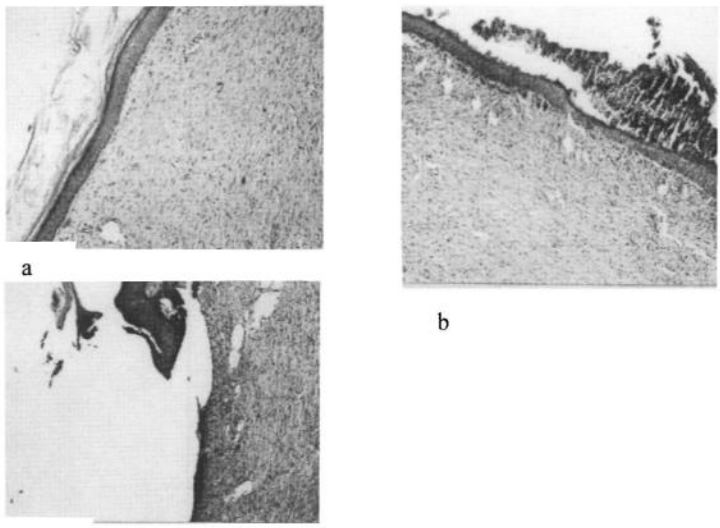


Fig 4. Microscopic view of the skin lesion after removing of (a) dressing material coated with DBC film (b) dressing material coated with RC film (c) the control gauze in the 14-th day after the surgery. Dyed with haematoxyline and eosine (HE). Magnification (OM): 120x.

The microscopic assessment showed that the healing of wounds covered with the dressing containing DBC was the fastest. By the tenth day a new, granulated tissue was observed in the site of lesion, epithelium almost totally covered by the squamous epithelium. On the fourteenth day most of the wounds were filled with the immature connective tissue with numerous blood vessels and collagenous fibres, and the connective scars were all completely covered with the epidermis. The healing of wounds covered with the dressing containing regenerated chitin was quite similar, except that the connective tissue that filled in the wound remained longer in the granulated phase. In the samples from the wounds dressed with the gauze only (control) the exudative phase was significantly longer, the formation of granulated tissue lasted until the fourteenth day and this tissue was covered only patchwise by the epidermis,

which migrated from the wound edges. Formation of the connective tissue scars with a fibrous texture and their complete covering by squamous epithelium in the case of the control wound occurred only after 21 days after the surgery.

CONCLUSION

α-chitin and β-chitin were tested on their physicochemical characteristics. A modification towards dibutyrylchitin (DBC) was made and preliminary results are presented in this paper. Biological evaluation of Polypropylene non-woven coated with chitin and DBC show that chitin has a beneficial influence on the wound healing. Further research on the material and the wound healing process is on going.

ACKNOWLEDGEMENT

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METRONIDAZOLE LOADED MICROSPHERES AND MEMBRANES OF DIBUTYRYLCHITIN: PREPARATION AND DRUG RELEASE INVESTIGATION.

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ABSTRACT

Dibutyrylchitin (DBC) – ester derivative of chitin, soluble in organic solvents has similar biological properties to chitin. DBC used as dressing material does not demonstrate cytotoxity effects or primary irritation and accelerates wound-healing process.

Metronidazole (MNZ) is used widely as an active antiprotozoal, antiamebic and antibacterial drug. New pharmaceutical formulations of this drug were made using ethanol solutions of DBC. Membranes and microspheres of DBC loaded with MNZ were prepared and kinetic of MNZ release into water (pH=5.5) was investigated at 37^0C and results described.

Chitin membranes and microspheres loaded with MNZ were obtained in the process of restoration of chitin in corresponding materials prepared from DBC. The process was carried out under heterogeneous conditions. Kinetics of MNZ release from regenerated chitin membranes and microspheres was investigated and compared with the results obtained for DBC MNZ-loaded materials.

INTRODUCTION

Chitin is known as a widespread natural polysaccharide [1]. It has very slight solubility restricts any practical applications. A few years ago at Technical University of Lodz the chemical modification of chitin was worked out. An introduction of bulky butyric groups into chitin chain was found to be a successful method for improving the solubility behaviour [2]. The method of the synthesis of the new ester derivative of chitin named dibutyrylchitin (DBC) with degree of substitution ca 2 was patented [3]. Thanks to easy solubility of DBC in common organic solvents a wide variety of products can be obtained: microspheres, strong transparent films and fibres [4]. All of DBC products can be converted into chitin materials by simple reaction of alkaline hydrolysis, carried out under heterogeneous conditions without destroying their structure. Degradation and digestion of chitin *in vivo* and it's derivatives by lysozyme is known and has been reported in literature [5]. Biological properties of the fibres and films made from DBC and regenerated chitin (RC) were achieved at Medical University of Wroclaw. The results of biological investigations *in vitro* and *in vivo* and all assessment procedure have shown that both chitin and DBC materials fulfil the basic requirements set up for medical devices by EN ISO 10993 "Biological evaluation of medical devices" [6-8]. Biological properties of DBC make this polymer a valuable chitin derivative for medical applications [9]. Technical University of Lodz is the designer and one of the main participant of the project "Biomedical textiles from

dibutyrylchitin and chitin", CHITOMED. In this context, DBC seems to be an attractive candidate for using it as a carrier of a variety of drugs for their controlled release application. Metronidazole is one of the best drugs for protecting patients from anaerobically infected burned wounds. It was found metronidazole administered orally, promoted healing in partial thickness burn wounds. The antioxidant effect of the drug might protect patients from some aspects of burn induced oxidative stress [10]. Metronidazole (MTZ), 5-nitroimidazole derivative is widely used as an active antiprotozoal, antiamebic and antibacterial compound, which is placed in the essential position on the drug list of the World Health Organization. MTZ, as antibacterial and antiprotozoal drug, has played an important role in clinical practice for over 35 years. At the present time MTZ is one of the most commonly used drugs in the world. It is one of the 10 most used drugs during pregnancy and MTZ is among the top 100 most prescribed drugs in USA [11]. The review of characteristic and clinical application of MTZ has been published [12].

The intention of this study was to investigate the possibility of using the dibutyrylchitin as a carrier of MTZ in slow-release dosage form such as microspheres or films, which could be adopted as a raw materials for construction of novel wound dressing materials. Such applications of MTZ might diminish the hard side effects, caused by MTZ during it's oral administration.

EXPERIMENTAL

Materials

Dibutyrylchitin (DBC) was prepared from krill chitin, Poland, with viscosity average molecular weight value $\overline{Mv}$ = 264,3.10^3 daltons and degree of acetylation 0,97 according to the method described in [4]. The molar ratio of the reagents used for DBC preparation was as follows: chitin : butyric anhydride : perchloric acid = 1 : 4 : 1. The final product of reaction, DBC, was characterized with intrinsic viscosity value [η] = 1,5dL/g, determined for the polymer solutions in dimethylacetamide (DMAc) at 25^{0}C.

Silicone oil Rotitherm ® H 250 (ROTH), DMAc, sodium oleate, methanol, n-heptan of laboratory grade were used without additional purification. Metronidazole (MTZ, 1-[2-hydroxyethyl]-2-methyl-5-nitroimidazole) with purity > 98% (HPLC) was produced by Fluka Chemie AG.

Samples preparation

DBC microspheres were prepared using a solvent-evaporation process [13]. For this purpose 10g of DBC were dissolved in 100ml of methanol. Obtained solution was divided into 2 parts of 50ml each. Metronidazole in amounts of 0,2g was dissolved in 2ml of methanol and was then added to 50ml of DBC solution. Common methanolic solution was well mixed and slowly dropped while stirring (ca 1500 rev/min.) to 200 ml of silicone oil containing ca 0,1g of sodium oleate. Formed emulsion was stirred for a further 1 hour. Then methanol was slowly evaporated under reduced pressure. Dry DBC microspheres containing MTZ dispersed in oil were obtained. They were washed 3 times with n-heptane and recovered on glass filter. Air-dried DBC microspheres with diameter size from 10 to 200 μm containing metronidazole were obtained. (SAMPLE 1)

The same procedure was applied to second part of DBC solution in methanol (ca 5g in 50 ml) without metronidazole. DBC microspheres of similar diameter sizes were obtained (SAMPLE 2)

2,0g DBC microspheres without drug (SAMPLE 2) were equilibrated in 10ml of water solution containing 0,1g MTZ. After two days water was subsequently evaporated and dry DBC microspheres containing the drug were obtained (SAMPLE 3).

