Electrospinning – A Novel Approach to Developing Drug Delivery System

By
Name: Peter Singh
ID: 17146043

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Student's Full Name & Signature:

Peter Singh

17146043

Approval

The thesis titled "Electrospinning – A Novel Approach to Developing Drug Delivery System" submitted by Peter Singh (17146043) of Spring 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy.

Examining Committee:

Supervisor

Dr. Md. Abul Kalam Azad
Assistant Professor, School of Pharmacy
Brac University

Academic Coordinator:

Namara Mariam Chowdhury
Lecturer, School of Pharmacy
Brac University

Deputy Chair:

Dr. Hasina Yasmin
Professor, School of Pharmacy
Brac University

Departmental Head:

Professor Dr. Eva Rahman Kabir
Dean, School of Pharmacy
Brac University

Ethics Statement

This study does not involve any human and animal trial.

Abstract

Drug delivery system impacts the mode of administration, release properties, effectiveness, and safety of a medication. Due to some disadvantages of the traditional drug delivery systems, scientists are in search of innovative approaches, e.g., electrospinning, a nanofiber fabrication technique from polymers. Electrospinning allows the combination of drugs and materials of different properties to develop a unique drug delivery system that can implement the desired release properties dynamically resulting in greater specificity in terms of targeting and drug loading which can make a leap in individualized medicine. Thus, electrospinning has proven itself as an innovative and effective candidate to mitigate certain drawbacks of the traditional drug delivery system as well as explore many other outstanding possibilities. In this review, unique features of electrospun fibers for drug delivery, different methods of this technique, it's various implications and future perspectives have been analyzed

Keywords: Drug Delivery System, Electrospinning, Drug Loading, Drug Release, Novel Method.

Dedication

Dedicated to my parents, who have sacrificed their worldly happiness in fulfilling my ones to their best and to my beloved sibling and friends and my project supervisor, Dr. Md. Abul Kalam Azad.

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List of Acronyms

- DDS- Drug Delivery System
- NDDS- New Drug Delivery System
- ECM- Extracellular Matrix
- PLA- Poly-Lactic acid
- PCL- Poly-Caprolactone
- PEG- Poly Ethylene Glycol
- PLGA- Polylactic-Co-Gycolic Acid
- HA- Hyaluronic acid
- PGA- Poly Glycolide
- DC- Direct Current
- AC- Alternate Current
- API- Active Pharmaceutical Ingredient
- TDDS- Transdermal Drug Delivery System
- TDS- Tungsten disulfide
- CAP- Cellulose Acetate Phthalate
- shRNa- Short Harpin RNA

Chapter 1: Introduction

1.1 Drug Delivery System (DDS)

Herbs, roots, and plants were the natural sources that owed to the discovery of elemental medicine. Prior to the mid-nineteenth century, man's aliments were mitigated by pharmaceuticals derived from natural sources. Chloral Hydrate was inaugurated as the foremost synthetic medicine in 1869 (Jones, 2011). From then onwards, science has progressed, and the whole pharmaceutical industry has leaped tenfold. A drug is defined in the area of pharmacology as a chemical substance used in the treatment, cure, prevention, or diagnosis of disease, or used to otherwise improve physical or mental well-being. Drugs often have an impact on either normal or aberrant physiological systems (Hejaz & Karaman, 2015). Typical models of drug administration usually depend on pills, eye drops, ointments, and intravenous solutions. Lately, various novel drug delivery applications have been advanced. A composition or a system that grants the immersion of medicinal material within the body reinforcing the competence and security through overseeing the rate, interval of time, also drug discharge location can be defined as a drug delivery system (DDS). This process comprises the application of the therapeutic drug, the discharge of active ingredients via the product, and the inevitable transmission of active ingredients by biological membranes to the site of action (R. Gupta & Rai, 2020).

Drug Delivery is a particular research field that deals with developing novel substances or carrier structures for safe and effective drug delivery. The most typical drug delivery methods are steady, managed, and targeted drug delivery. Several medications have been administered by several conventional drug delivery dosage forms such as solutions, lotions, mixtures, creams, pastes, ointments, powders, suppositories, injections, injectables, pills, rapid release capsules and tablets, and so on to cure numerous diseases since the development of pharmaceutical application technology. Traditional therapies include drawbacks such as fluctuating plasma concentrations, reduced concentration at the site of service, higher therapy costs, and decreased patient compliance.

The advancement of safety, efficacy, patient comfort, and compliance drug delivery technologies also amend the drug discharge and pharmacokinetic parameters. Intestinal, ophthalmic,

transdermal, pulmonary, intravaginal/intravesical, patch, prodrug, gene therapy, selective drug delivery systems, and other drug delivery methods are available (Lechner, 2015).

The drawbacks of traditional drug delivery processes are settled by the radical advancements of a novel drug delivery system. The method by which a drug is delivered has a significant impact on efficacy. The slow pace on the effectiveness of severe disease treatment has indicated a rising demand for a multidisciplinary technique for the therapeutic distribution of targets in tissue. This increase in interest resulted in novel concepts for regulating medication pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition, and efficacy. Contemporary medicine treats diseases by precisely locating the affected area inside a patient's body and administering drugs to that spot (Devi et al., 2010).

1.2 Electrospinning

Electrospinning is an early technique. Rayleigh in 1897 primarily noticed it which was then researched precisely (Zeleny, 1914). The fundamentals of electrospinning can be traced back to early twentieth-century experiments and patents, e.g., Formahls getting a patent for making artificial thread by electric charge (Langer, 1989). Taylor's ((“Electrically Driven Jets,” 1969)) study on electrically powered jets lay the electrospinning foundations. The word "electrospinning," which has arisen out of “electrostatic spinning," was coined only recently (around 1994), but its roots can be mapped to more than 60 years (Bhardwaj & Kundu, 2010). Formhals has made public a various range of patents that explains a testing environment depicting the manufacture of polymer strands through applying electrical energy (Z. M. Huang et al., 2003). A voltage of 57kv was used for the aforementioned electrospinning and is the first patent on it(Bhardwaj & Kundu, 2010). The process has been developed and patented by Antoin Formhals in 1934 and obtained grants down the line during 1938,1939 and 1940 (Pawlowski et al., 2004). In the recent past within 60 years electropssining and melts have registered around 50 patents (D. Li & Xia, 2004). A simple device was designed by Vonnegut and Newbauer (Kamra & Ahire, 1983) which produced consistent droplets of roughly 0.1 mm in diameter that have been electrified in diameter through electrical atomization. Simons designed and patented a machine that by the use of various electrospinning patterns could fabricate non-woven mats which were very thin and light weighted (Simons, 1966). Baumgarten ((Baumgarten, 1971)) invented a device that had the ability to

fabricate acrylic fibers ranging from 0.05-1.1μm. The spinning method has probably gained greater popularity since the 1980s, and particularly in recent years, because of an increased interest in nanotechnology. This process allows for the manufacturing of very fine fibers or of frameworks that is fibrous having diameters ranging from sub microns to nanometers (Z. M. Huang et al., 2003).

1.3 Benefits of Electrospinning

Following subsequent developments in the past years, the distinguishing features of electrospun fibers and matrices appeared to be the comparatively quick manufacturing technique, an extremely high surface-to-volume ratio of nano- to micrometer-sized fibers (Sill & von Recum, 2008a). The topographical resemblance of electrospun matrices to the extracellular matrix (ECM) was established to be beneficial for tissue engineering and medical implants. Due to having potential for loading drugs within the matrices, it has gained a rising interest. This technology outperforms all others in developing the fibers varying from micrometers to manometers scale. For regulating drug discharge and administering treatment of illness parameters like suitable polymer, methods of electrospinning have a significant role (Liu et al., 2019a).

Many features have made electrospun polymer nanofibers well-known in the sectors of drug delivery and tissue engineering, including reasonably simple drug entrapment at the time of the electrospinning process, the capacity to accomplish high loadings if required, burst control, drug/growth factor activity stability, and preservation, as well as a greater surface area-to-volume proportion (which develops drug release) (Krstić et al., 2017). In the last several decades, polymeric micro/nanostructures have gained a lot of attention as drug delivery devices. By the combination of various materials, multicomponent fibers have obtained novel properties, which has peaked interest in it. Cellular binding and bioavailability can be boosted by incorporating synthetic polymers that have solid processability and mechanical properties with natural polymers. The idea behind the application of micro or nanostructures to distribute drug is that raising the extent of the drug transporter's surface intensifies the rate at which the drug disintegrates (Zamani et al., 2013).

Large surface-area-to-volume proportion, strong interlinked porosity along configurable pore diameter, proficient surface activation, adjustable surface shape, and structural similarities

with extracellular matrix (ECM) these distinct and outstanding features have made the utilization of nanofibers in drug delivery applications (Zamani et al., 2013). Nanofibers came to be thoroughly investigated as medical reservoirs in active drug transport, therapeutic protein distribution, and gene therapy (Sofi et al., 2020). Another explanation to surging curiosity in the synthesis of matrices through electrospinning is their capability for getting packed with drug-delivery-capable materials.

