Section A -Research paper

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A REVIEW ON NANOFIBRE BASED TRANSDERMAL PATCH TECHNOLOGY FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

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ABSTRACT

Pharmaceutical researchers face significant obstacles when attempting transdermal medication delivery. Avoiding the effect of first pass, the transdermal route's lack of invasiveness, and substantial compliance among patients make it the preferable administration method. Therefore, it is important to create a carrier system that efficiently transports the medicine over the skin. Despite their benefits, TDDS have a few drawbacks, one of which being their inability to be used with hydrophobic medicines. New nanostructures present numerous openings for improving TDDS to deal with their inherent difficulties. Due to their high loading capacity and simple modification and functionality, polymeric nanofibres provide a novel framework for applications involving the delivery of drugs. Transdermal batch loaded with anti-hypertensive medicaments found its importance in cardiovascular diseases as hypertension is one of the most common diseases afflicting humans. Although not a medical condition in and of itself, high blood pressure is a major contributor to cardiovascular-related deaths and illnesses. In the present article, we take a quick look at what's been done so far to make and administer antihypertensive nanofibres as transdermal patches, which has been shown to significantly boost their bioavailability.The purpose of this study is to provide a comprehensive overview of the current status of research into polymeric nanofibres, focusing on: TDDS based on nanofibres.

Keywords: Hypertension, nanofibres, transdermal, bioavailability, cardiovascular, blood pressure

1. INTRODUCTION

Hypertension is among the leading causes of death and disability due to cardiovascular disease [1]. Patients with hypertension have reported receiving medications through a variety

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of ways, involving parenteral and oral administration. The oral drug delivery is typically chosen over the other routes because of its many benefits, including simple administration with high patient adherence. The oral drug administration strategy has a number of potential limitations, including poor specificity and drug targeting, high dosages needed to reach plasma drug concentration, and unpleasant side effects. Moreover, their limited solubility and, thus, bioavailability, are a barrier to successful dosage form formulation. When taken orally, many drugs cause undesirable effects including gastric discomfort and stomach trouble. Drugs administered transdermally can be absorbed both systemically and locally. Thus, it is acknowledged as a viable drug delivery mechanism. The transdermal medication delivery techniques have drawn most of the scientists because to its many benefits, including avoiding the first pass metabolism, prolonged release of drug, reduced side effects with intensity of administering drugs, and patient acceptance [2].A transdermal patch, also called a transdermal medication delivery device, is a therapeutic patch that can release its contents into the bloodstream via small portals with in skin at a controlled rate. It is the most convenient dose form because it does not require surgery, does not cause nausea or vomiting, does not cause first-pass metabolism, is usable for multiple days, and can be stopped at any moment. Locations for applying drugs, including such nitroglycerin all around chest, estradiol around the belly, and nicotine all around upper torso or right upper arm, ought to be not oily, clean and hairless. Considering drug loaded nanofibres have desirable properties such a high surface area, high porosity, and an extremely small pore diameter within in the fibers, formulating researchers have been focusing on their creation. Also, due to the vast potential for multifunctional applications offered by nanofibres, these can be helpful in directing medicinal molecules to certain areas.In order to mass-produce drug-loaded nanofibres, electrospinning has been demonstrated as the most popular method [3]. This is because electrospinning is a simple yet continuous approach that can generate nanofibres from a wide range of polymers. By applying a high enough voltage, the electrospinning can induce a charge in a water phase comprising polymer. At a crucial point, termed as the Taylor cone, the drop is extended owing to adhesion by the opposite charges collection, resulting in a jet of fluids from the top. Fibers are formed as the charged liquid jet evaporates during flight, and they are gathered on a revolving drum (collector) [4]. The formulation of drugs loaded nanofibre material with the potential to supply optimal medicine to manage the patient ’s condition with minimal side effects is required by the hour in light of the drawbacks associated with other routes of administration and the excellence of transdermal delivery of drugs. Treatment costs for hypertension over the long term are also expected to decrease as a result of this method [5,6].

Cardiovascular disease continues to be the primary resulting in an annual mortality toll of much more approximately 17.9 million [7]. By 2035, predicts that 46.1% of the United States community will have cardiovascular events, with such an overall cost of 1.1 trillion dollars [8] attributable to cardiovascular disease. This statistic alone is indicative of the enormous toll that cardiovascular disease takes on humankind. The myocardial infarction occurs when cardiomyocytes die from a shortage of nutrients and oxygen in the heart [9]. After an infarction, the cardiac tissue can no longer regenerate. Repairing infarcted myocardial by implanting myocardium into a sick heart appears to be the simplest option. The cardiac tissue

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repair has certain current limitations, such as an incomplete understanding of the structure or mechanical surroundings of native heart tissue [10]. Electrospun nanofibre scaffolding have been investigated extensively for use in cardiac tissue regeneration. Electrospun scaffolds are utilized to dynamically support as well as replicate extracellular matrix integrity to promote viability, cell adhesion and regeneration in the context of stem cell therapy for myocardial injury repair (Figure 1) [11].