Films of DBC containing metronidazole were cast from 5% DBC solution in methanol, containing 0,2% of MTZ (w/v).. Films with diameter size of ca 45 mm and thickness of a 40μm were obtained (SAMPLE 4)

Similar films of DBC, without MTZ, were cast from 5% (w/v) methanolic solution of DBC (SAMPLE 5)

Drug release investigation

Metronidazole release from the SAMPLE 1,3 and 4 was performed in constant temperature of 37^{0}C during sufficient stirring. Concentration of metronidazole was measured from the absorbance at 319 nm, using a Perkin Elmer UV/VIS Lambda 2 spectrometer. Samples with drug and without drug were held in release medium (water, 100ml). Small portion of water solution over samples were taken off in defined time and returned to release medium immediately after spectrophotometrical detection of UV MTZ absorbance. Water solutions without drug were used as references ones. Each experiment was carried out in triple.

RESULTS AND DISCUSSION

Relationships between M_t/M_∞ (fractional release drug amount) and release time *t* calculated for SAMPLE 1 (DBC microspheres with drug loaded during microspheres formulation) and SAMPLE 3 (DBC microspheres with drug loaded from MTZ solution in water) are presented in Fig.1 and Fig.2.
The same relationship calculated for SAMPLE 4 (DBC films with MTZ) is presented in Fig.3.

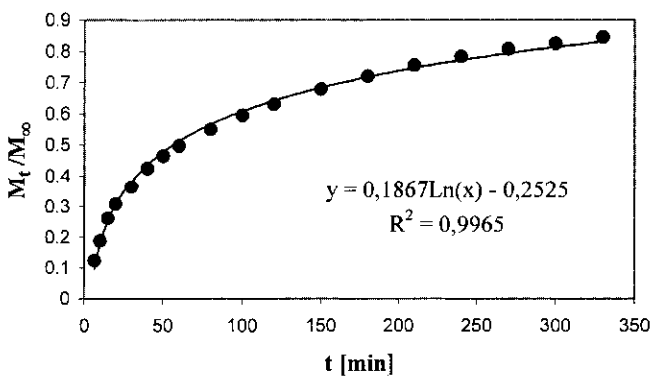

Fig 1. Drug release from DBC microspheres loaded with MTZ during microspheres formulation process (SAMPLE 1); half-release time of the drug quantity t ½ = ~ 60 min.

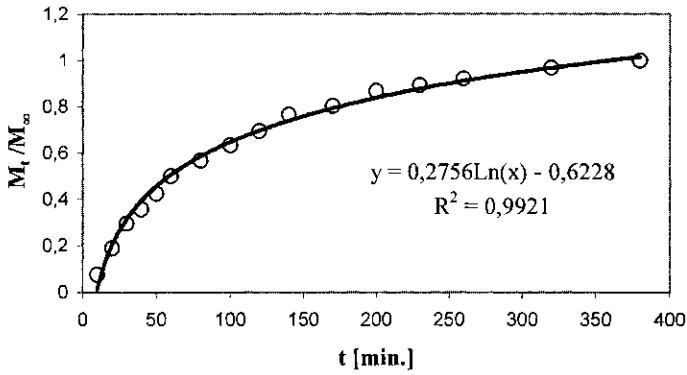

Fig.2. Drug release from previously formulated DBC microspheres loaded with MTZ from water solution of MTZ (SAMPLE 3); half-release time of the drug quantity $t_{1/2} = \sim 60$ min

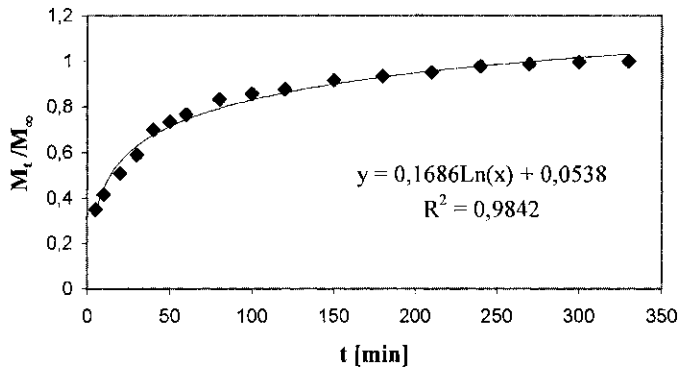

Fig.3. Drug release from DBC thin films loaded with MTZ during film formulation (SAMPLE 4); half-release time of the drug quantity $t_{1/2} = \sim 15$ min

Kinetic of MTZ release in every case is described with the best approximation by logarithmic equation:

$$M_t / M_\infty = k \cdot \ln(t) + b$$

where: M_t / M_∞ - fractional release drug amount,
t - time release,
k and b - constants for measured system

Approximation by logarithmic equation is independent from the form of carrier (microspheres or thin film) or the method of drug loading (during carrier formulation or loading to the pores of previously formulated microspheres). In every case MTZ is monomoleculary dispersed in the investigated sample: in SAMPLE 1 and 4 due to sample preparation from the DBC solutions containing dissolved MTZ, in SAMPLE 3 due to penetration of the small MTZ molecules into micropores of microspheres formed while solvent (methanol) evaporated during DBC microspheres manufacturing process.

Complete MTZ release into water was finished after ca 7 hours from each sample of DBC carrier, but the rate of drug release was different. From the microspheres loaded with MTZ (SAMPLES 1 and 3) half of the loaded amount drug released in ca 1 hour, while from thin film of the thickness ca 40 μm - during first 15 minutes. The release mechanism of MTZ, which is well soluble in water from initially dry polymer carrier, which is non-bonded with the drug by chemical units, is pure diffusion. DBC carrier do not absorb significant amount of water (drug release medium) and release process of enclosed MTZ is controlled by pure diffusion mechanism involving a thin diffusion layer near the polymer surface. Diffusion process in one dimension is described by Fick's second law of diffusion:

$$\partial C/\partial t = \partial^2 (DC)/ \partial x^2$$

where: x – the space coordinate
C – concentration of diffusing material within membrane
t – time
D – diffusion coefficient

Kinetics of drug release from different systems for many geometrical forms were investigated and described in many publications and several equations were proposed with different applicability [14,15]. They are different for specimens of different forms: spheres, discs, slabs or flat sheets. Generally it was stated that fractional drug release depends on the amount of loaded drug and thickness of specimens [16]

In our experiments amounts of loaded drug were compatible ones but the specimen thickness was different: microspheres had diameter sizes from 10 to 200 μm and thickness of the films were about 40μm, this results in quicker release of MTZ from SAMPLE 4 on the first stage of the process.

CONCLUSIONS

The first experiments of adding to the biological active carriers DBC, which accelerates wound healing, antibacterial, antiamebic and antiprotozoal properties due to introduction of metronidazole (MTZ) showed as follows:

1. MTZ can be loaded into DBC carrier in form of microspheres after two days of equilibrium with water solution of MTZ.
   The rate of drug release from samples such prepared is similar to the drug release from DBC microspheres loaded with MTZ during their formulation.
2. Time of complete drug release from DBC microspheres with MTZ is ca 7 hours.
3. Thin films of DBC cast from the polymer solutions containing MTZ are very effective during initial stage of drug release: half of loaded drug is released during 15 min. of the process.

Further formulation of systems containing DBC with drug, and investigations of their properties and using both as active dressings and drug delivery systems have been carried out.

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EPISTAXIS DEVICE AND NASAL SURGICAL DRESSINGS

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ABSTRACT

The Rapid Rhino® range of products utilise a special knitted fabric which promotes good healing in nose bleeding (epistaxis) and in post surgical dressings.
The fabric is composed of carboxy-methylated-cellulose reinforced by nylon.
The fabric is wetted before use and the CMC turns into a gell but is stabilised by the reinforcing nylon. The gell is a powerful haemostat and also promotes fast healing.
The epistaxis device consists of the CMC fabric over an inflatable PVC balloon and the nasal dressings have a CMC fabric bag over a special sponge. The dressings are also capable of acting as a drug delivery system.

