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Drug Release Medical Textiles: Fundamentals, Classification and Methods of Fabrication

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Advancements in the medical field have provided the best solutions to medical problems and improved the comfort of application. Textile systems can function as comfortable delivery systems for medication in a smarter way, as there is no need to take it orally or in the form of injection. It also has other advantages over the conventional methods of delivering drugs such as reduced doses as compared to oral dose, avoids metabolism in the liver, reduced side effects, and preferred when oral administration is difficult, e.g. with children, people with swallowing difficulties, or people who are forgetful. Such wearable medical textiles can be fabricated by making use of biodegradable polymers or nanoparticles. In recent years, the fabrication process technology of textile materials has witnessed significant progress. This has enabled "Smart Wearable Medical Textiles" which seemed a farfetched dream earlier turn into reality. This paper will classify the latest therapeutic drug release systems, and explain different methods of fabrication of medical textiles.

Keywords: Drug Delivery Systems; Encapsulation; Nanofibres; Nonwovens; Technical Textiles

1. Introduction

Textiles have become far more revolutionary than what was conventionally thought of them. The use of (smart wearable) medicated textiles which is unfamiliar to many is imminently going to have a huge impact on our daily lives. Considerable research in this field is going on, increasing day by day, implying exponential growth in knowledge, and is impacting human health like never before.

Conventional drug delivery systems may not always be the most feasible method for drug delivery. In oral drug delivery systems such as pills, tablets, capsules the absorption of the drug is meant to happen in the stomach or the intestinal tract. But many times, since most drugs are metabolized, they lose their activity before reaching the desired location. As a consequence, comparatively high drug doses are necessary to bring in the desired effect. Thus, due to either rapid acid-catalyzed degradation in the stomach or extensive metabolism in the liver, the concentration of the drug gets to be too low, necessitating repeated dosing. A direct repercussion of repeated high doses is toxicity.

Moreover, oral delivery does not work particularly well with children, people having swallowing difficulties, and people suffering from certain diseases such as dementia. Conventional dosage forms also lack target specificity. To circumvent these drawbacks, several pharmaceutical formulations having properties of sustained or controlled drug release have been developed. Prodrugs wherein the poor bioavailability of the drug is enhanced by chemical derivation have also been applied. [1], [2]

Textile materials are versatile and already are employed in a myriad of applications. They are seeping their way into the medical field too, for example in the form of wound dressings and protective clothing. Transdermal patches, which have been extensively researched upon, consist, along with an ointment (or other drug-releasing material), a regulatory system (for example, a membrane), which helps deliver the drug via the skin at a controlled rate to the circulatory system. [3]

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Of late, textiles are being developed to allow for controlled drug delivery applications to replace or complement conventional drug delivery methods. The major advantage of using medical textiles is that it requires very little patient contribution and conscious effort in realizing the drug administration procedure.[4] Smart medicated textiles are textiles coated with the particular drug carriers or incorporated with drugs inside their framework. These drugs are released in response to a very specific desired stimulus, say a change in temperature, or maybe pH, or the concentration of specific ions in the bloodstream.[5]

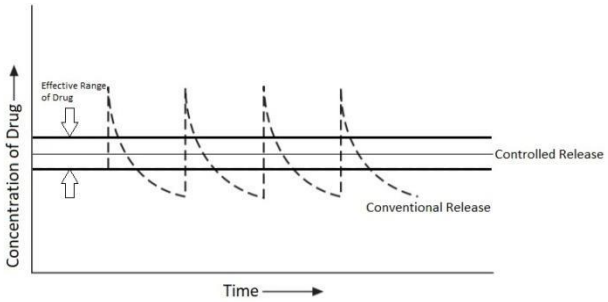

Figure SEQ Figure * ARABIC 1 Comparison between drug delivery by conventional DDS and controlled DDS

As can be seen from figure 1 controlled drug release systems such as transdermal medical patches can be specifically garnered to fulfill the drug concentration range of different drugs. This makes sure that the concentration of drugs in the bloodstream always lies between the required concentration range which makes them economical and effective. In contrast, in the case of conventional drug delivery systems, there is a sharp spike in drug concentration on oral administration followed by gradual depletion. Therefore, intermittent repeated dosing is necessary for the drug to be effective.

Along with the drug, the incorporation of a drug carrier is also of paramount importance that'll respond to certain stimuli. They could be long-circulating and targeted drug carriers which allow for maintenance of a particular pharmaceutical agent in the blood at the respective site so that the required concentration of the drug is slowly accumulated [6], or could be smart polymer-based nanocarriers that respond either to temperature or pH[7], or could be multifunctional carriers that serve a variety of purposes.