Electrospun polymers have been used to create scaffolds accompanying suitable features concerning certain purposes (tissue regeneration and drug trasport), including natural polymers such as collagen, gelatin, chitosan, silk fibroin, as well as hyaluronic acid to synthetic polymers like poly (lactic acid) (PLA), poly(-caprolactone) (PCL), polyethylene oxide, and copolymers such as poly(l-lactide-co-caprolactone) and poly (lactic-co-glycolic acid) (G. Ma et al., 2011). A drug-loaded nanofibrous membrane can be applied as a topical graft for antibacterial, antifungal, antimicrobial, and anticancer properties therapy or the treatment of skin and wound healing (Zamani et al., 2013). Direct encapsulation of drugs within electrospun fibers is possible through the use of electrospinning along with encapsulation of various kinds of substances ranging from biomacromolecules like protein, DNA to both hydrophobic and hydrophilic drugs. Nanofiber's greater range of surface area, along with their tactile, flexible framework with pores, contributes towards a more effective drug-release mechanism (Luo et al., 2012a).

Diminishing unwanted side effects, a decrease of systemic absorption, and shortening of minimum dosage of drug are also some major advantages by the local delivery of drug-using electrospun fibers. As compared to other types of drug carriers, such as liposomes, hydrogels, and nano/microspheres created using traditional methods, electrospun nanofibers can significantly increase drug-encapsulation performance and minimize burst release by a proper drug-polymer-solvent system or electrospinning technique selection (Zeng et al., 2005a). Furthermore, electrospun fibrous mats will allow molecular drug diffusion inside the medium in contrast with traditional films made using a solution-casting technique (Taepaiboon et al., 2006) When the polymeric substance is disintegrated, the byproduct shouldn't concentrate near insertion location. Membranes obtained through electrospinning can be curtailed to the required shape size, rendering it best suited for more specified clinical application (C. Xie et al., 2010).

1.4 Objectives

- Understanding the different types of electrospinning in relation to Drug Loading and biomedical applications.
- To inspect the capability of electrospun fiber to be a novel drug delivery system
- Comprehending the drug release kinetics and sustainability of electospun fiber over the course of time.
- Analyzing benefits and drawbacks of electrospun fiber in comparison to traditional approaches

Chapter 2: Methodology

2.1 Study Design

The review study has been designed in a manner to focus on answering the following questions:

- What is the implication of drug delivery systems in improving treatment possibilities?
- What are the drawbacks of traditional drug delivery systems?
- What is electrospinning and how can this overcome the common drawbacks of traditional drug delivery devices?
- Why is electrospinning different and what features makes it best for drug delivery applications?
- How can electrospinning be used to incorporate drugs into a delivery system?
- What are the methods used and which mechanism is used for its release and regulation of release?
- Current Applications of the aforementioned method
- Future implications of electrospinning in this field.

2.2 Literature Search

In order to answer the above questions designed for the study a thorough literature research was conducted. A wide range of updated articles were screened on the basis of relevance of the content towards the study and the materials that held more significance towards this study was utilized in this review article. Information from many reliable sources including peer reviewed media, online academic databases, books, journals and magazines was collected. The list of several publications which were carefully researched in the current study is given below:

1. Pubmed
2. Elsevier
3. Wiley

4. Nature
5. Springer Link
6. Science Direct
7. MDPI
8. Dovepress
9. Taylor & Francis Online
10. APL Bioengineering
11. Google Scholar

The keywords that have been used to avail the data are: electrospinning, drug delivery system, types of electrospinning methods, advantages of electrospinning over traditional therapy, drug release mechanism electrospinning, drug incorporation through electrospinning, current applications of electrospinning, drugs electrospun fiber, routes of delivery eletcrospun drug delivery system etc.

Chapter 3: Electrospinning and Electrospun fibers

3.1 The Electrospinning Process

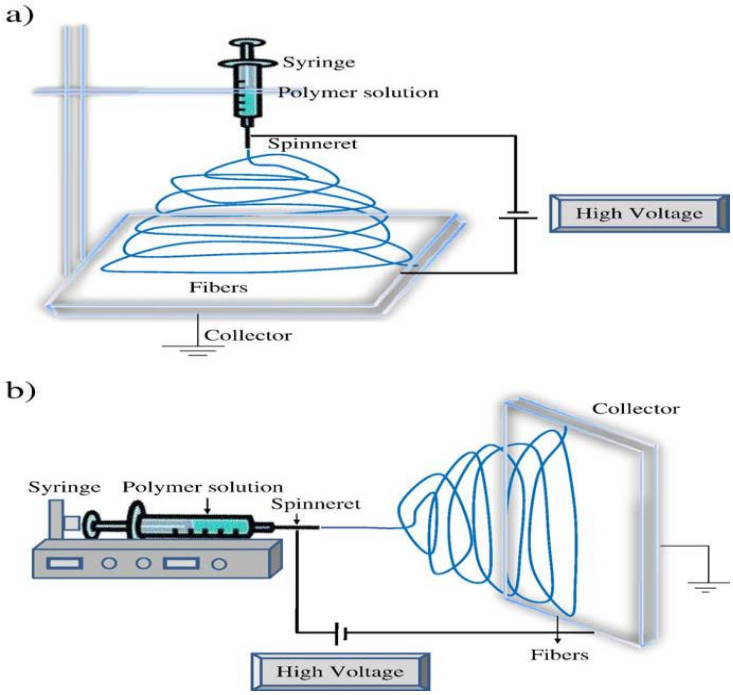

Figure 1: Schematic illustration of electrospinning instrument installation (a) Typical vertical configuration and (b) Horizontal electrospinning device configuration (modified from Bhardwaj & Kundu, 2010)

Electrospinning, a spinning technique employs a rare way through the use of electrostatic powers to develop fibers that can be obtained by the use of polymer solutions or melts. These fibers possess a narrower diameter (ranging between nanometer to micrometer) with a greater surface are in contrast to conventionally processed fibers (Bhardwaj & Kundu, 2010). Fundamentally the process includes three basic components. A very high voltage source (negative/positive polarity) for the purpose of charging the slurry or melt of polymers, a ground collector as well as a spinneret (Figure 1) (Bhattarai et al., 2019). Although direct current (DC) is generally operated for electrospinning, alternating current (AC) potential can also be beneficial (Kessick et al., 2004; Venugopal et al., 2004). It is recommended that the electrospinning process be carried out in an enclosed hood with limited ambient influence, since this acts like a precaution including both the fibers as well as people (Bhattarai et al., 2019). This method principally uses the doctrine that in the charged polymer liquid substantial reciprocal electrostatic repellent forces overwhelm surface tension

forces that are sluggish (Chew et al., 2006). Now, the spinneret is attached to a syringe which contains the polymer solution or melt. The solution can be pumped through the spinneret at a steady and controllable rate using a syringe pump. After the application of a high voltage (ranging from 1-30 kV) the pendent drop of polymer solution present at the nozzle of the spinneret will become exceedingly electrified. The liquid drop is warped in a conical object usually called the Taylor cone under the impact of these electrostatic interactions (Ojha, 2008; Venugopal et al., 2004). If an ample amount of repulsive charge builds up and equals to the surface tension, a Taylor cone starts to materialize in the drop surface of conducting tube. Under the effect of an electric field, the conductive polymer slurry/melt will develop an equilibrium cone shape at an angle of 49.3 (Taylor et al., 1969). The Taylor fiber passes via the atmosphere to the collector slab as well as evaporates the solvent, resulting in a hard accumulation of fibers in the collector slab (Sill & von Recum, 2008b; Taylor et al., 1969). After a small time in the air, the jet becomes unstable and begins to whip, raising the distance between the jet and the collector. Fiber thinning and solvent evaporation are aided by this process.

3.2 Parameters of Electrospinning

The method of electrospinning transpires to be relatively straightforward and remains not requiring bulky equipment (Bhattarai et al., 2019). The process of electro-spinning is controlled exclusively by many parameters, widely categorized in solution parameters, operation parameters as well as the environment. Individually all these parameters have substantial impact on the morphology of the acquired fibers. Through appropriate management of these parameters, intended structure and diameter of the nanofibers can be obtained (Chong et al., 2007). Table 1 summarizes all of the influence owing to various functioning factors on fiber morphology.

Table 1: Parameters of Electrospinning and its Effects (modified from Bhardwaj & Kundu, 2010)

Parameters	**Impact on Fiber Morphology**
Solution Parameters	
Viscosity	Reduced bead production, Greater Fiber diameter, Removal of beads
Polymer Concentration	Higher concentrations enable Higher diameter
Molecular Weight of Polymer	Higher molecular weight causes lower beads and droplets

Conductivity	Higher conductivity renders lower fiber diameter
Surface Tension	Greater Surface Tension causes fluctuation of jets
Processing Parameters	
Applied Voltage	Higher voltage renders lower fiber diameter
Space between Tip and Collector	Minimal distance creates uniform fibers
Flow Rate	Lower flow rate reduces fiber diameter, Excessive flow rates causes bead production
Ambient Parameters	
Humidity	Circular pores are created on the fibers due to greater humidity
Temperature	Fiber diameter is reduced due to higher temperature

3.3 Distinctive Characteristics of Electrospun Fiber

Electrospun nanofibers can distinguish themselves from the traditionally developed 1D nanostructures due to their rare features. For instance, since the electrospun fibers possess high charge during discharge, their trajectory can be regulated through the application of an external electrical field. As a result, various arrangements of the synthesized nanofibers are obtained (D. Li & Xia, 2004)**.** Usually, polymer nanofibres range from some nanometers to over 1μm with special features like exceptionally high surface area for each unit mass, remarkable high porosity, exuberant resilience, economically beneficial and marvelous structural, mechanical properties (D.-G. Yu et al., 2009).