DEFINING THE PROBLEM

Epistaxis

Epistaxis is the medical name for bleeding from the nose, or nasal haemorrhage. In most cases the bleeding may be stopped quite easily by simple, well known methods such as ice on the bridge of the nose or pressure to the top lip and base of the nose. The bleeding usually stops within 5 minutes and does not recur

The problem can, however, be considerably more serious and any large hospital Emergency Room may have 3 or 4 cases present each night. These more serious cases may be caused by trauma or by a more complex medical problem. They require the intervention of a physician to stop the bleeding. Some very severe cases can be life threatening.

Ninety percent of cases are bleeding in the anterior or frontal chamber of the nose. Far more serious is bleeding in the posterior or rear chamber of the nasal cavity or sinus. These latter cases sometimes go un-noticed since the blood will flow internally and not out through the nasal nares or nostril. Treatment is required for all these cases either by the use of a medical device or by surgery.

Currently available devices consist mainly of PVA sponges which can be compressed into a flat profile by drying. The device is entered into the nose and then wetted by a saline solution. The insertion of the device is a painful procedure. After wetting the sponge softens and expands to fill the nasal cavity. There is no active haemostatic ingredient and the device works by simply blocking up the space. The sponge is inefficient and takes a long time (days) to achieve haemostasis. Removal of the device is very difficult since the blood dries and hardens into the cells in the sponge. The patient suffers great pain and removal frequently displaces the newly formed clot of blood and bleeding will resume.

Nasal Surgical Dressings

In addition to Epistaxis there is a need to improve traditional methods and material for the control of bleeding and general wound care after nasal surgery. Current procedures are

somewhat crude and can cause considerable discomfort to the patient, especially the trauma caused by removal of the dressing after the blood has dried and solidified into the structure. Packing the nose with a long length of bandage-like material is time consuming for the ENT surgeon who performs the procedure and very stressful for the nurse who can take up to an hour to remove the dressing. During all the removal time the patient can be in considerable pain. An experienced nurse once commented that she would rather deal with knife or bullet wounds than Epistaxis.

Most of the modern procedures for surgery in the nasal and sinus cavities are now performed by minimally invasive technology. That is, there is no major incision to reach the surgical site. Access is gained via the nostril by endoscopic means. Any surgical dressing must, therefore, be small enough to pass through the nares.

REQUIREMENTS OF THE DEVICE

Haemostasis

The primary function of a haemostatic device is to achieve haemostasis which is the term for the cessation or absence of bleeding.

Bleeding stops when the platelets in the blood clump together to form a clot. This process is known as platelet aggregation and the most visible form is the formation of a scab. Blood has a natural tendency to form a clot whenever something disturbs the normal state. Foreign bodies and contact with air can accelerate this process. In a small wound the flow of the blood is slow and the scab will form without any extra stimulus.

In the case of Epistaxis the blood flow will be directly from a ruptured artery and the pressure and flow are too great to heal naturally. Pressure on the top lip and the base of the nose, will sometimes slow the rate of flow and allow the natural platelet aggregation to occur. In order to stop the more severe cases however, more drastic methods are required.

The first action to be taken is to apply pressure either directly to the wound or to the artery upstream from the wound. This procedure is known as tamponade. The procedure can be quite difficult when the wound is in the nose. The source of the bleeding is hard to find and prolonged tamponade usually impossible without a special device.

Early and current methods of achieving haemostasis

Various methods have been utilised by physicians and these range from the simple packing of the inside of the nose with gauze or bandage material, to the use of chemical agents to cauterise the wound. One such agent is the application of silver nitrate. An electric cautery may also be used if the bleeding point can be found.

A common device is a flat strip of hard dried PVA sponge. When forced inside the nose and wetted with saline solution the sponge softens and expands to soak up the blood. This device is very painful to insert and even more so to remove after the blood has dried into the sponge. Removal frequently also removes the scab and so the bleeding restarts.

Another available treatment is to use a long thin balloon which may be inserted into the nose and inflated. The pressure is distributed evenly over the mucosal inner surface of the nose which produces tamponade to stop the bleeding. Such crude devices are marketed but are of limited use since there is no agent to promote good healing. The available balloons are made of silicon rubber and hence are elastic. Since silicone is porous to air and gases it

has to be inflated with water or saline solution which can give very high hydraulic pressures and can damage the sensitive mucosal tissues inside the nose. Also, since the initial inflation pressure of the silicone balloon is high, there is no way for the surgeon to obtain a tactile feeling of the pressure inside the nose. In short, these types of balloons are at best barely effective and at worst potentially dangerous to the patient.

Modern device requirements

A satisfactory device should be simple to insert, be capable of holding in position, have the ability to produce homeostasis in minutes and be simple and pain free to remove. It should remain wet so that it does not stick to the wound and should promote healing in such a way that re-bleeding does not occur.

It should also be available in different lengths so that both anterior and posterior nasal chambers can be treated.

Properties Required for an Epistaxis Device

Any successful device must have two elements. The first is a therapeutic agent to be in contact with the inner wall of the nasal cavity. The second is a mechanical means to provide tamponade and to anchor the therapeutic material in place. The second element must also provide a quick and simple method of deployment.

Properties Required for a Perfect Therapeutic Agent

Any therapeutic agent must have, as a minimum, the following properties:

1. Soft and flexible
2. Elastic
3. Absorbent
4. Haemostatic
5. Remains moist to promote fast healing.
6. Is Bio-Compatible

The Winning Combination

Research has shown that the most suitable combination is a knitted construction, using as a material Sodium Carboxymethylcellulose.

THE ANSWER. - THE RAPID RHINO®

The Rapid Rhino® device consists of a long thin balloon covered in a soft specially developed knitted material known as Gel Knit®. The balloon is inflated with air to provide soft tamponade and the Gel Knit® provides all the requirements to produce rapid homeostasis and good long term healing, with the minimum of trauma to the patient. The haemostatic and healing agent is provided by the revolutionary "Gel Knit®" fabric which is described in detail later in this paper.

The Gel Knit® fabric turns into a Gel when the fabric is wetted and this Gel is soft and lubricious as well as being haemostatic. The knitted fabric stretches as the balloon is inflated and so presses the healing Gel gently against the inside wall of the nasal chamber. Because the Gel is soft and slippery and the balloon profile is small, the device is easy to deploy. Likewise, as the Gel does not dry out and remains slippery, the device is easy to remove after the balloon is deflated.

The Balloon

The balloon is made from very thin PVC film which is fabricated by RF welding techniques. It has a thin, fairly stiff tube in the centre which serves as a stiffener and also is the inflation means. The thin film balloon is rolled around the central tube to provide a very thin profile but is stiff enough to allow it to be pushed into the nose.

The thin film is relatively non elastic and the assembly is not so much a balloon but more of a fixed volume PVC bag. The reason for this is so that, when the device is being inflated, the physician will sense the actual pressure that is being applied to the inside of the nose and not the elastic force required to stretch the balloon wall.

The main balloon is connected by a thin inflation tube to a second, much smaller balloon known as the pilot cuff. The pilot cuff, which remains outside the nose, provides the doctor with a tactile indication of the actual pressure that is inside the nose. This is, therefore, a safety device which is used to ensure that the pressure inside the nose is not too high. A very high pressure could seriously damage the delicate mucosal lining of the nasal chamber.

The last component of the balloon assembly is a small valve which has an opening that fits on to a standard disposable syringe. When the syringe is attached, the tip of the syringe holds the valve open. When the syringe is removed the valve acts as a normal non return valve. Thus, the syringe may be used both to inflate and deflate the balloon.

Gel Knit® Fabric

Gel Knit® fabric is a small diameter weft knitted tube. This is knitted on a small diameter circular knitting machine with the provision for the positive feeding of two separate yarns. Positive feeding is used to ensure the good quality assurance required for a medical product.

The main yarn that is knitted is a staple (spun) yarn of cellulose. This may be any normal cellulosic textile material such as cotton or a number of different reconstituted cellulose materials such as lyocel or viscose. As will be described later in this paper, the cellulose is the precursor material since it will be chemically converted after knitting into the Gel forming material.

The second yarn is a very thin continuous filament nylon which acts as reinforcement and holds the fabric together after the Gel has been formed and the Gel forming yarn has lost all form and stability. The total nylon content of the fabric is about 10%.

SODIUM CARBOXYMETHYLCELLULOSE (CMC)

Carboxymethylcellulose is a long chain polymer polysaccharide related to natural cellulose.