For a thorough understanding of drug releasing textiles there are two important aspects; first is textile structures and materials and their judicial selection based on desired application and second is the drug delivery mechanism.

This review focuses on drug release textiles and their classification and how the drug is made a part of the fabric for sustained drug release.

2. Drug Release Textiles Classification

Drug release textiles are classified into two types: Woven fabrics, and non-woven fabrics.[8]

2.1 Woven Fabrics

Woven fabrics as the name implies are fabrics that are woven with drugs latched onto the fabric via physical adsorption or absorption, coated onto the surface, encapsulated, or attached to the fabric surface by strong covalent bonds. In addition to drug delivery, woven fabrics that are loaded with drugs have several applications, such as bandages that are bioactive, called bioactive bandages, artificial skin grafts, a scaffold that aid in tissue regeneration, etc.

Padma Kumar et. al. developed a drug-loaded woven fabric made up of polydioxanone (PDS) nanofibres. Paclitaxel (PTX) was incorporated into polydioxanone nano yarns developed from electrospinning that were then woven to form nano textiles. Different types of woven nano textiles were created that represented different packing densities.

They used Fourier-transform infrared spectroscopy (FTIR) to characterize the loaded PTX drug. A peak at 1251cm-1 corresponding to PTX was retained which proved that the drug had been successfully loaded into the nano textile. They also qualitatively confirmed the presence of PTX in PDS yarns by quantitative measurements of Nitrogen using EDAX (Energy-dispersive X-ray spectroscopy) analysis. The efficiency of PTX entrapment was quantitatively determined by High Performance Liquid Chromatography and came out to be 86±10%.

They tested the release kinetics of PTX using various techniques. They could demonstrate that the nanostructure of the woven fabric greatly affected the modulation of drug release kinetics. They concluded that at the target site of PTX i.e. peritoneum, PTX had enhanced residence when compared to intraperitoneal injections. Therefore woven fabrics at the nanoscale have the potential to become efficient drug delivery systems (DDS). [9]

2.2 Non-Wovens

Nonwovens are prepared by placing small (also nano) fibres together in the form of structures that represent webs and/or sheets and binding them physically, mechanically, or chemically. The drug-containing filaments lie entangled within the nonwoven. Nonwovens have been proved to be well suited for controlled and sustained drug release systems because their 3-dimensional structure is majorly composed of definite porosity and geometric fibres.

Freudenberg, a company based in Germany has invented 3-dimensional biocompatible scaffolds. These have an interconnected porous structure that exhibits bioresorbability. This brings into the picture a wide range of possibilities for medical applications. It is based on a new and innovative spinning process that allows for the production of nonwovens that are inherently bioresorbable. Natural and synthetic biopolymers are processed and spun into nonwovens, which take place under mild conditions that also allow for the incorporation of bioactive ingredients. The desired characteristics of the fiber such as resorption time, diameter, and local drug release behavior can be adjusted, according to the needs of the application, by variation of the processing parameters and the composition of the matrix materials.[10]

2.2.1 Nanofibrous Non Wovens

Nanofibres are fibres that have diameters in the nanometer range. These are considered to be a new and promising grade of materials that have the capability to make an impact on the medical field.

Some of the pertinent properties of nanofibers for their use in the textile industry are their low density, large surface area to mass, high pore volume, and small pore size. Particularly the high surface area to weight ratio of the nanofibres makes them ideal for a broad scope of functions in the medical field, especially DDS, thanks to increased drug loading and cell attachment attributes because of the high surface area to volume ratio of produced fibres. [11], [12]

We'll take a look at three main techniques that have come into picture for the preparation of nanofibrous structures.

2.2.1.1 Electrospun Non Wovens

The electrospinning method is being incorporated for developing fibres to be used in drug delivery systems because of its simplicity, easy to adapt manufacturing process.