Electrospun fibers are remarkably longer than traditionally manufactured 1D nanostructures (Reneker & Chun, 1996a). These electrospun long fibers can be amassed into three-dimensional non-woven mats as a result of the bending destabilization of spinning nozzle. For instance, these non-woven mats are ideal for simulating the extracellular matrix required for tissue engineering (D. Li & Xia, 2004).

Another intriguing feature of using nanofibers is the ability to change not just their morphology and content but also their surface composition to carry out different operations. Moreover, secondary structures of a nanofiber can be maintained to form nanofibers with core/sheath structures, cavern, and porous arrangements (Chronakis, 2005). Again, due to the entanglement of

fibers, high-density pores can be developed (D. Li & Xia, 2004). Despite having a lower surface area when compared to mesoporous substances like molecular sieves, electrospun non-woven mats possess a larger pore size that forms a three-dimensional network. For this reason, the surface is completely available to various chemical substances (D. Li & Xia, 2004). Furthermore, the nanofibers bear different dimensions at microscopic and macroscopic ranges. The nanofibers have an adequate biodegradability characteristic, and nontoxic degradation products are removed from or merged with the surrounding tissue effectively from the body's implant. The formulations of nanofibers are open and interconnected, enabling efficient interaction with bioactive molecules (Morie et al., 2016). The fiber mat's release properties are heavily determined by the drug's condition and the composition of the polymer that shapes the fiber. The crystallinity of the polymer, for instance, determines the rate of drug release and semi-crystalline polymers have a higher level of burst due to two reasons: on the one hand, the immediate release of the drug embedded at the fiber surface, while on the other hand, the slowed release of the drug from the fiber bulk due to reduced water absorption in the semi-crystalline regions (Kenawy et al., 2002a).

3.4 Polymers for Fabricating Electrospun Fibers

Electrospun fibers have been manufactured using natural and synthetic polymers also using a combination(co-polymer) of the both. Synthetic polymers posse’s significant pliability in terms of synthesis and alteration but have shortcomings in surface cell identification sites. On the other hand, natural polymers (Silk, Chitosan, Collagen, Fibrinogen, Gelatin) show better biocompatibility and less immunogenicity. Some natural polymers also show innate antibacterial characters and greater clinical applications (Hu et al., 2014). More than 200 polymers from many natural polymers have been effectively electrospun and characterized in relation to their use through the past (Bhardwaj & Kundu, 2010).

Chapter 4: Drug Incorporation Methods

4.1 Drug Loading Techniques

Various techniques are used to incorporate pharmaceuticals into electrospun fibers. Because drug loading has a significant impact on drug release profile, selecting the optimum loading method for the particular application is crucial (Nagarajan et al., 2019). Electrospinning is simple and affordable, while providing significant material flexibility, maximum loading capacity and effectiveness of encapsulation, making it ideal for medical and pharmaceutical research There are many other strategies of drug loading in polymeric solutions for electrospinning (Bhattarai et al., 2019).

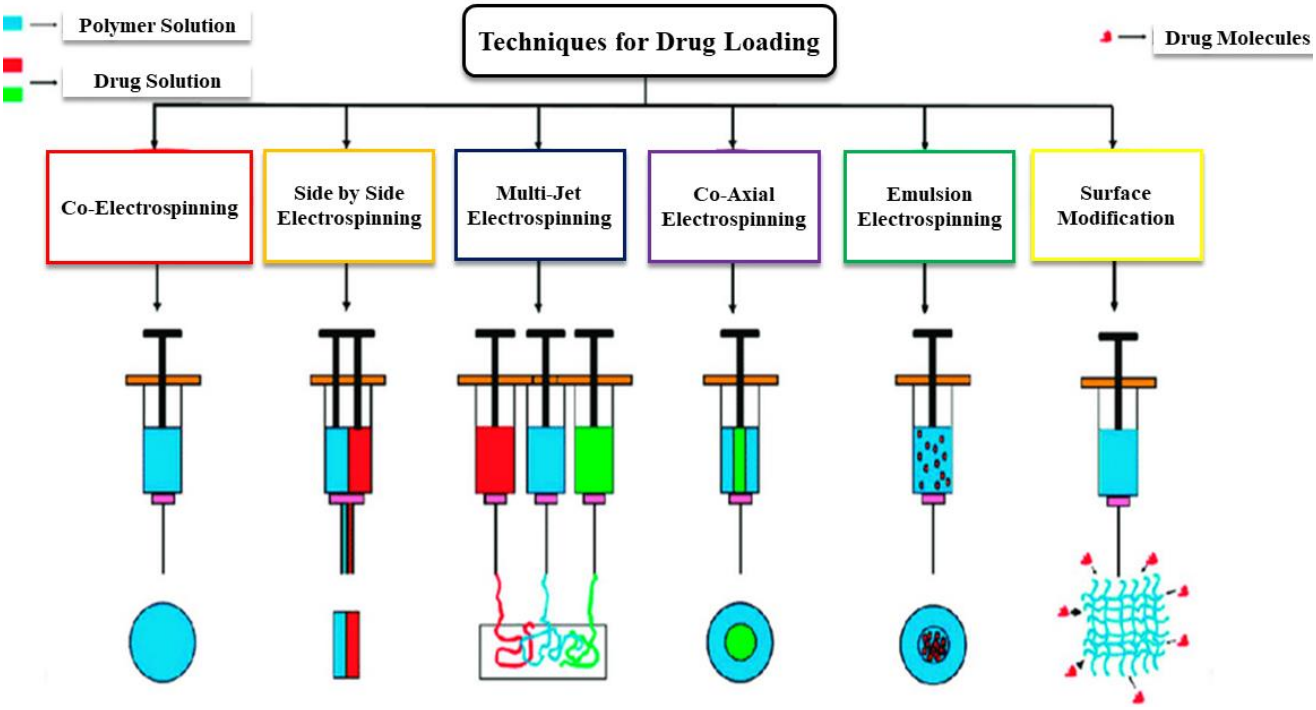

Figure 2: Different Techniques of Loading Drug (modified from Balaji et al., 2015)

4.2 Blending

Blend electrospinning is a common approach for electrospinning where the drug/biomolecules diffuse, distributes or dissolves in a polymer solution, leading to the creation of drug/biomolecules nanofibers throughout the fibers (Steyaert et al., 2012). The majority of the fascination into employing drug/polymer mixtures for the process of electrospinning arose from the promise of

achieving sustained drug release rather than for rapid or a standard burst discharge with post-spinning adsorptive drug loading. Electrospinning of drug/polymer blends with a handheld device, which would replace an additional post-spinning step for drug loading, will also permit for the accumulation of a drug-loaded fiber matrix delivered straight at the site of administration, such as the skin, for dermatic or cosmetic delivery (Meinel et al., 2012). Nevertheless, this approach seems basic also straightforward, the physicochemical parameters regarding the drug alongside the polymer requires careful evaluation since they impact encapsulation effectiveness, drug distribution throughout the fiber, also drug release kinetics. For improved encapsulation, lipophilic drugs (such as paclitaxel) ought to be incorporated in a lipophilic polymer and hydrophilic drugs (such as doxorubicin hydrochloride) inside a hydrophilic polymer. If the drug does not undergo dissolution correctly into the polymer solution, it might be dispersed, leading to an explosion if the drug migrates to the exterior of the fiber (Zeng et al., 2005b). The solubility of the drug inside the polymer solution also affects the distribution of a medication in electrospun fibers as well as the extent of burst release (Meinel et al., 2012). When compared to other approaches, blending has the maximum loading rate. The strength of the polymer-drug interaction, as well as the drug solubility qualities, will determine the release profile. Balancing the hydrophobicity of the medication and the polymer is critical for consistent release across a specific time window(Ye et al., 2019). The first effort to produce pharmacological formulations by electrospinning as described by Kenawy et al. in 2002 is blend electrospinning (Kenawy et al., 2002b). They stated that because electrospun membranes have a greater surface-volume ratio, drug release is possible in electrospun fibers was significantly quicker than in cast films, and that drug release kinetics may be controlled by altering the polymer compositions (Ding et al., 2019). Evidently, mixing is the most straightforward method of achieving medication administration using the process of electrospinning. One disadvantage concerning mix electrospinning is that biomolecules may undergo denaturation inside the presence of strident organic solvents and drug/polymer incompatibility combinations might result in undisciplined release behaviors (Meinel et al., 2012).