It is a hydrocolloid material and will form a Gel or dissolve when wet. In solution the material is highly absorbent and will absorb up to 20 times its weight of water. A saturated solution is extremely viscous and acts in a similar manner to a true gel. According to the manufacture, CMC can be made semi-soluble which forms a non soluble gel with water or a soluble form which will form a viscous solution with water.

The structure of the cellulose molecule is visualised as a polymer chain composed of repeating cello-biose units. These, in turn, are composed of two anhydroglucose units.
Each anhydroglucose unit contains three hydroxyl groups. By substituting caboxymethyl groups some of the hydrogens of these hydroxyls, sodium carboxymethylcellulose is formed.

The average number of hydroxyl groups substituted per anhydroglucose unit is known as the "degree of substitution" or DS. If all three hydroxyls are replaced then the theoretical DS of 3.0 is reached. Such a high degree of substitution is, however, impossible in practice.

The DS of Gel Knit® is chosen and controlled very carefully to obtain the optimum properties of solubility and therapeutic efficacy required for this particular product.

Conversion of the cellulosic fabric to CMC

The process of converting the cellulosic part of the precursor fabric is very complex and has to be controlled very carefully. The principal of the process is however more simple.

The fabric is treated in a vessel in three operations. The first two operations may be carried out sequentially or together in the same vessel.

In the first stage the fabric is treated with sodium hydroxide NaOH (caustic soda). This has the effect of loosening the bonds of the hydrogens in the hydroxyl groups of the cellulose molecule.

The next stage is treatment with chloroacetic acid $ClCH_2CO_2H$. This substitutes the released hydrogen for carboxymethyl groups. A sodium is also added to form the sodium salt of CMC.

The slight excess of sodium hydroxide is neutralized by the addition of acetic acid, the pH carefully adjusted and the material is dried. The pH of the dried material is critical since it affects the solubility in water. Below a pH of 6.0 the dried product has poor solubility and below 4.0 the product is insoluble in water.

RAPID RHINO® IN USE

The device is available in three lengths. A medium length for anterior bleeding, a short length for paediatric or small nasal chambers and a long one for the posterior chamber. The long may also be used in cases when the position of the bleeding cannot be determined positively.

In addition, the device is available with and without a central lumen or bore. The central lumen forms an airway so that the patient can continue to breathe through that nostril while the device is inserted. The disadvantage of the lumen version is that the device has a much larger diameter and so is more difficult to insert and more uncomfortable for the patient.

A special bifurcated version has two devices connected to the same pilot cuff and inflation system. This is used after surgical work on the nasal septum. The septum is the stiff central separator between the two nasal chambers. After surgical work on the septum it

is important that the packing is equal on both sides to prevent deformity causing a distorted nose. The bifurcated device ensures equal pressure on either side of the septum.

Using the Rapid Rhino®

When the patient presents to the emergency room with a bleeding nose the treatment is quick and simple. The patient is seated and the nose cleaned as well as is possible.

The device is removed from the sterile packing and immersed in sterile water for 30 seconds. This forms the Gel or viscous solution and makes the device soft and slippery.

The doctor then inserts the device into the nasal chamber. This process is very easy and causes no pain to the patient and very little discomfort.

The balloon is now inflated to fill the nasal chamber and gently press the CMC Gel against the mucosal wall. The inflation pressure may be constantly monitored by means of the pilot cuff. After inflation the pilot cuff and valve assembly is taped to the patient's cheek.

The patient is then sent home and asked to come back next day. On return the patient will normally now see an ENT specialist doctor for the device to be removed and the situation assessed.

Removal consists of simply deflating the balloon and carefully pulling out the device. Since the Gel does not dry out, and the whole nasal chamber remains moist, then there is no dried blood to impede the removal.

Removing the device does not disturb the new clot at the wound. The CMC acts a beneficial healing agent and re-bleeding is unlikely.

Healing properties of CMC

CMC has proved to be an active platelet aggregator and as such is a powerful haemostatic agent. In addition to the haemostatic properties the Gel provides a moist environment at the wound site which enhances natural healing after homeostasis is achieved.

Rapid Rhino® has proved to create homeostasis in a matter of minutes rather than days for earlier remedies.

POST SURGICAL DRESSINGS

Rapid Rhino® Epistaxis devices are used mainly in the emergency room of a hospital but Gel Knit® fabric lends itself to a range of dressings suitable for use after ENT surgery.

Most surgical procedures of the nose and sinus cavities are carried out by endoscopic means or the so called "minimally invasive technology". The procedure is known as Functional Endoscopic Sinus Surgery or "FESS". This procedure is used for various purposes including the removal of tumours or polyps and other disorders of the sinus cavities.

In some cases the purpose of the dressing is to keep different interior surfaces separate from each other. Much of the nasal interior is loose and flexible. For example the terbinates are sections of the nasal chamber which hang inside the actual cavity but may be in contact with other parts. This is especially true if there is swelling due either to disease or the trauma of the surgery. After surgery the various parts must be prevented from healing together.

Gel Knit® Surgical Dressings

Gel Knit® fabric has proved to be the ideal material for a post surgical nasal dressing. The primary property is that it is a reliable haemostat and controls bleeding, but it also creates the perfect moist environment for promoting fast and problem free healing. In addition the "always moist" property of the material makes it quick and easy to remove with the minimum of discomfort for the patient and no pain.

The dressing may be placed by forceps while viewing the site though an endoscope. Removal is achieved in a similar manner.

Dressing Construction

The first generation of dressings consist of a pouch of Gel Knit® filled with an elastic medium. The device is compressed by forceps during deployment and expands inside the cavity to fill the space and give light tamponade.

In most of the devices the elastic medium is a high quality, medically approved sponge. The sponge is shaped into various special configurations according to the particular use. The shapes are designed to conform to various nasal cavities.

The sponges are made of a material which resists bacteriological action and are covered in a thin watertight film. This film isolates the actual sponge from the blood to further reduce the risk of infection.

Drug Delivery

In all cases when using Gel Knit® devices, the fabric has to be soaked in water to create the Gel. The material has the capacity to absorb 15-20 time its own weight in water. This property makes the Gel Knit® dressings capable of being used as a timed release drug delivery system.

Any water soluble or dispersible therapeutic agent may be incorporated into the water used for soaking the Gel Knit®. This ensures that the therapeutic agent will remain part of the environment of the healing wounds.

Various therapeutic agents may be used including cortisone, anti-bacterial and anti-fungal compounds.

Intellectual property protection

All the devices and materials in the Rapid Rhino® range are subject to issued or pending patents.

CONDUCTING CLINICAL TRIALS IN WOUNDCARE

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ABSTRACT

Clinical trials in woundcare are conducted to assess the safety, efficacy and effectiveness of woundcare materials on patients. This paper will highlight the various designs of clinical trials, the pitfalls that commonly occur during the execution of trials, a critical literature review of previously conducted trials in woundcare, how trial design quality can be enhanced by incorporating patients' perspective and health related quality of life measures (HRQOL), and finally the paper proposes an innovative approach in conducting a clinical trial in woundcare.

INTRODUCTION

A clinical trial in woundcare is a planned experiment that involves patients and is designed to determine the safety and efficacy of a new or untested product. The main characteristics of clinical trials are that they use results based on a limited sample of patients to make inferences about how the treatment using the product should be conducted in a general population of patients who will require treatment in the near future. Human volunteers may be used only if practical and convincing laboratory and animal study have been undertaken. The objective of woundcare trials is to identify the magnitude of improvement of one product over another or to show its equivalency or show no significant difference exists between them.

PHASES OF CLINICAL TRIAL

Products pass through **four trial phases**[1] before becoming available on prescription:
l Phase I: testing on a small number of healthy volunteers (20–80) for the first time to evaluate product safety and to determine any adverse effects
l Phase II: performed on a large number of patients (100–300) to detect effectiveness and further assess safety
l Phase III: using a large number of patients (>1000) to confirm effectiveness. This is achieved by comparing with commonly used treatments or products. Information is collected on how or whether the treatment can be used safely.
Phase IV: conducted after the product has entered the market in order to study its long-term effect on various study populations.
Phase I and phase II trials are early evaluations which investigate the product's properties thoroughly in ideal conditions. Phase I can be omitted if sufficient data already exist.