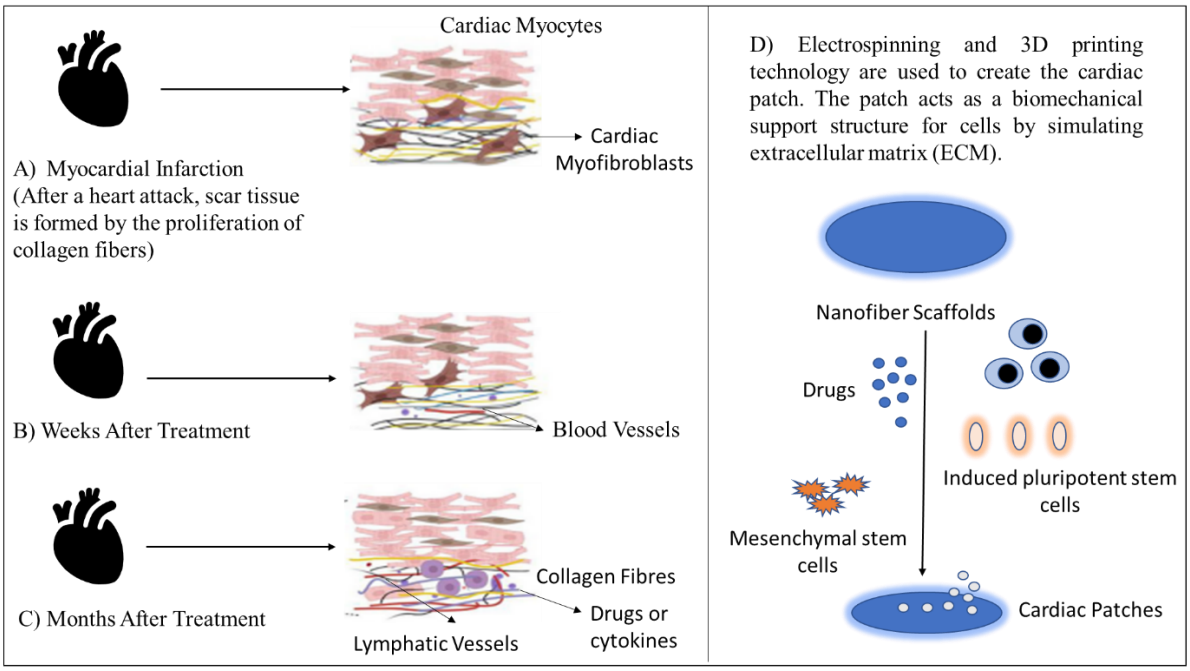

Figure 1: Illustration of a cardiac patch used to treat myocardial infarction

Almost 50% of all deaths from CVD can be traced back to vascular damage carried about by arterial plaque accumulation, which then in turn produces vascular obstruction causing sclerosis [12]. Scientists have been attempting to build artificial grafts and allografts for blood vessels that are functionally identical to those they replace. Yet, various sources weren't able to match the demands of the vessels, and the rate of patency with tiny transplantation's size continues to be a challenging issue internationally [13].

Bypass coronary artery grafting (CABG) is one of the treatments for heart failure for nearly 50 years [14]. As a result of rapid occlusion with thrombosis, inner size (6 mm) manufactured grafts often fail despite the high volume of bypass cardiac operations conducted annually. Hence, autologous vascular grafting is the only method that can be considered at this time[15,16]. The limited patency and biological compatibility of the vascular grafts with a small diameter created using traditional tissue engineering techniques severely limits their clinical translation [17]. There in past few years, cell therapy has made significant advances, and an effective graft which takes into consideration. Optimization approaches [18-20] in addition to functionalization can drive host tissue regeneration or recapitulate normal tissue creation [21-22]. To prevent stenosis and occlusion, a small vascular stent's thickness must have anticoagulant and antithrombotic capabilities in addition to maintaining blood flow within the lumen without or with minimum leakage [23].

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This has prompted a multitude of research into various methods of boosting the size of the capillary intimal endothelium whilst reducing the number of smooth muscles in grafts, as well as the utilization of electrospinning techniques for graft fabrication (SMCs). The electrospun surface is typically folded into a tubular form via passing through a sliding rod collection, and then filled with heparin [24], growth hormones [25], and other active compounds for the purpose of studying circulatory tissue regeneration [26]. Animal models, such the aorta of the abdomen of rat [27, 28], the rabbit's carotid artery [29-31], the sheep's carotid artery [32], and the femoral canine artery is commonly used to assess the efficiency of stents across time periods varies from a few weeks to a few months as illustrated in Table 1 [33,34].

Table 1: Use of various Nanofibre materials for the management of cardiac disorders

Nanofibre materials	Thickness (µm)	Diameter	Drugs or cells	Experiments	Animal used	Time (weeks)	Ref.
PCL-Gelatin	115±11	578±184nm	hiPSC-CMs	*In-vitro*	N/A	2	[11]
PCL/NO	600µm	690 nm/3.4 µm	NO_2	Cardiac patch	Mice	4	[27]
PLCL	500µm	6 µm/ 300 nm	Hyaluronan	Aortic replacement	Mice	24	[28]
PELCL/ chitosan	N/A	Inner:754± 385nm	Inner:VEGF	Carotidartery	Rabbits	4	[29]
PLCL	300±17µm	821± 102.87 nm	Heparin/Silk Fibroin	Artery-Carotid transplantation	Rabbits	32	[30]
PCL	N/A	263.1 ±90.2 nm	KSNO	Artery-Carotid transplantation	Rabbits	4	[31]
PLGA	110±10	N/A	Dexamethasone, Endothelialcells, granules, VEGF	Cardiac patch	Mice	2	[35]
PCL	100	300±99nm	Fibroblasts, Cardiomyocytes	*In-vitro*	Mice	1	[36]
PCL	50	200- 5500nm	Heart stem cells/Bone marrow	LAD in rats	Mice	3	[37]
AuNRs	60- 80/ 100–120	500nm/20–60nm	Leftventricular cardiomyocytes	Cardiac patch	Mice	1	[38]
β-PVDF	N/A	N/A	TiO2	*In-vitro*	N/A	6	[39]
PCL/GelMA-Ppy nanoparticles	N/A	948 ± 153 nm	Fibroblasts, Cardiomyocytes	1.5cm	Mice	4	[40]
AuNRs	60–80/ 100-120 µm	500nm/20-60 nm	Cardiomyocytes	Cardiacpatch	Mice	1	[41]
PCL/Heparin coating	295± 5.52µm	21.2± 0.79 µm	Heparin	Aorticreplacement	Mice	3	[42]
ADF4(C16)	N/A	1.6± 0.2µm	N/A	Arterio-venous loop model	Mice	4	[43]

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With the advancement of tissue engineering methods over the past few years, researchers' focus has been shifted toward a group of nanofibres of different materials using electrospinning technologies [43]. When compared to conventional regeneration methods, nanofibre technology offers several advantages in the area of cardiovascular tissue regeneration.

- The infarcted myocardial area can be repaired by stem cell-loaded cardiac patches despite compromising subsequent cardiac systolic action.
- Secondly, a structure of leaflet that is both anisotropic and mechanically strong is supplied, just like in the heart's natural leaflets.

2. NANOFIBRE MANUFACTURING PROCESSES

The size of each nanofibre is less than 100 nm, making them a nanostructured vehicle [44]. Nanofibres are typically produced by a process called electrospinning [45]. Formed fibers with the dimension in the region of 100-1000 nm are often recognized as nanofibres.