Table 2: Electrospun DDS using Blend electrospinning method, as well as the highlights and applications (*modified from* Ding et al., 2019)

Materials	**Drugs**	**Highlights**	**Applications**
PLLA/PEG blend	Papaverine	By adjusting the polymer mix ratios, papaverine can be quickly released in	Preventing vasospasm

		the first 2–7 days and subsequently sustainably released until 14 days.	
PEO/PCL blend	Niclosamide	Over the course of 21 days, 40% of the niclosamide is released gradually.	Cancer therapeutics
PCL/PGC-C18 blend	Cisplatin	Due to the superhydrophobic fiber meshes in the mix, the medication was released in a linear fashion over a period of 90 days.	Antilung cancer recurrence
BPU	Dipyridamole	Sustained drug release time exceeds 91 days due to strong compliance; the greater the drug ratio, the slower the release of the drug.	Vascular grafts
PVA	Antifungal Cm-p1	Burst release in 2 hours, followed by continuous release for up to 3 days.	Infection treated with antifungal medication

4.3 Emulsion Electrospinning

A further possibility that can be done is formation of an electrospinning emulsion, that emulsifies drug/protein solution in the polymer solution. The latter serves being the oil phase also spinning an emulsion like this results in a fiber with a low molecular weight and a well-distributed fiber medication and a core-shell that can sustain a drug with greater molecular weight (Bhattarai et al., 2019). The emulsion droplets are stretched into an elliptical form along the fiber trajectory. Additionally, the continuous phase solvent evaporates quickly, resulting in a viscosity gradient and droplet enrichment in the axial area (McClellan & Landis, 2016). The core material settles within the fiber matrix rather than on the polymer surface due to the viscosity gradient among the polymer matrix and the elliptical droplet. In comparison to co-axial electrospinning, this approach is very easy, and it also provides sustained release of the loaded cargo materials (Luo et al., 2012b). The diameters of nanofibers are significantly affected by the applied voltage. The formation of nanofibers with a smaller diameter occurs as the applied voltage is increased. Other factors like flowrate and spinning distance may further influence fiber arrangement (X. Zhang & Wang, 2012).

The emulsion stability, which is critical for effective biomolecule entrapment, may well be regulated through selecting proper surfactant, emulsification parameters, and various parameters of electrospinning (Nikmaram et al., 2017a). These elements work together to influence the effective spinning and dispersion of a collection of bioactive molecules (either a core–shell structure or a drug distributed arbitrarily placed inside a matrix) (Basar et al., 2017). There are two primary advantages: the first is reduced contact between the bioactive molecule as well as the organic solvent, which enables the utilization of varying configurations of hydrophilic drugs and hydrophobic polymers; and the second one is ease with which rigid core-shell structures can be formed without making utilization of specialized coaxial setup (Luraghi et al., 2021a).

Table 3: Electrospun DDS using Emulsion electrospinning method, as well as the highlights and applications (*modified from* Ding et al., 2019)

Materials	**Drugs**	**Highlights**	**Applications**
PCL **PHBV** **(Oil phase)**	Metformin hydrochloride or Metoprolol tartrate (Water phase)	Effects of polymer layout, surfactants, and drug properties on discharge behaviors were explored; Over a 21-day period, the medication is released at a slower and more consistent rate	Drug delivery System
PS **PVP** **(Oil phase)**	Fluorescein sodium salt (Water phase	Greater humidity cause increase in formation of pores in the fibers, resulting in quicker drug discharge. As the surfactant concentration increases, thick fiber surfaces may develop, as a consequence of which the drug's release is delayed	Drug transport System

Gelatin (Water phase)	Ketoprofen embedded in PCL (Oil phase)	PCL/drug fibers were layered by a cross-linked gelatin through emulsion	Drug Delivery

4.4 Co-Axial/Tri- Axial Electrospinning

Co-axial electrospinning is an upgrade over traditional mix electrospinning in that a pair of nozzles remain coupled towards a high voltage supply instead of one. Two separate solutions are put into individual nozzle as well as pushed exteriorly to produce core-shell structures in nanofibers (Nikmaram et al., 2017b). Core-shell nanofibers with superior physiochemical and biological characteristics may be created using both synthetic and natural polymers. This approach is superior to the mix electrospinning approach in that it can preserve and overcome decomposition of drugs/biomolecules among the biological system (Kai et al., 2015). As previously stated, the coaxial technique's applicability necessitates a special equipment as well as optimizing time However, it isn't only providing a way for endless polymer blend for the core and shell, but it may also serve as a flexible foundation for drug bundling in several sections of the fiber (Luraghi et al., 2021a). Moreover, some drug solutions that are not spinnable might be put to use with regard to co-axial electrospinning, allowing for incredibly high drug loading towards the center region regardless of drug solute solubility and viscosity (Sedghi & Shaabani, 2016). Growth factors, nucleic acids, and living organisms, among other chemicals and bioactive agents for drug delivery and tissue engineering, can be introduced into the core section without losing their functionalities (H. Jiang et al., 2014). When centrally positioned bioactive chemicals are insulated from the shell polymer, they may be made available via nano-path diffusion and/or shell polymer breakdown. As a result, by altering the composition of shell polymers, it is possible to induce prolonged or sequential release of several medicines (Sperling et al., 2016). Furthermore, the release timing may be easily modified by modifying the fiber surface roughness and shell width (relative to the feeding rate of the outer and inner solution).

Table 4: Electrospun DDS using Co- Axial electrospinning method, as well as the highlights and applications, (modified from Ding et al., 2019)

Materials (Shell)	**Drugs (Core)**	**Highlights**	**Applications**

ES100	Diclofenac sodium phospholipids	Dual phased drug release through pH-receptive mechanism; first, the ES100 shell was immersed in acid (pH 1.0, 2.1 percent drug release occurred within 2 hours) The drug was progressively released by the drug phospholipids at pH 7.0, reaching 79 percent after 22 hours.	Drug delivery aimed at Oral colon
ES100	Gd (DTPA)-loaded PEO and indomethacin	The colon received both therapeutic and imaging chemicals at the same time. Indomethacin exhibited a just under ten percent discharge at pH 1 plus a 29-hour continuous release at pH 7.4.	Oral drug delivery
PCL/ nanogels	Methyl orange loaded PEO /DOX-loaded PEO	The bulging and contracting of heat sensitive nanogels (LCST 32 °C) in the shell might form crevices as a drug diffusion pathway, allowing drug release to be controlled in reaction to temperature.	Drug delivery system
Ethyl cellulose	Ethyl cellulose / ketoprofen	Tri-axial electrospinning was used to create fibers with drug distribution gradients. Linear drug release over 20 h.	Drug Delivery Systems

4.5 Surface Modification

Surface modification is a procedure that involves binding or conjugating the therapeutic agent to the fiber surface in order to create it structurally and biochemically equivalent to the tissue. The drug release will be attenuated in this instance, and the biomolecules' functioning will be preserved (F et al., 2012). This method will reduce burst and short-term release, making it ideal for gradual and extended gene transportation along with growth factors. Incorporating DNA, growth factors,

also enzymes coupled through fibers retain the biological action and functioning. Surface modification of blended electrospun fibers can also be used to modulate medication release (Bhattarai et al., 2019). Drugs that must be endocytosed or interact with the cell nucleus, on the other hand, is not able to be incapacitated through this manner. In this case circumstances, the rate at which an immobilized target is released the molecules might be accurately regulated by sensing local environmental stimuli with responsive materials (Kim & Yoo, 2010). Surface modification of nanofibers using a range of chemical substances is possible for adjusting drug-discharge patterns between drug-blended along with drug immobilization. Nanofiber surfaces fluorination, for example, caused regulated drug release rate by adding hydrophobic functional groups over the surface of fibers (Im et al., 2010a).

4.6 Multiple technique Combination

Combinations of two or three drug-loading techniques have been used often since in the complicated in vivo environment, a single Drug Delivery System cannot fully fulfill the role and cannot meet the requirements. rising need of distribution as well as accurate release of the multidrug in a multiple-staged or sequential way. Table 5 shows numerous examples of multi-drug delivery using two or more electrospinning techniques (Ding et al., 2019).

Table 5: Electrospun DDS using Combined electrospinning method, as well as the highlights and applications, (*modified from* Ding et al., 2019)

Materials (Shell)	**Drugs (Core)**	**Highlights**	**Applications**
Cross-linked gelatin (shell)	DOX-loaded FA embellished micelles and PVA blend (core)	Mixing with co-axial electrospinning of a drug loaded micellar system. DOX bursts were released at 20 hours and more than 80% at 288 hours. Gelatin shell and micelles caused delayed release of DOX	Cancer therapy
PLGA	Paclitaxel along with Brefeldin loaded	Dual-drug release via micelles using blend electrospinning; burst	Cancer treatment

	polymer micelles	release of paclitaxel (60%) and extended release of Brefeldin A (20%) in the first 96 hours.	
PLGA	Rg3, PEG-NH2, RGD and bFGF	Surface functionalization and blend electrospinning are combined. Rg3 sustained release for 40 days;	Wound recovery

4.7 Comparison of Various Electrospun Technologies

The diverse methods of electrospinning influence fiber morphologies and nanostructures and contribute significantly to DDSs (Liu et al., 2019b). As previously mentioned, a wide range of electrospun scaffolds containing a variety of active substances may be easily created by selecting appropriate materials and methods. The resulting drug-laden designs allow vast differences in physical architecture, degree of drug loading, drug release pattern, plus eventual treatment benefits, possibly meeting numerous clinical demands (Ding et al., 2019).