VARIOUS DESIGNS OF TRIAL [2]

There are two types of parallel designs based on the type of groups used.

Parallel design – most common – has two groups- group 1: device group, group2: control group – patients are followed to determine the outcome – called ***Independent groups***.

In the other form of parallel design – patients act as his/her own control – baseline measurements taken – treatment or device applied – patient are followed – before and after measurements are taken – called ***paired groups***.

Designs of trial
1. Parallel design
2. Randomised control trial
3. Non randomised controlled trial
4. Historical control trial
5. Crossover trial
6. Withdrawal studies
7. Factorial design

Randomised controlled trial

Eligible participants are assigned to an intervention or control group using a randomisation procedure such as simple, blocked or stratified techniques. All subjects have an equal chance of entering either the intervention or the control group.

Randomisation prevents any assignment bias by the investigator or the subject and increases the chance that the characteristics of both groups will be evenly balanced. Any change observed can then be attributed to the intervention.

Non-randomised control concurrent studies

Here, participants are not assigned by randomisation technique but the treatment is allocated to the participants as they register for the trial; however both the intervention and control groups are treated simultaneously. For example, one group of patients is given a new product in a centre, while another group of patients with similar characteristics receive control or standard treatment concurrently at another centre.

In most cases the selection of subjects with similar characteristics is highly impractical as investigators often assume that selecting groups with few matching characteristics for age, sex, chronicity of the wound will enable the study to gain information about the predictive factors that will influence the outcome.

Historical control studies

These compare the outcomes of a group of patients given a new intervention with those of comparable subjects from an earlier study. It is used when the investigator believes the product has beneficial effects and helps to build up an initial impression about the product or treatment [3].

An advantage of this type of study is that patients are more likely to enrol in research studies when assured that they will receive a particular treatment. This increases patient compliance and helps to register patients for the trial quickly. Hence the study period is shorter and the results can be produced more rapidly.

In order to compare the present trial with a previous study there must be similarities in the study populations' characteristics, diagnoses and treatments and in the measurement, analysis and interpretation of the data. If not, the outcomes will be skewed.

Crossover design

Here, each patient acts as his or her own control. The new treatment is given to the patient once (first period) followed by a control treatment (second period). Another patient may receive the control treatment followed by the intervention. Allocation to the treatment or control group can be randomised, with approximately 50% of the patients receiving intervention-control order and 50% control-intervention order. Variations are kept to a minimum as the measured effect is only due to the patient's response to the control and intervention treatment.

For this design to be efficient, the disease must remain stable over a period of time. Therefore, patients who are given an intervention and are then cured cannot participate in the second period unless they revert to the initial disease state. In other words, the patient's condition should not be treated by the first intervention. This design is appropriate for trials where, for example, a drug's effect on lowering blood pressure is being studied. Even here, the effects of one drug should not carry over into the second period (carry-over effect). Hence, the period between the two schedules should be studied and the corresponding treatment given only when the subject returns to the original disease state [3, 4].

Withdrawal studies

These determine how long it takes for a patient to discontinue a treatment or for a change in frequency to occur in its administration. For example, how long a venous ulcer patient can withstand a certain amount of compression applied by a pressure bandage over a week? These trials can sometimes help to evaluate any intervention or material that has not shown any significant effects.

A serious limitation is that the investigators may select patients, who they believe will derive beneficial effects from the treatment, making the sample highly homogeneous. In such cases the study will underestimate any toxicity and exaggerate the benefits of the treatment.[3].

Factorial design

This is used to evaluate two or more experimental interventions separately (M alone or N alone) and in combination (M and N) and with the control (no M or no N). The study is designed to evaluate the ***interaction effects*** of the interventions.

Equal numbers of patients are 'block randomised' to each cell in the design. Therefore, 40 patients with a block of four allow 10 patients in each cell. In this case, 20 patients from cells (M and N) and from (M alone) can be assessed for the effect of intervention M. The design must have an appropriate sample size to be efficient and informative in order to study the interaction effects of the treatment. However, if there are no interaction effects between the interventions, then two experiments can be done in one design provided there is a moderate increase in sample size. Interaction is the effect of M depending upon the presence and absence of N and vice versa. It is likely to occur if the outcomes of both the interventions M and N are similar, for instance, reduction of wound odour.

PITFALLS OF CLINICAL TRIALS [2]

Selection of design

The selection of an appropriate trial design depends on the question the investigator is attempting to answer. For example, neither a simple comparative trial (say, of dressings A and B) nor a simple parallel trial will detect any interaction effect of the dressings. However, a four-cell factorial design would be able to do this. Alternatively, if a patient does not respond to dressing A, there is a chance that he or she might benefit from dressing B. If this is the case, a crossover design is ideal.

Similarly, it is impossible to randomise patients who are reluctant to rely on chance determining their treatment. In this case, a non-randomised trial will need to be used, although the characteristics of the treatment groups will not be balanced.

Inadequate explanation of the study population

The study population must be described as otherwise it is impossible to evaluate the outcomes or apply clinical research results into practice. The study should describe the inclusion and exclusion criteria clearly.

Selection bias

An investigator who has worked out the assignment process may then assign a patient to a particular group in order to achieve a chosen outcome — for example; assigning patients with less severe disease to the treatment group will increase the likelihood of a positive outcome.

Accidental bias

There is a good chance, particularly in small studies, of an imbalance in characteristics or risk factors occurring accidentally. Even a simple random allocation is not without its drawbacks [3]. Table 1 shows the imbalances that will occur with probabilities of at least 0.05 and at least 0.01 in various trial sizes. The smaller the trial (n=50) the more imbalances that might occur, especially if the ratio is 16:34 with a probability of at least 0.01. This would be difficult if, by chance, 16 patients are assigned a new treatment and 34 a standard treatment, especially if the investigator is studying the effects of a new treatment.

Table 1 Imbalance in simple randomisation in trials of two treatments[4]

Total number of patients	Difference in numbers	
	$P \geq 0.05$	$P \geq 0.01$
10	2:8	1:9
20	6:14	4:16
50	18:32	16:34
100	40:60	37:63
200	86:114	82:118
500	228:272	221:279
1000	469:531	459:541

Inadequate explanation of randomisation

For a study recommendation to be implemented with confidence, it is necessary to explain precisely how the randomisation was undertaken. Altman and Gorè [6] found that 30% of articles published as randomised trials did not provide any evidence that randomisation took place, 10% were called randomised trials but used non-random allocation methods and 60% did not report the method of randomisation employed.

Loss of blinding

In a double-blind study, patients may be randomly assigned to the study groups using a list with a pattern that follows a particular order. If the person administering the care becomes aware of this order, then double blinding is lost. Therefore, following a definite pattern of the order the carer will expect a better response from the patient if the outcomes are very low or very high then; he or she might recheck or modify the measurement [6]. Some physiological responses will be an indicator for the effectiveness of a patient's treatment and will also lose the masking of treatment identity, especially if a patient gives a better response to one intervention followed by another patient who has given a poor response, this will result in the carer anticipating the outcomes of the treatment.

Inadequate duration to study the outcome

In trials into the aetiology of the chronic wound-healing process it is necessary to allow sufficient time for the wound to progress through the various healing stages. A study conducted by Kantor and Margolis[7] measuring ulcer healing progress, claimed that venous ulcer healing was not a linear process, although the linearity of healing existed for the first 12 weeks but during subsequent weeks the trend of linearity fell rapidly. Hence the authors reported that at 20 weeks 63% of the wound would have healed with standard woundcare. These observations could not have been made in a shorter timeframe.

Inadequate sample size

A small trial inevitably has less power to detect the difference between treatment groups. A trial's power is defined as the probability of finding a difference if it exists. The smaller the sample variation, the higher the trial's power. If insufficient patients are enrolled into the study, there is the probability of making a type I error (rejecting a null hypothesis wrongly) or a type II error (not rejecting null hypothesis). The null hypothesis states there is no difference between the treatments.

Subconscious bias

Most woundcare trials are open trial (discussed in the recent review [8]) and are rarely single blind that is, either the patient is aware of the treatment product or the nurse knows the treatment material. Patients who are aware that they are taking part in the trial can either exaggerate or under-report the events — *the Hawthorne effect.*

Withdrawals

Patients may withdraw or drop out due to loss of confidence in the trial or adverse affects. Bias occurs if the data on these patients are neglected, as the result will favour the new treatment. In such cases, the data from the trial should be analysed using the intention-to-treat procedure — for example, withdrawals from the control group should be analysed along with the patients who took the control. However, this is not necessary in efficacy studies where the objective is to show the effect of intervention on patients who actually receive treatment [3].