A particular polymer melt is filled inside a syringe pump, which forces the polymer to melt by way of the needle. There is a high voltage DC supply that is connected to the needle through which charge of either positive or negative polarity is forced into the polymer solution. As the solution is continuously being pumped with charges of similar polarity, the electrostatic force of repulsion due to these charges starts increasing and when finally this force exceeds the surface tension of the polymer solution, the Taylor cone comes into the picture and a fiber jet of small diameter compared to the needle is emitted from its apex. The fibres that are emitted are collected onto a rolling metal cylinder which is known as the collector. The distance between the spinning site and the site where collection takes place is configured such that the solution evaporates before reaching the collector.[13]

Owing to its hassle-free setup, electrospinning can be used to produce nanofibers of many materials ranging from organic to inorganic materials and their combinations. Stimuli-responsive polymers are a grade of materials that have enormously promoted the swift advancement of electrospun mats in the niche of smart fibres. Drug delivery textiles with the facilitation of stimuli-responsive polymers have paved the way for smart drug delivery textiles.[14] A

lot of different kinds of drugs ranging from anticancer drugs, antibiotics to protein, DNA, and RNA have been successfully incorporated into various electrospun fibres for drug delivery applications. [15]

Electrospun fiber mats made by researchers, who used tetracycline hydrochloride as the model drug, were made from either polylactic acid (PLA) or polyethylene co-vinyl (PEVA) or a 50:50 blend of both. 14 w/w% of solutions of PLA, PVA, and a 50:50 blend of both were used for the same. The researchers achieved the incorporation of the drug into the nanofibers by the dissolution of the drug in methanol and then adding it to the polymeric solution that was to be taken ahead for spinning. The flow rates for the setup were 18-21ml/h, 3ml/h, and 10-13ml/hr. respectively for PLA, PEVA, and the 50:50 blend. A 90% loading efficiency of the drug inside the nanofibers was obtained. They concluded by carrying out various drug release tests that PEVA and the 50:50 blend electrospun mats exhibited satisfying drug release properties over a period of 5 days. [16]

2.2.1.2 Self Assembly

In this process, the "bottom-up" approach is utilized wherein supramolecular entities (in our case nanofibres) are built molecule by molecule (even atom by atom sometimes) spontaneously with preprogrammed non-covalent bonds. The inspiration for such an approach is natural, which has created proteins, crystals, and other such patterns and structures autonomously without human intervention. Compared to the electrospinning process fibres with much smaller diameters (mostly in the nano range) can be prepared. However, due to the procedural complexity, productivity is low.

For example a variety of nanofibres could be fabricated by use of self-assembling peptides and proteins, for biomedical applications.[17], [18]

2.2.1.3 Phase Separation

In this method, solvent is removed from polymer scaffolds by freeze drying or extraction method, leaving a porous structure. A change in temperature or inclusion of a non-solvent to the polymer solution can bring about phase separation.[19]

J. Nemoto et. al. were able to produce nano-porous networks by simple air drying of aqueous TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)-oxidized cellulose Nanofibril (TOCN) dispersions. A dispersion was formed which contained both TOCN and dodecyl trimethylammonium bromide (DTAB). The latter was added to form a stable dispersion. Nanostructured porous supports were immersed into the TOCN/DTAB dispersion on which the components of the dispersion got adsorbed. The support with the adsorbed TOCN/DTAB was allowed to dry to form the nano-porous networks. Only when the support pore size was less than 20µm and the concentration of TOCN in the dispersion was less than 0.1% w/w could the networks be formed. For the experiment, J. Nemoto et. al. used a 0.05% TOCN/ 0.02% DTAB dispersion and a 7.5 µm pore-sized 2000-mesh copper grid. LSM and SEM techniques were used to characterize and visually interpret the formation of the nanoporous networks. [20]

Agarwal et. al. were able to produce Polyvinyl Alcohol/Polyethylene-Oxide/Carboxymethyl-Cellulose (PVA/OCM/CMC) Membranes with PET nonwovens as a support layer using freeze-drying method and incorporated ciprofloxacin hydrochloride (an antibacterial drug) into it, to test for promising drug delivery capabilities. They prepared PVA/OCM/CMC solutions in 90/10/20, 80/20/20, 70/30/20, 60/40/20, and 50/50/20 proportions. They dissolved these solutions into deionized water using a magnetic stirrer to homogenize the solution. The total concentration of the polymers as a whole was kept at 5% by weight. 1% w/w Ciprofloxacin hydrochloride was also added to the blend solution. The entire homogenization process was carried out for 8h at 70^{o}C. The final step to convert them into membranes was carried out by two approaches i.e. either by freeze extraction or by solvent casting. In solvent casting the solution was cast onto a petri dish and was allowed to dry at room temperature followed so that a membrane was obtained due to the evaporation of water. This membrane was carefully removed from the petri dish and subsequently was kept to dry in a vacuum chamber. The other approach was via the freeze drying method. Here the solution was first poured onto

nonwovens made from PET and then as a whole were placed in a deep freezer at -82°C for 24 h followed by freeze-drying at -82°C for 12 h, followed by drying in a vacuum oven at 80°C for 4 h.