Table 6: The Benefits, Drawbacks, and Potential Drug Release Characteristics of various Drug Integration Strategies, (*modified from* Ding et al., 2019)

Techniques	**Benefits**	**Drawbacks**	**Release Trends**
Surface Modification	Preventing toxic biomolecular solvents; Maintenance of the original matrix physical characteristics or deterioration;	Long-term releasing necessitates the use of a cross-linker.	In the case of poor bonding, rapid and burst release is possible. In the event of strong covalent bonding, there is a possibility of long-term release.
Blend Electrospinning	A straightforward one-step procedure	Drug denaturation is a possibility in the strong organic solvent.	As the event of an incompatible drug-polymer interaction, the

		Drug delivery that is uncontrollable	drug is released in burst manner. Sustained release in the event of a suitable drug-polymer interaction.
Co/tri-axial Electrospinning	Optimal for constructing a core–shell construction. Trapping water-soluble or delicate medicines inside core is a possibility. It is possible to employ a non-spinnable medication solution; It is possible to achieve dual-drug release;	Configuration of complex spinnerets Inadequate interfacial interactions may lead to breakdown of the core–shell structure.	In the event of a hydrophilic and rapidly degradable shell, rapid and burst release is possible. Sustained release in the case of a hydrophobic, slow-degrading shell;
Emulsion Electrospinning	Single one-step approach for core–shell structure;	Surfactants and other emulsification parameters must be appropriately tuned to ensure emulsion stability.	Similar trends to co-axial electrospinning
Combinational Electrospinning	Appropriate for multiple-drug release; integration with other stimulus sensitive carriers is feasible.	Difficult Procedure	It is possible to achieve multi-drug and multi-stage drug release.

4.8 Kinetics of Drug Release

An appropriate drug release curve originating through the polymeric scaffold is required for treatment concerning a certain illness. Knowing the release kinetics enables for simple adjustment of the required behavior by selecting from the various fiber manufacturing processes (Pant et al., 2019). When medications are discharged through fibers, they undergo a series mechanism of

segmentation and diffusion inside the fibers, followed by dissolution in media (Ding et al., 2019). Because the typical drug diffusion route remains consistent in fibers that don't-degrade, the drug release rate is primarily determined by the rate of water diffusion towards the matrix, the rate of drug diffusion out of the matrix, along with rate of drug dissolution inside the medium. Nevertheless, because moderate diffusion route changes with time, the polymer degradation rate is also important in degradable polymer fibers (Munj et al., 2017). Specifically, during the production of electrospun DDS, a variety of parameters pertaining to the build, matrix material, and pharmaceuticals might influence the aforesaid two-way diffusive process, hence impacting drug release behavior (Ding et al., 2019).

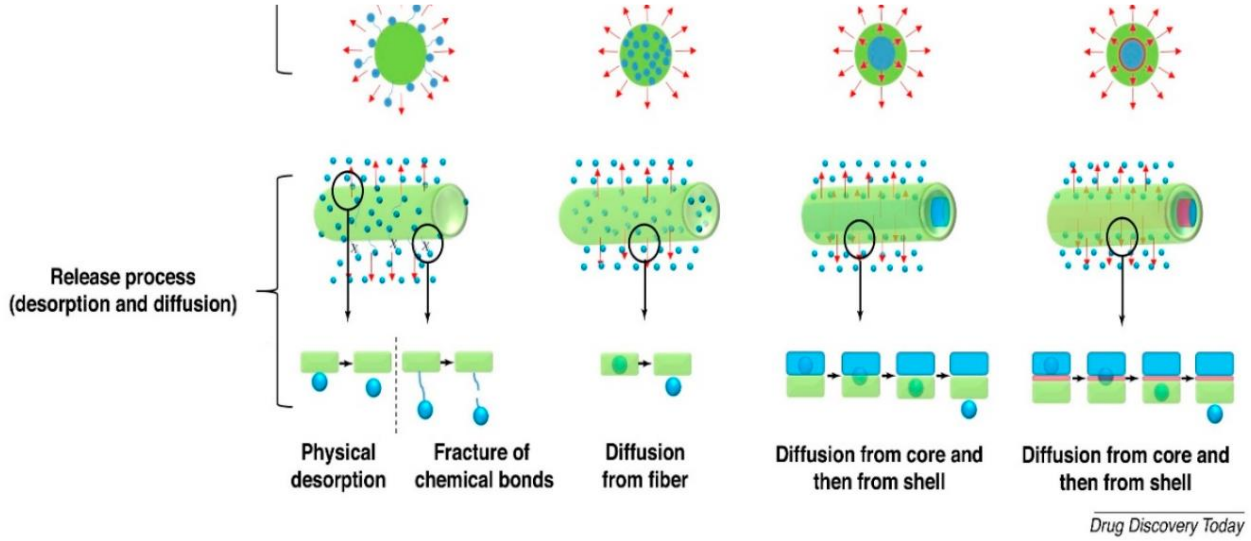

Figure 3: Drug loading and Release (Desorption and Diffusion) from Polymeric Nanofibers (modified from Q et al., 2017)

The release profiles are highly influenced by different methods, morphology and drug loading. For instance, various medications were employed in various polymers to develop a tri-layered structure to be used in the therapy of breast cancer (X. Li et al., 2020). The researchers had established timed release of several chemotherapeutic drugs with a synergistic impact by utilizing diverse drug-polymer combinations. Blended fibers are the most basic nanofibers produced by electrospinning. In this situation, drug release is highly influenced by the extent to which the drug is encapsulated within the polymeric matrix as well as the drug-polymer attraction (Luraghi et al., 2021a).

Table 7: Use of several Drug incorporation techniques at different field(*adapted from* Nangare et al., 2020)

Polymers	**Drug**	**Procedure**	**Field of Operation**
PCL/SLS	Doxorubicin	Emulsion Electrospinning	Cancer therapy
PLGA	Paclitaxel	Blending	Cancer therapy
PLA/ PEVA	Tetracycline	Blending	Antibiotic
PLLA	Lidocaine/Mupirocin	Dual spinneret electrospinning	Antibiotic
PCL/ PTMC	Shikonin	Blending	Antibacterial
PCL	Ascorbylpalmitate	Blending	Antibacterial/Antibiotic
PLLA	Rifampin	Blending	Antibiotic
PCL, Span 60, SLS	Doxycycline	Emulsion Electrospinning	Antibiotic
PCL	Resveratrol/gentamycin	Coaxial electrospinning	Antibiotic
PLGA/PEG-b-PLA	Cefoxitin	Blending	Antibiotic
PCL	Metronidazole	Blending	Periodontal diseases
PVA	Ciprofloxacin	Blending	Antibiotic
PLGA	Nifedipine	Blending	Anti-hypertensive
PLLA/PLCL/PLGA	Captopril	Blending	Anti-hypertensive
ERS/ES	Indomethacin	Blending	Colonic drug delivery
PVP	Ketoprofen	Blending	Anti-inflammatory
PCL	Cilostazol	Direct Blending	Anticoagulant
CAP	Tenofovir	Blending	Antiviral
PVA	Tenofovir	Electrospinning without Nozzle	Antiviral

Chapter 5: Drug Delivery Via Electrospinning

5.1 Drug Delivery via Various Routes

Drug-eluting implant, electrospun fibers have innate benefits over traditional scaled down drug vehicles for greater drug loading and greater encapsulation ability and thus can be referred as a novel drug administration technique by oral, transdermal, or oral routes (Ding et al., 2019). Most traditional medications are hydrophobic and have poor bioavailability, solubility, and stability in biological systems. Furthermore, these medications lack the required capablity of active targeting that might induce general systemic repercussion or quicker clearance through the human body while failing to achieve the intended therapeutic efficacy (Shahriar et al., 2019). Drug Delivery Systems are methodologies, formulations, and systems that allow the transfer of therapeutic agents to the body's designated therapeutic location (Potrč et al., 2015). Moreover, the target medication is encapsulated along with the adjusting of absorption, distribution, release as well as elimination

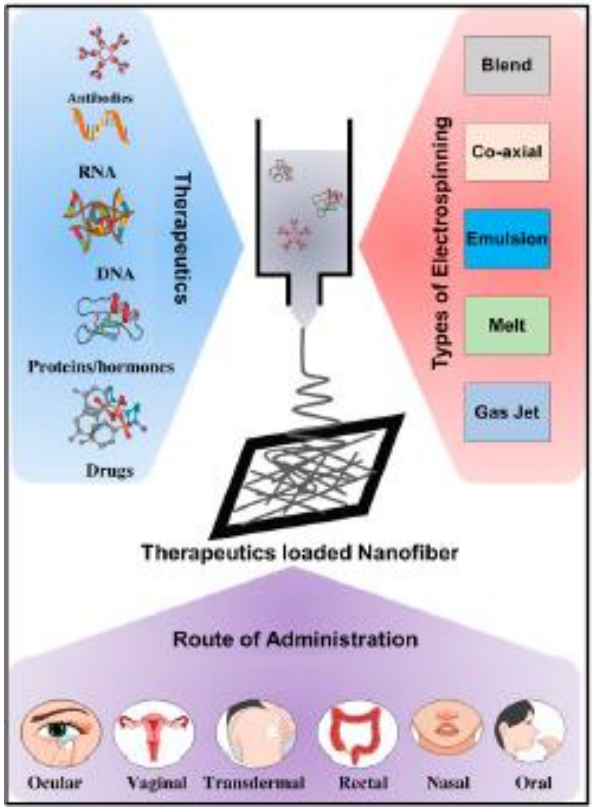

Figure 4: Various Nanofibers loaded for therapy and their Administration Routes (adapted from Shahriar et al., 2019)

at greater loading effectiveness also security. Drug discharge originating through the Drug Delivery System relies within diffusion, degradation, swelling also affinity-based processes (Fu & Recum, n.d.). Electrospun nanofibers are gaining popularity as potential medicinal nanocarriers. Furthermore, their remarkable properties, such as biocompatibility, biodegradability, and greater drug payload capacity match the requirements for a suitable therapeutic delivery candidate (Xue et al., 2017). Using electrospun nanofibers, therapeutics may undergo administration to each and every region/organ in the body by typical routes including oral, parenteral (subcutaneous, intramuscular, intravenous, and intrathecal), sublingual/buccal, rectal, vaginal, and intravenous. ophthalmic, nasal, inhalation, also transdermal (Figure 4) (Mohammad Karim Haidar, 2017). The usual routes of administration by electrospun fibers are discussed below.