LITERATURE SEARCH

A literature search[5] was carried out in online databases and journals to identify the trials evaluating woundcare products in chronic venous ulcers over the last 10 years. The literature was critically appraised to analyse the quality of clinical trials. Out of 20 studies 15 had been included because the rest simply reported the earlier work and were comparative studies and were not clinical trials. Hence the five studies were excluded because they did not meet the inclusion criteria.

Literature survey results

Design: 12 parallel trials; 1 cross over and 1 non-comparative trial.
Duration of study: Except for 4 trials all 11 trials were less than 12-week treatment duration
Sample size: Four trials had a sample size of more than 80 and 8 trials had n (sample size) less than 50 and 3 trials had sample size $n > 50 < 80$
Significance: Trials reporting significance were only in the secondary measures such as ease of removal of dressing, application and odour control. Trials reporting healing as the main outcome did not gain significance.
Randomised: 9 Trials were randomised out of 13 trials and 2 did not give details about randomisation
Blinding: except for 2 studies that were single blinded all the rest were open trials
Clear inclusion and exclusion criteria: 8 did not state the criteria; 5 stated clearly the criteria and 2 did not report any criterion for inclusion/ exclusion of patients.

Only two trials reported quality of life as an outcome variable. The literature findings clearly indicate that there is not enough evidence in favour of any dressings being evaluated, pointing out a need for well-designed trials that could gain statistical and clinical significance. The findings also show that this is due to a lack of appropriate design methods and inadequate sample sizes.

WHAT CAN BE DONE TO IMPROVE THE EFFICIENCY AND QUALITY OF WOUNDCARE CLINICAL TRIALS?

A wide range of issues may influence the conduct of clinical trials such as using appropriate trial design, adequate sample size, adequate follow up and precise end points but in this paper we focus on one main aspect of trials, namely measurement of events relating to patients' perspective, patient compliance and health related quality of life (HRQOL) through a questionnaire survey. Ten different quality of life

questionnaires (Table 2) were compared and contrasted in a recent systematic review [8] for their appropriateness to venous leg ulcer patients.

Table 2 Type of quality of life questionnaires [8]

GENERIC TOOL	DISEASE SPECIFIC TOOL
1. Nottingham health profile (NHP),	1. Cardiff wound impact schedule (CWIS)
2. Short form health survey (SF-36)	2. Hyland new ulcer specific tool
3. McGill pain questionnaire (SF-MPQ)	3. Charing cross venous leg ulcer questionnaire
4. Frenchay activities index (FAI)	4. Freiburger questionnaire (FLQA)
5. EuroQol (EQ)	5. Chronic venous insufficiency questionnaire (CIVIQ)

The review [8] unearthed the profound factors that influence patients suffering from chronic wounds such as venous leg ulcer. Out of the ten questionnaires the FLQA questionnaire was selected based on its comprehensive discussion of quality of life and therapy related questions. A pilot study [9] was undertaken to determine the feasibility of the selected questionnaire. The 89-item venous ulcer specific quality of life questionnaire (FLQA) was administered to a cohort of 16 venous ulcer patients who had been registered at an outpatient clinic for participating in a forthcoming clinical trial. The study design was a cross sectional survey where the patients were surveyed once. Twelve additional questions were added to the end of the English version of the questionnaire such that the added questions did not interrupt the flow of the validated questionnaire.

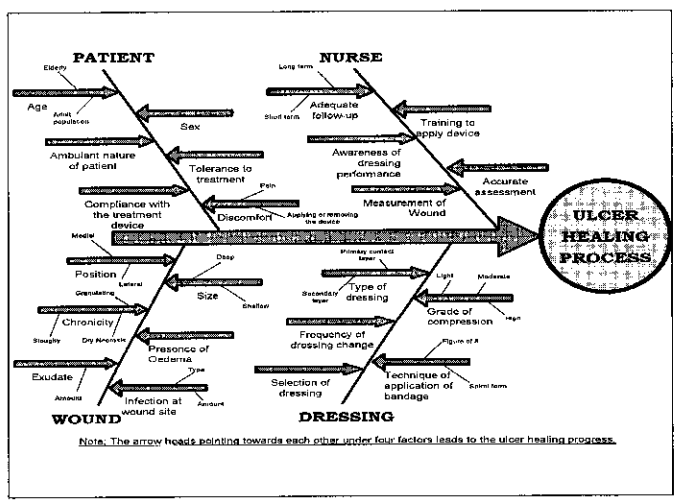

Figure 1 Contributory factors to venous leg ulcer healing

The questions related to the patients' opinion on compression therapy treatment, compliance with wearing bandages and their overall opinion of

compression bandages. The questions were added based on a comprehensive review [8] that identified the factors (Figure 1) contributing to venous ulcer healing. There was a 94.0% response rate with 72% of respondents reporting that the questionnaire was suitable to reflect their perspective on quality of life and compression therapy. The pilot study results are given in Table 3 and in Figure 2.

Tabel 3 Visual analogue scale scores [score 0-10]

	Mean	Mode	Median
Visual analogue score for pain $^{\alpha}$	5.2	7.0	5.8
Visual analogue score for general health*	6.0	8	6.3
Visual analogue score for venous illness*	5.6	6	5.7
Visual analogue score for condition of leg*	4.3	6	4.0

α - The higher the score the poorer the QOL
* - The higher the score the better the QOL

The average QoL score of respondents was 45.27, meaning that the respondents had a moderate quality of life. Men had an average score of 52.0 and women had scored 39.0 in a 0-100 scale, where 0 reflects good QoL and 100 reflects poor QoL. Hence men had poorer quality of life than women. 73% reported that they wear compression therapy at all times and it meant that they are compliant to the treatment. When asked about their opinion about the compression therapy, 4 [27%] said it helped to heal ulcer; 3 [19%] said it prevented from further injury; 4 [27%] said they do not improve wound healing and 4 [27%] were not applicable to answer either because they do not know or have not used compression therapy recently.

The Cronbach's alpha [$\alpha_{Cronbach's}$] was calculated to measure the internal consistency of this multi-item survey [where 0 indicates no correlation between the items and value 1 indicates a perfect correlation between the items that make up a scale]. $\alpha_{Cronbach's}$ = 0.934 determined from the pilot study, informs that the survey items are highly inter correlated and meant that all the items were measuring the supposed survey dimension. No major changes were required in the structure and flow of the questionnaire. This assured that the tool can be confidently implemented in the forthcoming clinical trial at an Infirmary in the North West of England for investigating the HRQOL and patient perspectives on compression therapy.

The crux of this paper is to show that there is a need to improve the clinical trial design if results of the trial were to achieve significance and can be put into practice. The main aim of the woundcare clinical trials is to gather unbiased evidence on products so that future patients can benefit from the new products or therapy when conventional treatments have failed. The results of the pilot study shows that patients' suggestions and opinions can be a significant factor in determining the usefulness of a woundcare product. This is because they are the individuals who are finally going to benefit from the research by using the product. Hence measurements such as HRQOL and patients' perspectives can be used in the clinical trials in situations such as **a.** to investigate the advantages and disadvantages of new treatment medical devices, **b.** when the efficacy of two devices evaluated in a clinical trial is found to be equivalent, the device associated with a better quality of life score is more likely to be adopted for clinical practice and **c.**

quality of life can be a main end point in clinical trials evaluating treatment devices on chronic incurable diseases. Such a disease specific HRQOL survey is implemented in an ongoing clinical trial on chronic venous leg ulcer patients conducted in a hospital in the North West of England.