They confirmed effective release of drugs in the medium which showed that such a system can be used as an effective antibacterial wound dressing. [21]

Although an inexpensive method, it can be useful only on a laboratory scale.

3. Fabrication of Drug Release Systems

3.1 Coating

Here, the drug which is either micro or nano encapsulated is directly coated onto the surface of the fabric by dipping the fabric in the drug solution. The coating can consist of binders, dispersing agents, and other materials to carry out specific purposes, in addition to the bioactive material. Sometimes dispersion coatings are used to seal the active ingredient from a particular side.[22] For example attachment of cyclodextrin to prefabricated textiles is relatively easy, the cyclodextrin forming an interface between the target site and the textile, to form a cyclodextrin drug delivery system.

Mostafa et. al. developed an effective textile patch to treat chronic wounds made up of functional threads. Herein, the functional thread that was composed of a conductive core thread as a microheater was coated with an alginate (Alg)/poly(ethylene glycol) diacrylate (PEGDA-Alg) hydrogel embedded with thermoresponsive drug carriers from hybrid hydrogels. The patch that was formed from weaving proved capable enough to manage delivery in various doses and rates of multiple drugs.[23]

3.2 Encapsulation

Here, hormones, antibiotics and other drugs are encapsulated into various functional textile structures. Microencapsulation is an effective technique to deliver various active agents from textile fabrics to the skin and leads to textiles with added value and attributes. Different approaches such as spray drying, extrusion, fluidized bed coating, free drying coacervation, emulsion, liposome entrapment, spray cooling, in situ polymerization, solvent extraction, etc. can be used for the encapsulating various micro-capsules.[24], [25] the technique of electrospinning for the preparation of such a drug loaded fiber has already been discussed in detail.

In addition, microfluidic devices and wet spinning techniques have been used to prepare homogenous drug-polymer solutions or suspensions which are then further subjected to extrusion.[26]

Mathematical models have also been created that quantify microencapsulated drug release mechanisms from textile fabrics to the skin which can prove effective in designing drug delivery textiles.[27]

3.3 Bioconjugation

In this method, the surface of the textile is functionalized so that the active ingredient could be physically or chemically conjugated to it. Site specific and controlled release both can be achieved via this method. One advantage that this method offers is that high loading of the drug is possible.[28]

S. Chatterjee et. al. produced a polysaccharide-based nano-conjugate along with pH and thermoresponsive polymers to develop a dual responsive hydrogel DDS for gallic acid. The conjugate was prepared using a two-step synthesis. A much better and efficient release condition behaviour was seen for gallic acid in neutral pH condition after the addition of the polysaccharide-based nano-conjugate in the system at a higher concentration than its CMC (critical micelle concentration). Studies of the mechanical integrity and release property of the hydrogel were conducted in the simulated skin pH condition (pH 6.4). Astonishingly, the hydrogel seemed to show enough mechanical integrity and sustained drug release properties despite diminished stability of the system due to increasing acidity of the external environment. Therefore bioconjugated textile

materials can be utilised as effective drug release mediums.[29]

3.4 Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides made up of a hydrophilic outer surface and a central cavity that is hydrophobic in nature. This enables them to form water-soluble inclusion complexes with poorly water-soluble drugs. Cyclodextrins α, β, and γ have 6, 7, and 8 glucopyranose units respectively. These CDs have been attached to the textile material's surface either by physical or chemical immobilization. They can also be entrapped in the structure of the fiber itself during spinning. The most common method of attaching cyclodextrins onto textile surfaces is through grafting. Even after fixation on the textile surface, the CDs retain the ability to form complexes. The CD and the drug form a host-guest complex wherein the CD is the host and the drug is the guest. The drug fills the cavity of the CD and is released in response to a skin stimulus such as sweating, rubbing, or in the presence of different skin enzymes. [30]–[32]

β-cyclodextrin modified with a reactive monochlorotriazinyl group is used. Such a modification is imperative for the cyclodextrin to permanently covalently bond with the hydroxyl group in cellulose with the help of the anchor group. Therefore it is also important to study toxicological data for this particular cyclodextrin derivative. Researchers were able to confirm, after carrying out OECD (Organization for Economic Co-operation and Development) tests that this cyclodextrin derivative had no irritating or sensitizing effects on the human skin. Even the Ames test proved the absence of mutagenicity. [33]