5.1.1 Delivery of Drugs Via Oral Mucosa

The oral route has been regarded as perhaps the most desirable yet practical way of administration, capable of overcoming issues linked with alternative administration routes (Jager et al., 2018). For obtaining fruitful administration of medicines aiming the oral route of administration is a strenuous affair. Before developing a successful oral delivery system, scientists must recognize the major key challenges, such as the acidic nature of gastric juice in the stomach, as well as proteases, mucosal barriers, and intestinal retention, all of which can impede drug delivery system absorption into the body (Caffarel-Salvador et al., 2017). Electrospun nanofiber scaffolds grant an immense chance to load also conveys both of micro as well as macromolecules marking the oral route

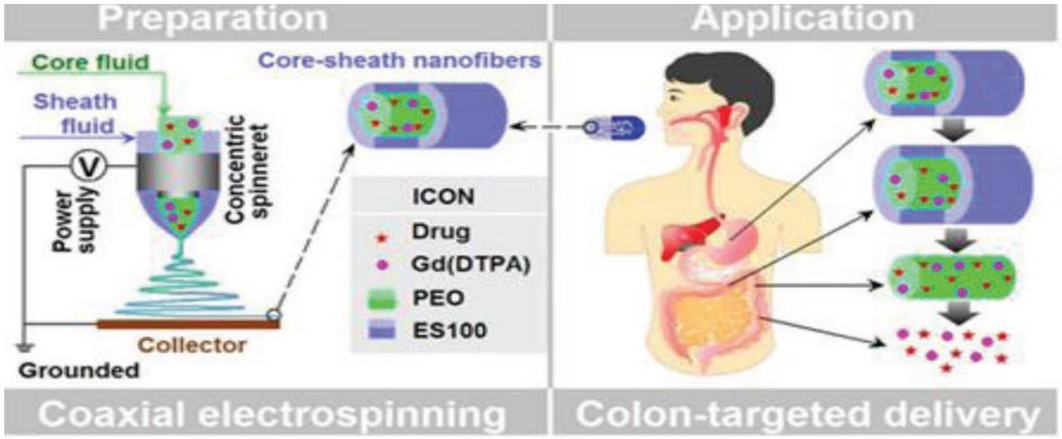

Figure 5:Oral formulation of lecithin diclofenac sodium/ES100 core–shell fibers for colon-targeted drug delivery. The proposed drug release mechanism is sensitive to neutral and acidic environments (adapted from Ding et al., 2019)

(Moroz et al., 2016). Targeted therapeutic delivery, prolonged release capabilities, greater transfection effectiveness, quick start of activity, also intriguing pharmacokinetic profiles are among the most frequent aspects in oral drug delivery systems through electrospun nanofiber. Another appealing benefit of employing electrospun nanofibers would be that scientists may create any palatable release features including quick release, controlled, biphasic or delayed releases of the drug (Shahriar et al., 2019). Highly porous and fibrous membranes having continuous fibers can be developed by electrospinning processes. Electrospun fibers' highly interconnected porosity structure leads to quicker moderate penetration, which results in quicker hydrophilic polymer dissolution or disintegration. Furthermore, the nanosize element implies that drug substances are effectively dispersed over the polymer matrix, resulting in a significant improvement in drug solubility (Williams et al., 2012).

These unique characteristics allow the electrospun fibers to be a suitable candidate for Floating drug delivery system (FDDDS) in the delivery of bitter drugs in oral cavity. Electrospun PVP/ Cyclodextrin (CD) fibers were studied for transporting Meloxican inside the oral cavity, the investigation displayed better taste concealing formulation that were noncytotoxic and physical stability of 6 months which when tested in replicated moisture environment disintegrated in one minute. It is to be noted that the formulation also had quicker disintegration time than commercial tablet and casting film (Samprasit et al., 2015).

To produce colon-targeted release, electrospun membrane can also be employed in oral formulations (Ding et al., 2019). Co-axial electrospinning was employed to encapsulate lecithin diclofenac sodium (phospholipids PL-DS) inside ES100 fibers to develop a pH-responsive drug transporter. The outer ES100 coat shielded the centrally situated drug from the acidic stomach juice and only began to breakdown inside neutral pH conditions while the drug carriers reached the colon. Following that, when the Diclofenac Sodium-loaded lipids had undergone transformation towards sub-micron sized particles, partial Diclofenac Sodium became liberated, and additional DS was constantly discharged through the lipid particles. Ex vivo permeation experiments revealed that fiber dose had much higher intestinal membrane penetration potential than free drug (C. Yang et al., 2016).

Transmucosal drug delivery systems have furthermore been studied in animal models as well as pre-clinical human research (Fig: 5). A study demonstrated loading of clobestol-17-propionate into

a mixed nanofiber of polyvinyl pyrrolidone also Eudragit® RS100 through electrospinning (Colley et al., 2018). These nanofibers have been used to treat chronic inflammatory disorders concerning the oral mucosa, including recurrent aphthous stomatitis, which is distinguished through erosive as well as painful lesions. The medication was delivered inside a sustained way when the nanofiber scaffolds were applied to an ex-vivo porcine oral mucosa model. Furthermore, the nanofiber patches stayed adhered without inflicting any harm to the mucosal tissue. These nanofibers have been used to treat chronic inflammatory disorders concerning the oral mucosa, such as recurrent aphthous stomatitis, which is defined via erosive also stinging lesions. Clobestol-17-propionate nanofiber patches adhered effectively to gingival and buccal mucosa along with tongue epithelium in human volunteers, with a documented residence period of up to 120 minutes. Most human subjects said the patches were either satisfactory or had no flavor (Sofi et al., 2020).

Electrospinning nanofiber, Eudragit® L and S, were employed to cure oral mucositis oral mucosal inflammation which is an unpleasant side effect of radiation or chemotherapy(Reda et al., 2017). The topical anti-inflammatory anti-steroid medicine ketoprofen has demonstrated potential effectiveness in the treatment of oral mucositis and the distribution by means of electrospun nanofibers has been studied through buccal cavity administration. In the pre-clinical assessment of the mentioned nanofibers inside the Rabbit Cheek pouch model the severity of mucositis was significantly reduced within six days of therapy. Histopathological results were also supported (Sofi et al., 2020).

For delivering tetracycline and triamcinolone by oral mucosal administration bioadhesive chitosan nanofibers were synthesized (Behbood et al., 2018).

5.1.2 Sublingual Drug Delivery

The oral mucosa is divided into three main areas: buccal, sublingual, and gingival. The scientists were equally intrigued in developing drug delivery devices through nano-fibers for sublingual (under the tongue) or buccal (between the gums and teeth) administration routes. Sublingual /buccal delivery methods often grant drug-loaded electrospun nanofibers for the breakdown inside the presence of mucus, allowing the medication to enter tiny blood arteries directly. Surprisingly, those oromucosal modes of administration have been the most common researched for nanofiber-

based treatments, providing diverse and multifunctional drug, DNA, RNA, protein, peptide, growth factor, as well as vaccine delivery platforms (Nanomed et al., 2017).

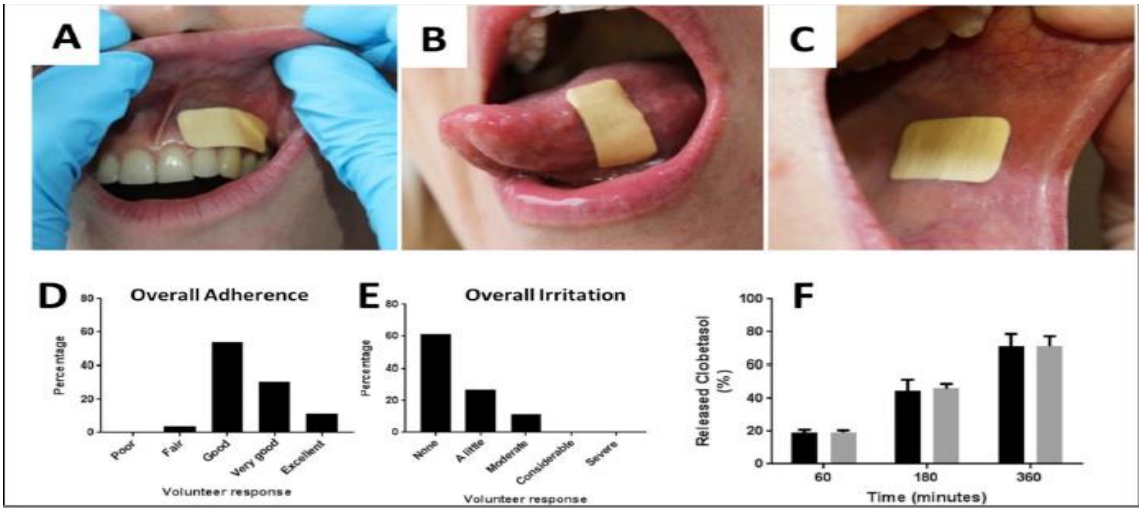

Figure 6: Administration of clobestol-17-propionate nanofiber patches (A) gingival mucosa, (B) tongue epithelium and (C) buccal mucosa. Overall Adherence (D), Irritation (E), Drug Release pattern (F) Release, (adapted from Colley et al., 2018)