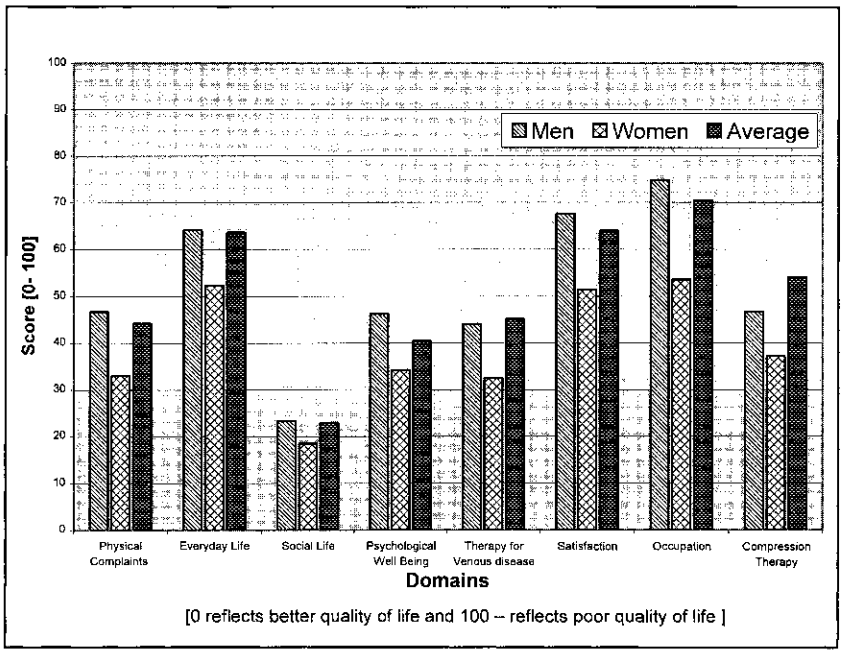

Figure 2 Quality of life of men and women

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NEW APPROACH TO PRODUCE ABSORBENT PADS FOR NEW END USES

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ABSTRACT

The use of hygiene pads is increasing rapidly. They are used for baby's diapers, sanitary products and incontinence pads for the elderly etc. But the use of pads with a dual mission of healing and protecting by absorbing the discharged liquid whilst releasing healing cream or chemical to the infected area without mixing the discharged liquid with the healing chemical is a relatively new one.

In this study a new novel approach has been tested in the care for wounds, haemorrhoids etc.

INTRODUCTION

Apart from the more conventional uses natural and man-made fibres are also used in medical, protection in health and in hygiene. Technology in this area is moving forward. Textiles in medical and hygiene applications are mainly used in the form of non-woven. However knitted and woven products are also used. In this sector products include; operation room gowns and drapes, wound dressings, bandoleers feminine pads sanitary products etc as non-woven. These products depending on their uses can be classed as; hygiene absorbent hospital and protective health products, implants and scaffolds.

In this wide range of end uses the absorbent products are very important in terms of production and in use. In medical applications as absorbent materials varieties of fibres in the form of non-woven are used to absorb the liquid released from the body. In the case of excessive release super absorbent materials are used.

Absorbent materials are usually in the form of press bandages and pads. There are two main functions absorbent materials have to complete, one is to absorb the liquid released from the area or the infected area and the second is to help heal the infected or bleeding area by pressing in to it.

In some cases pressing in to the problem area of the body alone does not help in the healing process. The problem area in some cases has to be treated with medicine. Under those circumstances bandages are opened up, medicine or healing cream is applied and then new bandages are placed on the problem area. However if the problem area is infected and releases exudates and blood constantly, medicine or cream mixes with exudates and blood and does not show the full effect.

In some cases medicine absorbed materials are used on the infected areas. But in some cases if the infected area is releasing exudates and blood, which are then mixed with the medicine, cream applied reduces the effect of the medicine.

In this work, new mechanism of absorbance and healing was put to the test. With this system exudates and blood will be absorbed and medicine or cream will be applied to the problem area of the body without the two being mixed. The amount of medicine applied to the affected area is also important. To release the medicine to the affected area requires first of all little pressure and releasing mechanism. In this work for the cream realising mechanism, fibres in the form of non-woven were used which were

impregnated with cream and the successful work of this system will allow controlling of the applications of medicine as well as cleaning or keeping clean and dry the affected area.

The first part of this study was mainly concerned with the preparation of the new system, which allows the waste liquid to be absorbed as well as the application of medicine and cream to the affected area of the body without mixing the two. This explained system was successfully produced and the system worked as planned. Application of the required amount of cream or healing medicine is also a very important factor affecting the healing time. This paper mainly concentrates on the performance of textiles (non-woven) to make these systems work as required.

The system as shown in Figure 3 consists of two main parts one is the absorbent part which absorbs exudates and blood and the second part applies the medicine or cream to the affected area thus all parts are separated and do not mix with each other.

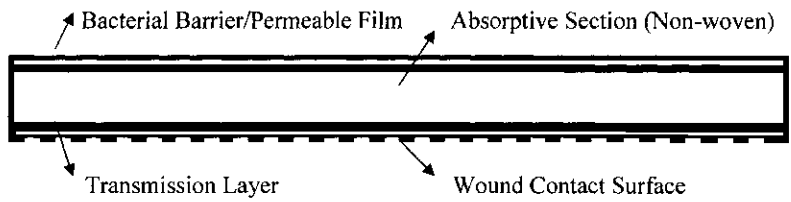


Figure 1 Standard Wound Care Plasters

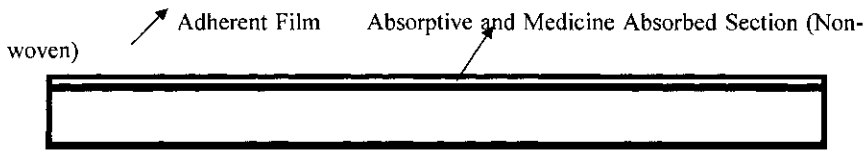


Figure 2 Single Layer Non-woven for Wound Care

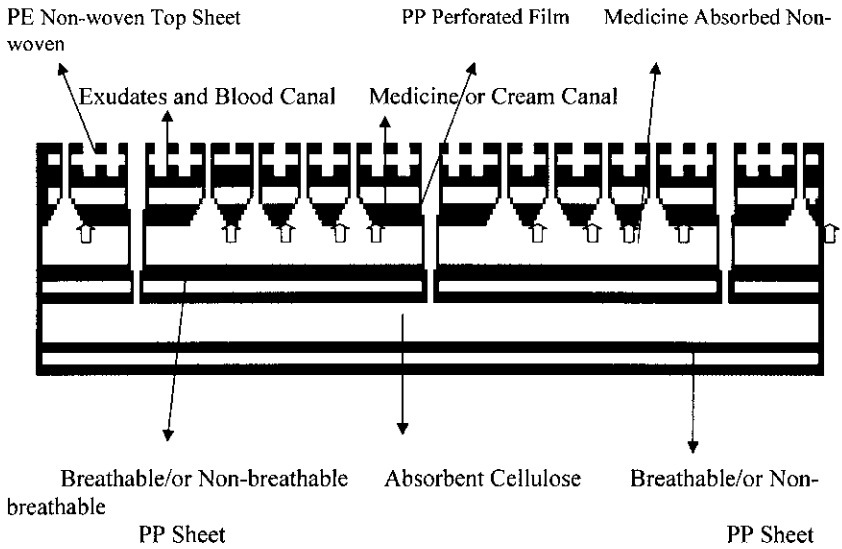


Figure 3. New System Suggested by this Work

EXPERIMENTAL

Material

The first part of this project mainly concentrates on the medicine or cream releasing mechanism and the releasing of required amount depending on the fibres used on the production of the non-woven.

Two different non-woven produced from polypropylene and polyester were used to apply the cream or medicine and properties of the non-woven used are given in Table 1 below.

Table 1 – Physical Properties of Nonwovens

Materials	Production Method	Fibre Count (den)	Fibre Length (mm)	Fabric Thickness (mm)	Fabric Weight (g/m^2)
Polypropylene	Needle Punched	6	55	2.1	200
Polyester	Needle Punched	6	55	2.0	200

Cream applied on to the non-woven sheets were one of the most commonly used haemorrhoidal creams. The properties of this cream are outlined in Table 2.

Table 2 The Contents of the Cream Used (Haemorrhoidal Cream)

Contents	5 g Tribenosid, 2 g Lidokain, Hydrochlorur, Metilparaben, Propilparaben and other axillareies
Viscosity (mPa.s^{-1})	25000
Colour	White

Four grams of this cream was applied on to polypropylene and polyester non-woven containing section of the new system.