A certain caveat in the case of dermal drug delivery using wound patches employing cyclodextrins is that they can only be effective and can enhance drug delivery when the rate-determining step for drug absorption is an aqueous diffusion layer at the outer surface of the skin. This is because cyclodextrins are unable to penetrate through the "stratum corneum" which is the outermost layer of the skin.[34]

3.5 Ion Complexes

In addition to cyclodextrin-inclusion complexes, drugs could also be attached to the textile surface as a result of interaction between charges present on the fiber surface and the drug, leading to ion complexes of neutral charge. In this type of DDS the drug acting like mobile counter ions exchanges ions in its physiological surroundings. Ion exchange materials are particularly advantageous because they can achieve controlled transdermal drug delivery thanks to their ability of binding and exchanging charged drug molecules. [35], [36]

T. Kankkunen et al. tried controlling the transdermal delivery of zwitterionic levodopa by iontophoresis and ion-exchange fibers. The ion-exchange fibers were fabricated by first incorporating the staple fibers in a porous membrane and depending on whether cation-exchange groups were to be activated or anion-exchange groups, different solutions were used. To activate ion-exchange groups of cation-exchange fibres a 1:1 solution of 0.1 M NaCl and 40.1 M NaOH was used. To activate ion-exchange groups of anion-exchange fibres a 1:1 solution of 0.1 M HCl was used. The fibers were then rinsed with deionized water and were immersed into a 1mg/ml solution of levodopa at different pH. The drug loading was determined by HPLC analysis of the leftover levodopa solution where the difference in the initial and final amount of levodopa is the amount of levodopa taken up by the fibres.

They tested the release of levodopa in the presence of various electrolytes such as NaCl and $CaCl_2$ by HPLC. Its release did not depend on the concentration of NaCl present in the release medium but increased in the presence of $CaCl_2$ at different pH conditions. At a pH of 2 in the presence of NaCl the release was only 6-7% as compared to a release of 47% in the presence of $CaCl_2$. They concluded that Ion-exchange fibers provide a potential substitute to carry out controlled drug delivery and to store drugs that have fast degradation times. [37]

3.6 Layer-by-Layer Self Assembly

Layer-by-Layer or LbL Self Assembly is a spontaneous process that can be used to form different layers on top of different substrates. It offers exceptional versatility, superior control and is cheap when compared with other thin film deposition techniques. LbL is a cyclical process where a charged polyelectrolyte is adsorbed on top of the substrate, after which an oppositely charged polyelectrolyte layer is adsorbed over the first layer. This is known as the first single bilayer which is generally in the order of nanometers and this process is continued to achieve a desired thickness of the multilayer film. Different drugs can be incorporated in these layers on a textile substrate for the fabrication of drug delivery textiles.[38], [39]

Junthip et. al. successfully devised a drug delivery textile system by using layer-by-layer self-assembly. They chose Polyethylene Terephthalate (PET) as a base. They were able to form alternate layers of cationic β-cyclodextrin polymers (poly EPG-CD) (product of the cross-linking reaction between epichlorohydrin (EP) and βCD) and anionic β-cyclodextrin polymers (poly CTR-CD) (obtained from the crosslinking reaction between citric acid (CTR) and βCD) in the presence of glycidyl trimethylammonium chloride). These layers were formed on evaluation of loading capacity and sustained release properties of the polyelectrolyte multilayer film (PEM) by using Tert-butyl benzoic acid (TBBA) as a drug model.

Steps that were followed to get the finished product: First poly CTR-CD was thermofixed on PET textile to start the formation of layer by layer build up. After that subsequent layers of alternating anionic and cationic charged compounds were added to get the multilayered final product.

They characterized the formation of multilayers using Raman spectroscopy, SEM, NMR studies. After the addition of 10 layers a thin film can be visibly noticed on the virgin nonwoven in the SEM scans. They confirmed the formation of multilayers through the analysis of 2D NMR peaks of the final product. [40]

Summary

This review has highlighted the fundamentals of drug-releasing textiles as attractive alternatives to conventional DDS, their classification, and the different methods that could be used for their fabrication. Both woven fabrics and nonwovens have the capability for the development of DDS and medical textiles. A lot of research is ongoing in this area and there are considerable advances in the optimization of drug delivery textiles in a variety of biomedical applications. Their versatility is increasing and textiles hold considerable promise in incorporating a broad class of drugs for both topical and systemic administration.

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