2.1. Method of Auto-Assembly

In this technique, atom aggregates spontaneously organise into a defined nanofibrous shape. Nanofibres are as small as 100 nm and they can be created using this technology. This strategy is less frequent since it takes more time to create nanofibres. The tissue engineering has looked at natural substances like chitin (a polysaccharide), but nanofibres made via a self-assembly approach can mimic them extremely nearly [46].

2.2. Synthesis through template approach

Nanofibres can be fabricated using a variety of methods. A few examples of such processes are template synthesis, bicomponentextrusion, melt blowing, drawing, centrifugal spinning and electrospinning.

2.1.1. Bicomponent extrusion

A bicomponent fiber is a fiber that is made by extruding two distinct polymers through a single spinneret[47]. The filaments are made by spinning a mixture of the polymers in desired ratio, with one polymer trapped as droplets in melted state of the other. An essential part of the fiber-making process is a rapid cooling of the fiber underneath the spinneret's pores. This blend's spinnability would be significantly nearly hindered by the variances in spinnability among the two polymer compounds, having the exception of the lower concentrations of the combination. Heating, employing a chemical or solvent, or manually eliminating some of the fiber constituents are all viable options[48].During bicomponent extrusion, multiple polymers are fed into parallel configurations through a hole of spinneret that is divided by an edge of blade or septum [49]. The pipe-in-pipe technique is widely employed to produce the fibers of bicomponent in which one stream component encloses another stream component within the tube's final stage of production. Continuous PET nanofibres of 39 nm width were generated by Nakata et al. [50] using sea-island-type drafting with elimination of the sea element from the flow-drawn strand.

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2.2.2. The Phase Separation

Phase separation involves combining a polymer and a solvent before the polymer gels. In this framework, phase separation due to physical inconsistencies is the primary mechanism. After then, the phase of solventis eliminated, leaving behind the other phase behind. The team of Ma and Zhang [51] laid up the basic steps as polymer dissolving,extraction of solvent, gelation, freezing, as well as freeze-drying—in a technique for generating poly(L-lactic acid) nanofibrous.

2.2.3. Template Synthesis

Another frequent method is template synthesis, which is typically used to create inorganic nanofibres such carbon nanotubes [52], polyaniline (PANI) [53] and polypyrrole (PPy) [54], etc.To obtain a desired framework, a mold is employed in template synthesis. Both the casting method as well as DNA are persuasive examples of template-associated synthesis. A nanofibre template mentioned by Feng et al. [55] is a membrane of metal oxide having pores on the nanometer scale. The nanofibres with controlled diameters are produced by extruding a polymer through a membrane that is porous and then exposing the polymer through a solidifying liquid.

2.2.4. Drawing

The act of sketching can be conceptualized as molecule dry spinning. Only components that are viscoelastic and can undergo high distortions while still being sufficiently strong to withstand the produced stress while pulling can be used in the process. The unconventional technique for drawing nanofibres calls for a SiO_2 surface, micromanipulator and micropipette. While this method worked well in the lab, it generated nanofibres once at a time, making it impractical for commercial use [56]. To do this, a micromanipulator was used to dip a tiny pipette through a droplet near or in the contact point line. After removing the micropipette into the liquid at a rate of approximately one x 104 ms-1, a nanofibre was obtained. With a touch of the micropipette tip, the extracted fiber was spilled over the surface. Each droplet was drawn on many times with nanofibres. When the material evaporated, its viscosity of the boundary layer rose. Therefore, a viscoelastic material that can sustain significant deformations while yet being sufficiently cohesive to retain the produced tension for pulling [57] is required for extracting a fibre.

2.2.5. Meltblown technology

The polymer melt is extruded via an orifice die, then the extrudate is drawn down by hot air, often at the same temperature that the molten polymer, within a single process to create fibers using meltblown technique. As the meltextrudate is exposed to air, the force of drag reduces the material to fibers, that can then be aggregated to create a nonwoven mat. Using this method, thermoplastic polymers can be spun in a cost-effective manner[58].

2.2.6. Electrospinning

Creating polymer nanofibres using electrostatic forces is known as electrospinning [59, 60].In 1934, the Formhals filed a patent for a method of making artificial threads using

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electrospinning [61].Because of its ease of usage and the high volume and area ratio of the non-woven mats typically produces, electrospinning is a great option for obtaining nanofibres.A droplet of polymer solution is electrostatically charged and then a jet is released from its tip using the electrospinning technology [62-65]. Typically, the manufactured nanofibres are woven into a nonwoven mat. Numerous centimetres' worth of nanofibre fragments can be organized and gathered singly [66]. The polymeric solutions were kept in the 0.6 mm tip of plastic syringe. At the very last point of the syringe, the polymeric solution continued forming a pendant droplet [67]. The solution of polymer droplet's jet emitted downwards and was drawn to the horizontally rotating collection disk's pointed frame. Embed the frame two hundred millimetres below the droplet's surface. To generate a more powerful converging electrostatic field, the 200 mm diameter of disk of aluminium had a curved frame with a half angle of 26.60 degree. As a result, a difference in electric potential of approximately 15–40 KV was established across the outermost layer of the liquid drop with the disk that rotates collector.

2.2.7. Centrifugal spinning

Despite its popularity, electrospinning may not be suited for mass-producing of particular substances [68-71] due to its high electric field requirements, solutions in superior dielectric characteristics, minimal production rates and high manufacturing cost. The forcespinning, also known as centrifugal spinning, is a cutting-edge technique for creating nanofibres that has garnered significant attention in recent years [72]. The centrifugal spinning generates force of centrifugation to achieve good synthesis rateof nanofibres [73], as opposed to employing electrostatic force. The nanofibres are able to be produced via centrifugal spinning utilizing solutions of polymers or melts of polymer with no the need for an intense electric field or the limitations imposed by the constant known as the dielectric constant. Additionally, fibers made of ceramic, carbon and metal can be created using centrifugal spinning [74, 75].It is worth noting that Hooper created the centrifugal spinning technique in 1924 to create artificial silk fabric from viscose using centrifugal forces [76]. Consequently, ever since Hooper created this process, it continues to be utilized by the fiber industry. The force of centrifugal rotation with the Laplace force (arising through surface curvature) competes during the fiber creation process in centrifugal spinning [77].The procedure of nanofibre production during centrifugal spin can be broken down into three phases:

- Initiating the jet to drive the solution of polymer stream into the orifice.
- Extending the jets to increase the outermost area of driven polymer stream.
- Evaporating the solvent in order to harden and reduce the polymeric jet.