Instead of Floating Drug Delivery System, oral formulations have furthermore been studied to provide sustained drug discharge through the sublingual route. This is a non-invasive method of administration method that is ideal for pharmaceuticals that must be continually absorbed into the bloodstream (Shahriar et al., 2019). An antidiabetic patch was developed through electrospinning, insulin – loaded PVA/ Sodium Alginate (NaAlg) blend fiber. This was expected to be taken in through the oral mucosa after being delivered sublingually. The in vivo trials were carried out by placing the patch underneath the tongue of a diabetic rat. The diabetic male Wistar rats' blood glucose concentrations were dramatically lowered as a result, and the impact lasted for 10 hours. (A. Sharma et al., 2013a).

In the event of angina pectoris, a medical emergency caused by coronary heart disease that results in a decreased amount of oxygenated blood fast onset of drug activity is a must (Thadani et al., 1982). Pharmacological intervention of this aliment is the instant administration of vasodilator medication. An essential type of these drugs is Potassium channel openers such as Nicorandil (Sofi et al., 2020). Many drug delivery methods have been tried in order to distribute this medicine and overcome the difficulties connected with it, such as delayed beginning of action, mucosal ulceration, and poor storage stability (Abdelbary & Tadros, 2008). A research was carried on the

synthesis of biocompatible nanofibers blended with Nicorandil with hyaluronic acid, poly (vinyl alcohol) and vitamin B12 (Journal et al., 2015). In terms of morphology, the manufactured nanofibers were found to be homogeneous, non-woven, and bead-free. The permeability of the medication from this nanofiber composite through goat mucosa indicated long-term retention of the carrier system at its absorption window, with 71% of the drug released after 9 hours. When compared to a commercial formulation, the pharmacokinetic investigation using test patches applied to the sublingual portion of the oral cavity (in Wistar rats) revealed the therapeutic efficiency of this preparation (Sofi et al., 2020).

For migraine therapy, a combination of sumatriptan and naproxen is often used (Vrbata et al., 2013a). Traditional dosage forms like tablets have innate drawbacks of low bioavailability although nasal sprays of sumatriptan are present in the market for quicker actions. The liquid sprays delivered in the nostrils clear out causing in loss of dose. Sublingual mucosal delivery of both medicines integrated in nanofibers has a number of potential benefits, including rapid onset and mitigation of first-pass metabolism. For assessing this the drugs were blended into chitosan/poly(vinyl) alcohol nanofiber where β-cyclodextrin was employed as a crosslinker (Vrbata et al., 2013a). During in-vitro investigations, the release of both medicines from the nanofiber membranes was fast and independent of one another. Sublingual drug permeation from nanofibers was investigated using porcine buccal mucosa, and it was discovered that both drug moieties penetrated preferentially as non-ionized moieties. The disadvantages of such a system include the availability of a tiny mucosal surface, saliva flushing effect, and administration/application problems (Sofi et al., 2020).

5.1.3 Transdermal Drug Delivery

Transdermal drug delivery (TDS) distributes a drug locally that bypasses unwanted drug dissemination and has admirable skin permeability (Shahriar et al., 2019). This delivery system has various benefits over hypodermic injections like easy ease of access because to the increased skin surface, less invasive surgeries and averts first pass metabolism (Prausnitz & Langer, 2008). Because stratum corneum is the skin's outer layer, it is accountable for poor medication absorption as well as just a tiny quantity of medications may permeate the skin. Long-term medication release may be easily produced by putting suitable drug carriers to the skin (Goyal et al., 2016). Electrsospun fibers can be advanced into Transdermal Drug Delivery System (TDDS) for its

greater solubility morphology and sustained drug release. Electrospun nanofibers can heighten solubility and create a drug using a transdermal patch for biopharmaceutics category systems II with immense therapeutic competency and has shown no cytotoxicity. The opportunity to use drug loaded electrospun nanofibers have been studied both in vitro and in vivo tests where hydrophilic polymers with greater permeation is suitable for TDDS (Kamble et al., 2016). More research has been conducted to investigate the possibility of electrospun fibers made by various polymers as transdermal patches, such as PVP, PVA/chitosan, PU/cellulose, and PVA/Alginate (Ding et al., 2019).

Daidzein-loaded lipids were incorporated successfully into electrospun PLGA nanofibers as transdermal patches to aid the issues with inadequate oral absorption and finite bioavailability of daidzein to mitigate cardiovascular as well as cerebrovascular disease (Song et al., 2016). Azone, a skin permeation enhancer, was additionally mixed into the PLGA matrix to increase the rate of drug diffusion by engaging with the stratum corneum's structured lipids. In vitro drug release and skin permeation experiments revealed that fiber-released daidzein permeated the skin barrier 3.8 times more than pure daidzein solution (Ding et al., 2019).

Another skin condition Psoriasis, a chronic autoimmune systemic disease distinguished by squamous lesions, searing pain, and bleeding of the inflamed skin. The elbows, knees, scalp, and lower back are the most commonly affected areas by Psoriasis (Sofi et al., 2020). A novel drug delivery with the help of electrospinning has been studied by consolidating salicylic acid, methyl salicylate and capsaicin with previously commercialized poly (methyl vinyl ether-*alt*maleic ethyl monoester) fiber (Martínez-Ortega et al., 2019). These nanofibers were investigated in human volunteers in order to determine the stability and reactivity of topically given electrospun nanofibers. The outcomes were compared to adhesive dressings. After more than 6 hours after application, it was discovered that these nano-dressings released the medicine via breakdown of the nanostructure. (Figure- 7) (Sofi et al., 2020).

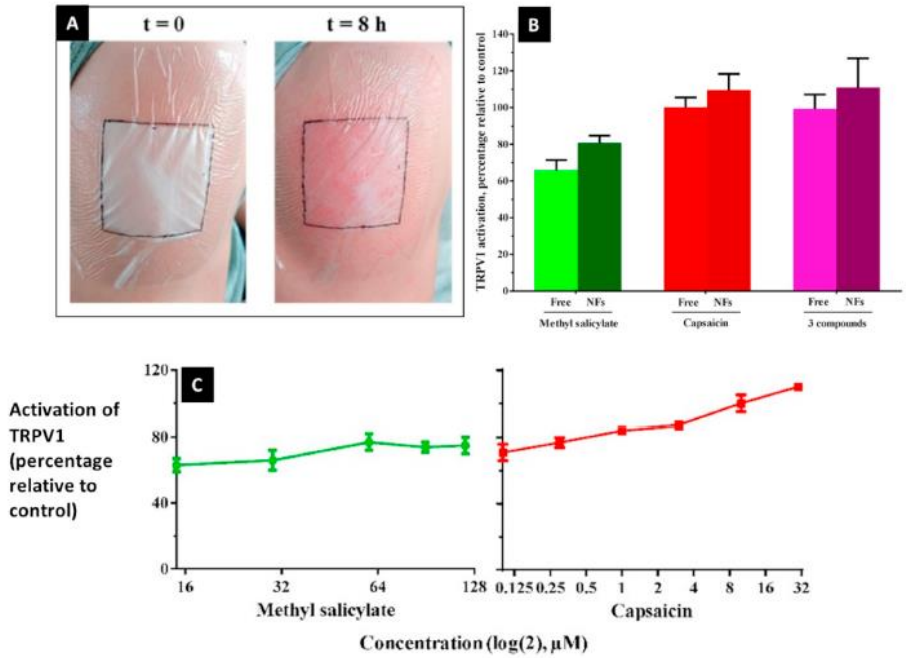

Figure 7: Application of Transdermal Patches to treat Psoraisis. Activation and effects of Capsiacin, Methyl Saicylate and Salicylic Acid, (modified from Sofi et al., 2020)

5.1.4 Ocular Drug Delivery

Usually, different drops or ointments are applied to treat ocular infections. For these cases, the drugs get cleared out of the eye very swiftly and thus this sector requires advancement in therapeutic competency. To reduce redundant dosing nanofiber base ocular inserts seems to be thought of as well as contrasted to traditional eye drops Drug-loaded nanofiber scaffold give controlled discharge of consolidated drugs put in the oral mucosa. Brimonidine tartrate (BT)-loaded electrospun was used like ocular insets for mitigating ocular infection also inflammation (Shahriar et al., 2019).