Method

The area of medicine release in the new system is 28.5 cm^2. Each non-woven section of the pads have been applied with 4g haemorrhoidal cream. After the application of the cream on to the non-woven section of the pads, they were then left under standard atmospheric conditions for six hours before the experimental work for the cream to be evenly distributed on to the non -woven section.

To assess the cream release with pressure application dependent on time a new test system was developed. For the experiments 60, 70 and 80 kg average human weights were chosen. When a person sits the area they cover is approximately 500 cm^2. The pressure applied to the face of the pad then becomes for every weight as follows; for the 60 kg; 120g/cm^2, 70 kg; 140g/cm^2 and 80 kg; 160g/cm^2.

Based on the standard weights mentioned above for 60 kg 3420 g, for 70 kg 3990 g and for 80 kg 4560 g weights were applied to the surface of the pads to assess the cream release quantity of the pads. For absorbance of cream release needle punched non-woven structure made from viscose covering the full face of the pad was placed on top of the pads and the absorbance of the cream by viscose non-woven was measured in terms of 30, 60 and 90 minutes time intervals. Five repeats were carried out for each weight and averages were taken.

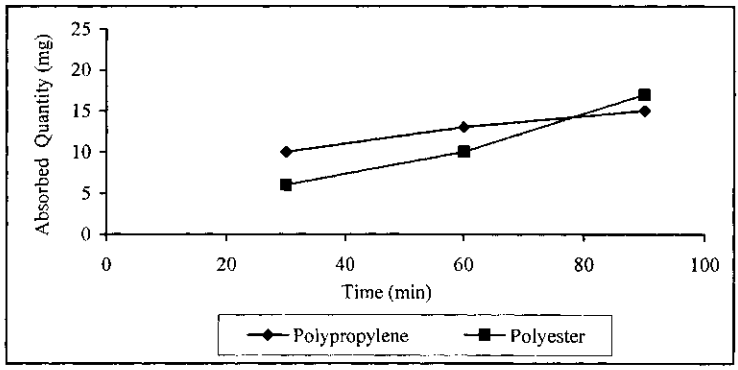
RESULTS AND DISCUSSION

The results obtained for different weights and time are given in Table 3.

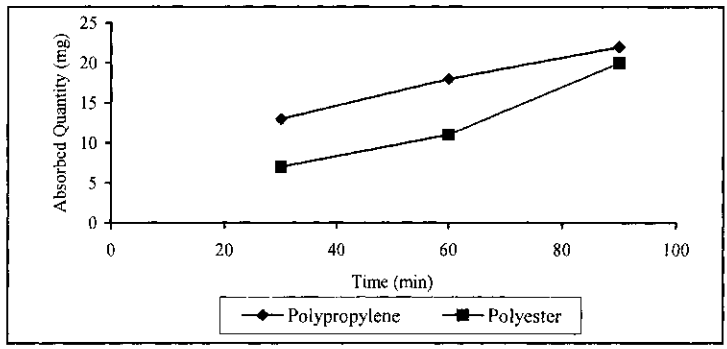
Table 3 – Cream Release Results

Time (minutes)	**Medicine Quantity Absorbed (mg)**					
	60 Kg		**70Kg**		**80Kg**	
	PP	**PES**	**PP**	**PES**	**PP**	**PES**
30	10	6	13	7	15	5
60	13	10	18	11	19	12
90	17	15	22	20	37	34

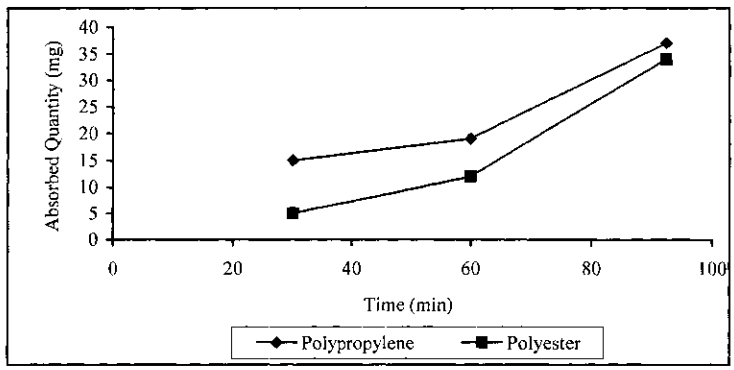
First of all the system works, and the samples were and are still being tried at Medical School of Marmara University. But the aim of this study was to be able to see the medicine releasing amounts of fibres. For this purpose two different types of non-woven fibres were investigated. Figure 3 below outlines the observed quantity in terms of time for different weights and Figure 4 shows the absorbed quantity in terms of weight applied for different types.



60 kg



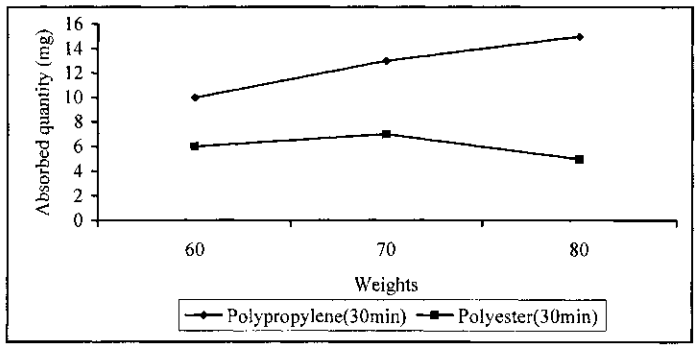
70kg



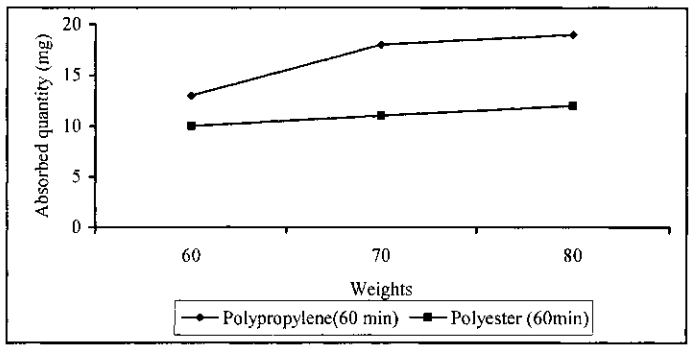
80 kg

Figure 3 – Cream Releases in Dependence of Time

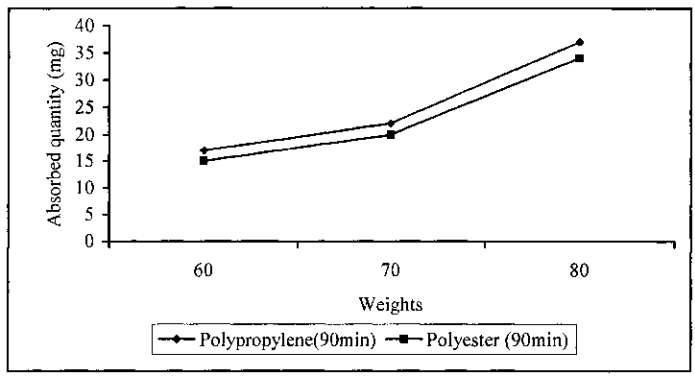
Results have shown that increasing time of weight apply increases the medicine released for both samples. This could be seen in 3 separate figures of 60, 70 and 80 kg weights of Figure 4. It could clearly be seen Polypropylene fibre non-woven released more cream in dependence of time. In other words the amount of cream released increases with the time increase.



30 Minutes



60 Minutes



90 Minutes

Figure 4 – Cream Releases in Dependence of Weights

However when cream-releasing mechanism in dependence of weight is investigated again the cream release is observed with weight increase (Figure 4). Polypropylene fibre non-woven releases more cream than polyester fibre non-woven in dependence of weight or time.

CONCLUSIONS

- First of all the system introduced by this study, works and samples are still being tested on patients at Medical School of Marmara University.
- Production of this new pad system is not explained in detail in this study, only the healing mechanism and the rate of release of the healant system dependence of fibres weights and time were put to the test.
- Application, rate and amount of the healing cream release depends on the fibre and the state of the non-woven used.
- From these results it could be said that polypropylene releases this particular healant (Haemorrhoidal cream) faster than polyester non-woven.
- Cream released at a slower rate and less amount of polyester could be related to oil phobic behaviour of polyester.
- Even though results are not shown here the increase in heat (body heat) increases the amount and rate of cream released.

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