In the first stage, the polymer is pushed past the nozzle capillaries as a jet due to an interaction of centrifugal as well as hydrostatic pressure within the capillary end exceeding the flow-resistant force of capillary [78]. The polymeric jet is stretched by an outside centrifugal force exerted in a radial direction as it approaches the collecting wall and the jet follows an elliptical path because of rotation-depend on inertia. The circumference of the polymeric extruded jet decreases substantially due to stretching as it travels from the nozzle to the collecting glassware. Meanwhile, the polymer solution's solvent evaporates and the

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polymer crystallizes following jet contracts. The stability of a solvent affects how quickly it evaporates. Fast evaporation promotes fast solidification, which limits the length of the jets for highly volatile solvents [79].

3. DRUG LOADING STRATEGIES FOR NANOFIBRES

The Co-electrospinning involves a form of electrospinning in which a medicament and polymer are both dissolved in the same solvent [80]. Drugs are distributed uniformly across the nanofibrous system; therefore, the loading efficiency is good using this method [81]. The efficiency with which the polymer loads the nanofibres is determined first by the polymer's physicochemical qualities, and then by the polymer's connection to the therapeutic molecules [82]. The rate at which a medicine is released from a nanoparticle could be affected by factors such as the shape of the particle and how the drug is packed inside. Since these natural polymers dissolve entirely in water, they are ideal for use in creating nanofibres filled with hydrophilic medicines [83,84]. The electrospinning procedure is hindered because the nanofibres created in this way collapse upon cross-linking. This may be because the solution has a lower viscosity, however it can be remedied by adding synthetic hydrophilic polymers such as PEO (Polyethylene oxide). This technique for creating nanofibres may end up in a burst releasing effect [85].

4. DELIVERY VIA TRANSDERMAL PATCH

The skin is the body’s biggest organ and its primary defence against harmful environmental factors. The transdermal method's potential as an alternative to the oral route is supported by evidence that medications applied topically enter the systemic circulation. However, the physicochemical as well as pharmacokinetic properties of the medicines have hampered distribution via the transdermal route. TDDS could be engineered to deliver the active chemical or treatment to the epidermal segment of the skin's outermost layer, as well as for widespread absorption through the highly-vascularized epidermal portions [86-87]. Pharmaceuticals with hydrophilic properties are absorbed via the transcellular route, while drugs with hydrophobic properties are absorbed via the intercellular pathway. Water-soluble compounds are thought to travel via the transcellular method, while molecules soluble in lipids are thought to travel via the intercellular route. Both the corneocytes cytoplasm as well as the lipid structure of the stratum corneum are permeable to the substances that are water-soluble. To get past the layer of stratum corneum's indigenous lipid composition, however [88-91] lipid-soluble medicines must take the intercellular pathway.In order to infiltrate the skin, the water-soluble drug molecules may use shunt channels such as sweat ducts, hair follicles, or sebaceous glands. Studies from the past have shown that skin appendages can only inflow less than 0.1% of medications; as a result, developing TDDS cannot be justified as a permeation technique. As a result, it has been suggested that TDDSmostly penetrate through the stratum corneum [92]. There are 4 distinct pathways for transdermal distribution. However, the molecular structure and its affinity for water/oil, that could have an integral part in transdermal administration, are strongly dependent on the adsorption pathway. Therefore, the transport of molecules that are water- as well as fat-soluble is addressed by the intercellular and transcellular routes, respectively. On the other hand, shunt pathways are

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among the best ways for TDDSs, and one of the common pathways for this particular method of skin penetration is through sweat ducts as well as hair follicles.

Percutaneous administration refers to the process by which an active chemical is absorbed via the skin and then distributed throughout the body via the bloodstream. The most important factors in absorption of percutaneous involve the spacing of drug molecules among the tissue as well as carrier and the posterior diffusion of pharmaceuticals through the stratum corneum. Diffusion, driven by the concentration differential that exists between TDDS as well as the skin tissue, is the process causing the dispersion of the TDDS concentration and ensuing skin absorption. Because of such actions, we can create sustained-release mechanisms that can release their payload gradually over a long period of time [93]. The systems have the flexibility to deliver their payload to any of the layers that make up the skin, based on the principal function they serve. Most commonly used techniques for percutaneous absorption include ultrasound [94], micro injection [95], liquid jet injection [96], patches [97], gene gun [98], micro needles [99], because they are unable to penetrate the deeper layers of skin, patches are only effective for a topical application. However, they do have a few advantages and conveniences, such as being cheap, secure, and painless [100]. Because of their dependability and precision, microneedles as well as microinjection are ideal devices for dermal content release [101]. Ultrasound radiation is an established technique in this field because of its ability to disrupt the skin barrier structure and allow medication access; yet sprinkling is an evident fault in this approach [102]. Many precedents have been set for the TDDS beyond the oral route, as was indicated earlier. The most notable advantage that prevents drug metabolization is the first-pass action of the liver during escape. Some negative qualities, such as pain during delivery and the danger of disease distribution, can be avoided with TDDSs as opposed to alternative delivery routes such hypodermic injection. Cost-effectiveness, slow-release properties, individual application, and extended shelf life are further positive aspects. Despite the many advantages of TDDS, several problems still need fixing. Due to its exclusivity to low molecular weight and lipophilic medications with minimal dose needs, TDDS severely restricts the number of pharmaceuticals that can be given. Therefore, it is a huge problem to create novel TDDS to transport hydrophobic medicines [103]. In light of the many benefits associated with TDDS, we have discussed a variety of nanofibrous scaffolds derived from natural sources that have been experimentally tested for use in TDDS. (Figure 2).

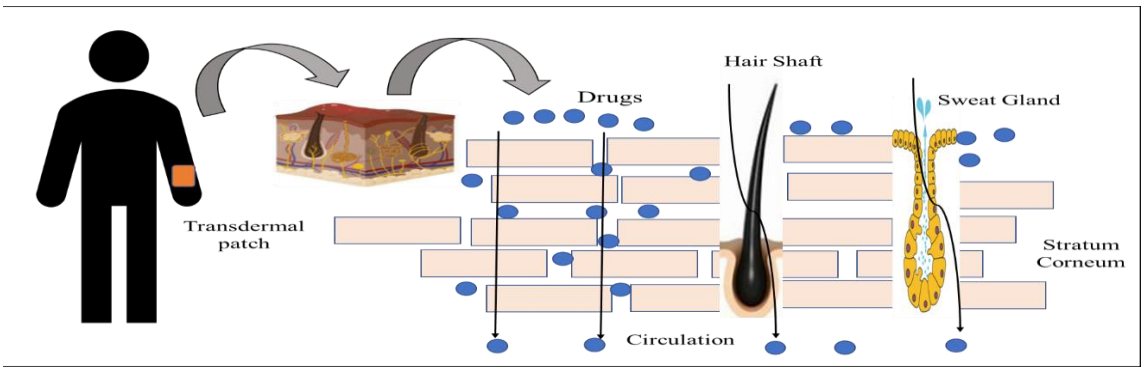

Figure 2: Delivery of nanofibres across the stratum corneum through transdermal patch

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4.1. Nanofibre-based drug delivery system via transdermal route

The medicine must pass through biological barriers regardless of its means of delivery before it may reach the primary site of the infection or the circulatory system. The biological circumstances must be taken into account when targeting certain routes, and as a result, the characteristics of the nanofibres ought to be modified to suit these parameters. The stratum corneum, the topmost layer of the epithelium having porosity that ranges from 250 to 500 m with an average thickness of 20 to 25 m, is used for its porosity in transdermal routes [104,105]. The cell membrane typically influxes non-polar medicines since it is semi-permeable as well as contains endogenous lipid as well as sebum [106]. Because of their high porosity, a large specific surface area, or moisture permeation, nanofibres have shown the capacity to transport hydrophilic medicines in a controlled way as well [107,108]

To improve the transdermal delivery of the allergy medication fluorescein iso-thiocyanate, the team of Gomaa El Fawal (2020) utilized ethosome, a type of phospholipid nano-vesicle.90 PVA/HEC nanofibres were electrosprayed with a PVA solution containing the drug-loaded with ethosome. The amount of medication released via the dorsal skin of the rat became greater when compared to drug released using the same route lacking the ethosome approach (25% in 10 h). The authors chose HEC polymer to improve PVA's adhesive qualities in addition to ethosome. The hydrophilicity was also added to the Alzheimer's medicine donepezil hydrochloride by blending it with hydroxypropyl cellulose [109]. Transdermal delivery has been studied extensively for use in healing wounds and regeneration of the skin.92–94 In addition to facilitating medication release, nanofibres have the unique ability to both anchor damaged cells and guide their subsequent differentiation. Using nanofibres has been shown to lessen scarring because they help keep the bed of the wound moist [110]. In a groundbreaking study published in 2019, PranbeshSasmal et al. created a chitosan/PVA nanofibrous barrier coated with tranexamic acid (an antifibrinolytic medication) to stop bleeding [111]. It was discovered that PVA's increased hydrophilicity accelerated the release of drugs to 90% following 10 hours. Drug administration via transdermal nanofibrous patches is simple, painless, self-administered, and user-friendly [112]. Subcutaneous injections are a common method of administering drugs for both systemic as well as local effects. The form of administration can be lowered to account for local toxicity.

5. NANOFIBRE TRANSDERMAL DELIVERY BASED ON BIOPOLYMERS

Biopolymers are synthetic polymers derived from biological sources. Biopolymers can either be synthesized chemically from biological ingredients or created entirely by live organisms [113]. Biopolymers come in many forms; chitosan, cellulose, hemicellulose, lignin and silk are just a few examples. These biopolymers could prove useful in medication administration because they are biocompatible and biodegradable [114]. Nanocellulose refers to nanoparticles that are typically generated from cellulose. The nano-fibrillated cellulose, microbial nanocellulose, and cellulose with nanocrystalline structure are the three broad groups into which these materials fall [115]. Surface area is increased, chemical alteration is simple, and specific strength is improved in nanocellulose-associated materials. Therefore,

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nanocellulose can be investigated for potential use in a wide range of biological settings [116]. The wound-healing capacity of the extract of coffee impregnated with bacterial cellulose (made from the fungus that grows in kombucha tea) bio-composites was studied by El-Wakil et al. [117]. Highest tensile strength as well as water vapor transfer were observed in bio-composites made from minimal amounts of coffee extract as well as cellulose, while the lowest polyphenol production using-vitro in Phosphate-buffered saline at pH ranges 7.4 was observed. In addition, calcium linked gelatin/sodium alginate nanofibres with integrated cellulose nanocrystals have been created for effective wound healing by Shan et al. [118]. The improved cell attachment and in-vitro low toxicity of the generated nanofibres were observed in mouse embryo fibroblast. Incorporating calcium interconnected with gelatin/sodium alginate nanofibres with cellulose nanocrystals improved the healing of wounds in Sprague Dawley rats via a re-epithelialization process [117].

6. THE ROLE OF NANOMEDICINES IN CARDIOVASCULAR DISORDERS

Among the leading causes of death and disability around the world is cardiovascular disease (CVD). Although there is a wide variety of treatment medicines to choose from in the cardiac cohort, their efficacy has been hampered by poor tissue penetration. Additionally, nanomaterials are not quickly excreted by the kidneys, thus they can stay in circulation for a long time. This property enables for enhanced accumulation and distribution of nanomaterials in the target tissue or organs following extravasation via the circulatory system, allowing for optimum therapeutic efficacy with minimal medication dosage.

6.1. Blood pressure

High BP, often known as hypertension, is the epidemic that ravages the cardiovascular disease population at large. High blood pressure is a crucial contributor to the development of various cardiovascular diseases.133 There are a plethora of medications used in the management of hypertension, but they all have drawbacks, such as inadequate dosage, poor permeability, poor bioavailability, and undesirable side effects [119]. Circadian rhythms in BP mean that nanomedicines with continuous drug release could be useful in managing BP swings [120]. These difficulties may be surmounted if the required drug concentration could be maintained for a longer period of time through the encapsulation of pharmaceuticals into nanocarriers. It has been discovered that conventional (instant release) anti-hypertensive medications can be improved upon by using various systems of nanoparticulate, including lipid-related and polymeric nanoparticles [121]. The therapeutic effect of medications is hampered not only by problems with bioavailability and permeability, but also by the acidic stomach and the basic gut. For instance, candesartan cilexetil's bioavailability decreases in an acidic environment [122]. Currently, the most widely utilized nanomedicines are polymeric nanocarriers coupled to conventional drugs that have been approved by the Food and Drug Administration. Drugs that are sensitive to changes in pH could be delivered using polymeric nanoparticles includingchitosan, PLGA, PCL, PLGA and eudragit [123]. Nisoldipineeudragit S100 which were composed of a polymer, discharged drug through polymer around pH level of colon, potentially avoiding the metabolism of drug in the gastrointestinal tract and the liver [124].Due to the enhanced bioavailability and solubility, felodipine enclosed in PLGA NPs

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demonstrated enhanced antihypertensive properties [125]. Amlodipine, and candesartan and Hydrochlorothiazide three additional regularly used hypertension medications, were additionally conjugated having PLGA NPs with similar outcomes [126]. For effective and regulated drug distribution, several well-established polymers besides PLGA are also being conjugated using antihypertensive medicines. The promise of nanoparticles made of polymers in controlling BP is supported by multiple lines of data. Better blood pressure management and bioavailability were seen using PLA magnetic NPs of aliskiren [127,128]. Nifedipine enclosed in PCL, PLGA, and eudragit nanoparticles was shown to significantly and persistently lower blood pressure in different research by Kim et al. [129] Sustaining elevated and prolonged levels of plasma drugs is the primary benefit of sustained-release anti-hypertensive formulations in the management of BP variations. In addition, the drug dosage for continuous release via drug delivery systems is lower than that for traditional pharmaceuticals. The minimal plasma level of indapamide at 1.5 mg/d with the long-acting formulation was comparable to that at 2.5 mg/d using the standard medication formulation [130]. As a result, nano formulations have significant possibilities for improving safety in the clinic along with patient compliance through decreased doses. Effective trials of liposomal medication formulations in animals as models of hypertension have recently been reported. Systemic blood pressure (BP) has been shown to remain normalized for extended periods of time after a single intravenous injection of a liposomal solution encapsulating vasoactive intestinal peptide (VIP), an established vasodilator as well as immunomodulator [131]. The antihypertensive properties of this liposomal medication can also be delivered effectively when administered subcutaneously or intratracheally [132,133]. A similar increase in bioavailability of drugs and decrease in BP was observed when lercanidipine was encapsulated in liposomes. Hydrophobic reservoir of the cyclodextrins shields the drug from rapid degradation that extends the bioavailability, making cyclodextrin NPs another powerful drug carrier option. Captopril encapsulated in cyclodextrin nanomaterials improved BP significantly, even at low doses, as shown by research by Mariangela et al. [134] Cyclodextrin complexes have recently been found to shield hydrochlorothiazide against fast hydrolysis, hence enhancing the drug's therapeutic properties in a rat model [135]. In addition to the siRNA-associated management of gene expression, nanoparticle related gene silencing is an attractive method for controlling BP. Since endo- and exonucleases are found in the blood as well as cells, siRNA needs a means of delivery to protect it from being degraded [136]. In short, the nanoparticulate method's capacity to bind to anti-hypertensive medications maintains the medication in blood and extends the long-term systemic accessibility of drugs in the ideal level, thereby regulating BP.In short, the nanoparticulate method's capacity to bind to anti-hypertensive medications maintains the medication in blood and extends the long-term systemic accessibility of drugs in the desired concentration, thereby regulating BP.Limited accumulation of lipids was observed in an atherosclerosis associated apolipoprotein E-deficient (ApoE/) heart failure animal model after administration of sugar-associated amphiphilic macromolecules (AMs) synthesized form serum-stable NPs [137]. The aortas of ApoE/ mice have been shown to receive NPs targeted specifically toward lesions caused by atherosclerosis. In the aforementioned mouse model, the aortic arch with carotid ostia bears the greatest weight of plaque.Imaging with fluorescence and associated

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quantitative data indicated that NPs accumulate at their greatest intensity in these aortic regions. According to confocal microscopy, NPs are concentrated at the necrotic centers of plaques.In addition, NPs were observed to be significantly linked with cells encoding vascular cell adhesion proteins. When comparing untreated (ApoE/) and treated (M12PEG) mice, cross-sections of the aorta reveal the existence of plaques having necrotic centers in the former group. After therapy, there was a noticeable decrease in the morphological evidence of arterial occlusion. M12PEG's effectiveness in atherosclerotic disease was further demonstrated by its ability to reduce lipid buildup (Oil Red O), inflammation (COX-2), and neointimal hyperplasia (smooth muscle cell, α-actin) [138]. Due to its suitable particle size, biocompatibility, and targeting ability, SPIO has found use as a contrast booster in magnetic resonance imaging (MRI) [139]. Poly(lactic-co-glycolic acid) (PLGA) and poly-lactic-co-glycolic acid (PLA) nanoparticles are two potential polymeric nanoparticles that have been authorized by the FDA for application in clinical settings as drug delivery vehicles [140]. One of the main focuses of cardiovascular imaging is the early detection of susceptible plaques in asymptomatic individuals. Delivery of FTIC-associated PLGA nanoparticles to atherosclerotic areas is possible, most likely through a rise in permeability within atherosclerotic lesions or mechanistically by phagocytosis by macrophages and monocytes, allowing for imaging-related diagnostics [141]. Plaque rupture was also attenuated by pitavastatin (HMG-CoA reductase inhibitor) encapsulated in PLGA-NPs, which blocked MCP-1/CCR2-mediated monocyte recruitment by decreasing the blood flow of Ly6Chigh monocytes as well as the macrophages infiltration into atherosclerotic lesions [142]. Macrophage recruitment towards the atherosclerotic lesion or arteries was also reduced by liposome-dependent release of siRNA targeting the chemokine receptor CCR2.158 CCR2-silencing siRNA, when given systemically to mice, accumulates in the bone marrow and spleen and was shown to be mostly expressed in monocytes. Reduced levels of CCR2mRNA in monocytes prevented them from congregating at the site of inflammation. Additionally, therapy decreased their prevalence in plaques with atherosclerosis and decreased the extent of infarcts caused by coronary artery blockage [143].

6.2. Ischemia-reperfusion damage to the heart

Myocardial ischemia-reperfusion (IR) damage causes cardiomyocytes to die by necrosis as well as apoptosis. This happens because of high amounts of reactive oxygen compounds and problems with the mitochondria. The main reason why most clinical studies for myocardial IR injury don't work is that there isn't enough delivery of drugs within the treatment time window. In this way, PEGylated liposome-depends upon adenosine delivery protects the heart by giving a higher quantity of adenosine compared to free adenosine in the rat model of ischemic myocardium [144]. In cases like cardiac IR, where inflammation makes blood vessels more permeable, nano medication delivery vehicles build up in the damaged tissue [145]. The nanoparticles made from PLGA show potential for application during myocardial IR injury because they can target both inflammatory cells as well as the heart that has been damaged by ischemia. In a mouse model of ischemic myocardium (myocardium IR), indocyanine green-associated PLGA nanoparticles were gathered only in the ischemic

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myocardial [146]. Among the most current forms, intravenously administered ONO-1301 (Ono Pharmaceuticals, Japan) with nanoparticles demonstrated selective aggregation and greater retention in ischaemic myocardium comparison to other subgroups [147]. The blood flow to the heart muscle got a lot better, and the size of the damaged area got a lot smaller. Also, pro-angiogenic cytokines like the growth factor vascular endothelial as well as angiopoietin-1 were found to be upregulated within the ischemic myocardium. This keeps the dense network of blood vessels and makes it easier for blood to move to the myocardium. Downregulating troponin I and the inflammatory cytokines IL-1β, IL-6, as well as tumor necrosis factor- via ONO-1301 NPs led to better circulation to the heart muscle and a smaller stroke [148].

6.3. Tissue Engineering on Heart Valves

At the moment, biological valves are experiencing some problems, especially in young people, so it is very important to keep coming up with new materials. But there are still problems with heart valve tissue technology. For instance, the valve component possesses three layers that are circular, random, as well as radial, which makes it harder to prepare the materials. Wu et al. [149] believed that a hydrogel system made of methacrylic hyaluronic acid and methacrylate gelatin (Me-Gel) mixed together could mimic the distinctive 3D physiological microenvironment of the extracellular matrix (ECM) that exists in native aortic valve leaflets. Nevertheless, it subsequently emerged that those hydrogel content was lacking a macroscopic anisotropic framework as well as had little capacity to stretch, Researchers made three new collectors to make three layer of nanofibre utilizing these directions compared to biomaterials made of polymers in an electrospinning device [150].

6.4. Cardiac Surgeries

Researchers first made chamber-patches deficient out of medical-grade polyurethane infused with bioactive agents' nanoparticles of chitosan as well as collagen. These patches were then coated with heparin to make the latest generation of biomaterials for closing atrial septal defects [151]. During the recovery period after sternal, cardiac surgery, and epicardial deposits raise the possibility and difficulty of heart reoperation. This is a big problem for individuals who have had cardiac surgery more than once and need to recover. Feng et al. [55] made a bioabsorbable GT/PCL hybrid membrane to stop adhesions in the rabbit model of cardiac surgery and suggested that it could be used as a new pericardial replacement for cardiac surgery**.**

6.5. Vascular Patches

Vascular patches are used in heart surgery, but they have a number of problems, such as calcification, material degeneration, and pseudointimal hypertrophy, which can cause problems with blood flow [152]. Chantawong et al. [32] first used an electrospinning method to make three distinct patches. Many of them were made of silk fibroin (SF) as well as a synthetic material called thermoplastic polyurethane. (TPU). They put each kind of patch (n = 18) into the aorta of the abdomen of rats and looked at the histopathology one, three, and six

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months later. They came to the conclusion that a rise in SF concentration found in SF/PU patches had a good effect on the remodeling of the vascular system. Later, Shimada et al. [153] upon the team substituted part of the dog's decreasing aorta wall with SF/TPU patches over this experiment. Three months later, the patches were taken off for histological analysis. Angiogenesis Caused by Surgery Even though there have been some good successes with the use of tissue engineering, one of the biggest problems is still that tissue-engineered structures don't integrate well with the host's blood vessels in the short term [154]. Surgery-associated angiogenesis seems to be a potential way to enhance vascularization, along with adding endothelial cells [155] and angiogenic growth factors [156]. In 1980, Erol as well as Sira showed that the skin can grow new blood vessels via an arteriovenous fistula. Prolonged interpositional vein grafts may be used to make a venous bed[157].

6.6. Vascular Grafts with a Miniature Diameter

At the moment, non-tissue-engineered transplants for big vessels can be used in clinical settings, but physicians often fail with smaller caliber vascular grafts because thrombosis tends to be easier to form in them. Researchers [158] came up with two improved coaxial electrospinning approaches for achieving vascular compliance. These techniques are meant to avoid thrombosis. In past studies, vascular implantation experiments were only watched for the maximum of three months [43], but Qin et al. [159] evaluated that the time could be up to six months. They all acknowledged that the layer of smooth muscle is important for keeping the mechanical durability and vasoactive responsiveness of the blood vessels.The context of the study, hyaluronic acid was put on quickly vascular grafts that is biodergradable in nature, as well as the results showed that it helps smooth muscle recover. Researchers investigated that the cells of smooth muscles (SMCs) tend to multiply too much and promote restenosis at the end of the procedure of implantation [160]. In order to make an artificial blood vessel that is safe and doesn't get in the way, they made a small-sized artificial circulation vessel with a composite of structure of nanofibre nucleo-capsid using a mix of electrospinning as well as lyophilization. Over the restoration of blood vessels, the inner layer offers mechanical assistance. The shell, which is made of heparin as well as silk fibroin, makes the graft more biocompatible, and the quick dissolution of heparin following transplantation can control the surrounding environment, help vascular cells grow, and stop smooth muscle cells from multiplying. This test on animals demonstrated that the graft stayed healthy for over eight months, which is much longer than the 3 months Wu described [27] used an electrospinning method to make nanofibres out of hyaluronic acid oligosaccharide-altered collagen. This was done to help the endothelialization of transplanted blood vessels and mimic the extracellular matrix. In vitro experiments showed that it helped vascular cells grow and that it stopped blood clots from forming. By using a method that combines 3D printing and electrospinningresearchers[80] put ASC spheres in the alginate-associated structures of scaffolding. Dorati looked into replacing broken peripheral arteries with artificial vessels of blood as a way to manage peripheral arterial occlusive disorder. This demonstrated that the electrospinning method was a good way to get grafts.

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7. PATENTS DESCRIBING THE TRANSDERMAL ADMINISTRATION OF SEVERAL MEDICATIONS USING NANOFIBRES

Nanofibres have great therapeutic promise for treating a variety of aberrant skin diseases, according to a literature review. Transdermal therapies for skin problems may benefit from the investigation of these nanofibrous scaffolds as an improvement over traditional drug delivery technique. Thus, scientists in the pharmaceutical industry are filing patents on methods of using nanofibres for transdermal medication administration. The patents that have been issued in this field are listed in Table 2.

Table 2. List of patents with descriptions for nanofibre based transdermal medication administration

S. No.	Title/ Number of Patent	Description	Author	References
1.	WO2014089650A1	The method of preparation and anti-cellulite efficacy of nanofibres doped by nitrogenated xanthine molecules are described in this patent.	Maria Halena Ambrosio Zanin	[161]
2.	US7235295B2	This patent discusses the manufacture of nanosized hydroxypatites-loaded polyphosphazene-associated nanofibres for use as a wound dressing.	Cato T Laurencin Lakshmi	[162]
3.	WO2007052042A2	The aforementioned patent details the manufacturing process for a multilayered, hollow-fiber transdermal medication delivery device having pores smaller than 100 um.	SemaliPriyanthi Perera	[163]
4.	WO2013144206A1	The preparation technique of electrospun nanofibres for efficient transdermal distribution of an extremely low water-solubility medicinal drug	Jose Antonio Tornero Garcia	[164]

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		is disclosed in this invention.		
5.	CN101390814A	The process of loaded a biodegradable nanofibrous scaffold with a pharmaceutical or cosmetic substance in a concentration range of 0.01-50% is described within this patent.	Gu Zhongze	[165]
6.	KR101080203B1	The present invention details a procedure for preparing a biodegradable polymer-based nanofibrous skin adhesion patches for the therapy of diabetic skin cancer.	Cho Jae Yong	[166]
7.	CN101358383A	This patent reveals a process for creating biodegradable nanofibres laden with lithospermum, which can be utilized for treating skin damage and cancer.	Zhu Limin	[167]
8.	CN101724934B	Ketoprofen is loaded into cellulose acetate nanofibres, which are then used to treat cutaneous inflammatory and discomfort, as described in this innovation.	Zhu Limin	[168]

8. NANOFIBRES FOR TOPICAL DRUG DELIVERY: LIMITATIONS

Polymeric nanofibres have shown promise as a way to deliver drugs through the skin, but there are still many big problems to solve. The research studies that are published in the literature describe the effectiveness of transdermal nanofibres in numerous animal models. It is still hard to figure out the practical effectiveness of nanofibres tested via the transdermal route. Nanofibres will be very expensive and hard to test in the clinic. It will take a lot of guesswork on the part of businesses or government bodies that give money to countries. The second big worry will be about how to make more transdermal nanofibres. Electrospinning is an effective way to make nanofibres by applying a low flow rate of polymeric

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fluid. Electrospinning could go in a certain direction in the future. The primary objective of electrospinning equipment for the cardiovascular cells repair is to make effective biomimetic frameworks for regenerating myocardium as well as vascular tissue while regaining its function, followed by test their biocompatibility as well as particular functionality in vivo [169]. We might try to enhance their mechanical characteristics by combining electrospinning alongside nanofibre hydrogels [170]. There is a need of additionally continue making more 3D-printed supports that can be used as models to help cardiomyocyte infiltration. Electrospinning technique is always getting better, which will help advance the field of heart tissue engineering. For example, melt electrospinning-made sinusoidal fibers have a lot of promise for heart regeneration of tissue [171,172].

Despite the promising results seen in preclinical research investigating cardiac repair using cell-associated nanofibre scaffolding produced using the method of electrospinning [173-175], and despite the fact that cardiac patch treatment currently necessitates surgery to repair the heart, leading to anxiety in the majority of individuals with myocardial infarction, there exist numerous obstacles to overcome before clinical applications [176-177].To create highly functional as well as treatment-based functional engineered cardiac tissue (fECTs), advances in nanofibre scaffold technological advances must be made to address the following challenges:

- Poor porosity prevents the extensive penetration of seed cells.
- While cardiomyocytes develop on a rigid substrate imitating a post-infarct fibrous scar, they ought to lose their beating of synchronized.
- It is challenging to expand the methods that are currently employed [178,179-203].

To improve the function of carotid arteries in rabbits, Kuang et al. implanted composite nanofibrous minor artery grafts made by coupled electrospinning with lyophilization procedures [30] while this group takes into account synchronizing the stent breakdown rate and the frequency at which new tissue is formed over an extendedperiod of time this is still a difficulty [180].

9. CONCLUSION

Nanofibres have been looked at as a way to deliver drugs through the skin because of their substantial loading of drugs, high ratio of surface and volume and resemblance with the extracellular matrix. Choosing the right polymers as well as solvents for electrospinning is important if you want to make a nanofibrous mat. Using various combinations of polymers for electrospinning, you can make a nanofibre that is good for delivering drugs through the skin. Transdermally, a polymeric nanofibrous mat with a healing agent on it can control or slow the dispersion of the agent. Several preclinical studies done by pharmaceutical researchers have demonstrated that transdermal nanofibres could be used as a therapy. But they won't be able to get into the pharmaceutical business until they have developed good technologies for scaling up and done a comprehensive clinical assessment.Another of the biggest factors of death around worldwide is cardiovascular disease (CVD). Electrospinning

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is method to generate nanofibrous technologies to aid in the management of cardiovascular illnesses has received attention over the past few years due to the field's increased emphasis on regeneration medicine, the engineering of tissues, and the creation of new materials. From the standpoint of cardiovascular an operation, this study goes beyond previous reviews by cataloguing the experimental techniques and potential uses of electrospinning equipment paired with nanofibrous materials toward myocardial infarction repair, heart valve replacement, artificial blood vessels, as well as cardiovascular patches. Finally, this study outlines the likely future paths of this technology for applications in cardiovascular illness as well as its constraints and outstanding technical hurdles.

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