A nanopatch was developed using PVA and PCL to transport a mix of Timolol Maleate and Dorzolamide Hydrochloride to treat against glaucoma. As-developed drug-loaded nanopatches were 200–400 d nm in size with about total drug entrapment efficiency—no interaction amongst polymers also encapsulated drugs was discovered. In addition, the in vitro drug release experiment suggested a first blast release of integrated drug from nanopatches, then comes regulated release behavior lasting a maximum of 24 hours. Patches electrospun with micro/nanofiber diameters as

well as a large surface area were thought to be superior to bulk material in topical administration or treating the anterior region of the eye disorders (Gagandeep et al., 2014a).

Two separate patches of Dexamethasone loaded PLA/PVA patches were synthesized through electrospinning method and solvent casting where the drug release behavior was analyzed. The results showed that almost 90% of the medication was discharged from the electrospun implant after 40 hours and just 24 hours from the solvent-casting inserts. Electrospun inserts demonstrated more constant and predictable drug release than solvent-casting inserts (Bhattarai et al., 2017).

Acyclovir, cyanocobalamin, and ciprofloxacin was concurrently consolidated into PCL fibers to synthesize fibrous matrices as intravitreal implants. The half-life was increased to 6 days using an in vitro eye model, this was much longer as opposed to small molecule drug solutions, indicating the suggested matrix might be a feasible choice for intravitreal implant.

5.1.5 Rectal Drug Delivery

For Pediatric Patients that are unable to swallow drug rectal route presents the most suitable substitute to oral drug delivery routes. It is also suited for patients that are unconscious or have regurgitation. Electrospun nanofibers are obtaining more attention for nanofiber based rectal drug delivery. Electrospun nanofibers might be regarded a harmless, biocompatible, and biodegradable sealing fiber in the therapy of post-operative peritoneal effusion after rectal/pelvic surgery (Shahriar et al., 2019). The first clinical investigation of electrospun nanofibers' safety and sealing capabilities in lymphorrhea was studied in 2014. A synthetic material (Pura Matrix) having 16 amino acid peptides was used to create a self- assembled nanofiber. The clinical trial included a total of 20 individuals with colorectal cancer. A substantial reduction in post-operative drainage volumes was seen following a 2–3-month follow-up period inside the experimental group vs the control group. The clinical trial included a total of 20 colorectal cancer patients. When compared to the control group, the experimental group saw a decrease in post-operative drainage volumes to the control group after a 2–3-month follow-up period (Yoshitaka Kondo, Takeshi Nagasaka, Satoru Kobayashi, Naoya Kobayashi, 2014). Another study researched on the permeability of penicillin through various biological membranes and found that ciprofloxacin loaded in PVA fiber showed greater permeability in rectal mucosa membrane and controlled release behavior in contrast to control group with a high level of variability (Modgill et al., 2016).

5.1.6 Vaginal Drug Delivery:

For drugs that need local delivery vaginal mucosa route can be employed a drug- eluting electrospun nanofiber as a novel approach. For instance, to deliver anticancer drug Cisplatin for mitigating cervical cancer, the drug was consolidated into poly (ethylene oxide)/ polylactide fiber. A mouse cervical cancer model was used for the nanofibers system to investigate the mucoadhesion and in vivo vaginal retention. The findings of the in-vivo release showed highest accumulation of cisplatin, the medicine used mostly for the peripheral organs of kidneys and livers or the circulation, in the cervical area in contrast to the intravenous cisplatin injection (Zong et al., 2015).

For the aliment of Vaginal Candidiasis antifungal drug Fluconazole was studied through nanofiber delivery system. Co-electrospinning of the drug with poly (vinyl alcohol) was done to obtain non-woven fiber mats. This was implied to surmount issues related to toxic effects for long term administration of fluconazole (150 mg-6 months) to mitigate fungal vaginitis (Inman et al., 1994). In the first 2 hrs., a first explosion released 35.13 percent of the medicine, followed by a persistent releasing pattern of 97.8 percent up to 6 hours, was seen during permeation investigations on nanofiber mats performed with vaginal skin of goat in a Franz diffusion cell (R. Sharma et al., 2016). Nanofibers carrying progesterone have also been researched in order to avoid preterm birth as a convenient vaginal delivery mechanism (Brako et al., 2018).

5.2 Instances of Biopharmaceutical Applications

Table 8: Examples of commercial electrospun products for healthcare. b-TCP: b-tricalcium phosphate; SiV: siloxane-containing calcium carbonate (modified from Z. Liu et al., 2020)

Commercial products	**Company and country**	**Stage of products**	**Electrospun material**	**Application**
AVflo TM	Nicast (Israel)	CE certified (2008)	PU	Nanofibrous vascular grafts
PK Papyrus	Biotronik (Germany)	FDA approved (Sept. 2018)	PU	PU covered coronary stent system
ReDura TM	MEDPRIN (Germany	Clinical use	PLLA	Dural substitute patch

NeoDura TM	MEDPRIN (Germany	Clinical use	Synthetic polymers /gelatin	Dural substitute patch
Rivelin Patch	Bioinicia (Spain)	Clinical trial (phase 2)	Drug delivery layer: PVP/Eudragit RS100 Hydrophobic backing layer: PCL	Mucoadhesive drug delivery patch
HealSmart TM Personalized antimicrobial dressings	PolyRemedy (USA)	Clinical use	Hyaluronic acid	Personalized wound-care system

The unique characteristics and facile adherence of nanofibers makes them extremely versatile for the treatment of many diseases. Due to the intrinsic variation of diseases, a distinct release and mechanical feature of nanofiber are required in each area of application (Maleki Dizaj et al., 2019). Below will be discussed all the various applications of nanofibers:

5.2.1 Antibiotics/Antibacterial

Since the revelation and development of a real antibiotic called penicillin by Alexander Fleming, antibiotics are the most often used medication for diverse bacterial illnesses. Their adequate administration routes, toxicological profiles, low solubility as well as most critically microbial resistance are key constraints regarding the therapeutic efficacy, despite all the beneficial properties of antibiotics. Although numerous techniques to the delivery have been presented in recent decades, the translation into clinical settings of problems connected with low loading efficiency, systems toxicity, and drug release profiles was restricted (Shahriar et al., 2019).

One of the most recent difficulties for medicine is bacterial infection. One of the world's top causes of mortality may be sepsis from a serious infection (Ulevitch, 2004). Bacteria also have a great tendency to acquire drug resistance. Antimicrobial resistance is expected to result in 50 million deaths annually around the world by 2050 (Luraghi et al., 2021a).

Electrospun nanofibers are regarded an alternate for the administration of antibiotics in this scenario since the wide area and adjustable pores give highest capability for antibiotic loading and

encapsulation efficacy. Furthermore, the latest generation of nanofibers can indeed control continuous as well as regulated activity regarding antibiotic releases, optimize the dissolving rate and the systemic toxicity of low water-soluble antimicrobials Nanofibers commonly include antibacterial medications that hinder cell walls production, protein synthesis, synthesis of DNA/RNA, synthesis of mycolic acid, and folic acid synthesis (Shahriar et al., 2019).

The capacity of a bacterium to grow in an inhibitor of an antibiotic called antimicrobial resistance. The development of novel, more effective antibiotic systems might therefore limit the disadvantages related to overdose and an increase in bacterial resistance by maximizing the impact at the location of the activity (Shahriar et al., 2019).

Aminopenicillin drug like Amoxicillin (AMX) had been incorporated to a nanomicelle like a hydrophobic antibacterial drug by film dispersion after that it was loaded into core of nanofiber through Co-axial electrospinning. ((AMX/NM/NF). On further analysis it was found out that it made an inhibiting zone of 9.2mm and 7.3mm when opposed to E. coli and S. aureus respectively (H. Yu et al., 2019).

Another study was done where ultrasound-assisted drug release was obtained through the development of an electrospun scaffold loaded with second- generation Fluoroquinolone antibiotic (Ciprofloxacin). This alginate embedded nanofiber showed 3 times greater release characteristic by ultrasonic stimuli at 15 W/ cm^2 concentration also enhanced greater bacterial DNA production inhibition in both E. coli and S. aureus. In vitro and in vivo investigations revealed that the bactericidal and bacteriotic activity of antibiotics can be enhanced by electrospun nanofiber scaffolds (Khorshidi & Karkhaneh, 2018).

For averting the development of bacterial biofilm after surgical operation, Gentamicin loaded Polyactide-co-polycaprolactone nanofibers produced by electrpospinning were studied. Another research was done on the synthesis of gastro-retentive drug delivery system with the possibility of use in regular day to day life. The system was designed around a B.Stirata polysaccharide which is a naturally occurring glucomannan material. Glucomannan was not employed for electrospinning, however, but instead as a lyophilization wafer encapsulated with levofloxacin hydrochloride. As a covering for the tablets PCL electrospun fibers are employed. Chitosan and gelatin loaded with Vancomycin was synthesized similarly as a mucoadhesive oral delivery system. The three principal advantages of such implants include enhanced absorption and

bioavailability, consistent release, and prevention of first-pass hepatic metabolism. Great absorption of vancomycin and serious adverse effects in the gastrointestinal system might lead to the controlled release of vancomycin to maximize the dose and benefit of the medical product (Luraghi et al., 2021a).

An oxazolidinone antibiotic Linezolid was loaded with elecrospun PLGA and PCL fibers to make a controlled drug distribution regarding ailment of skeletal prosthesis concerned infections. It had aimed to obtain capable treatment through optimal dosing that enables accelerated healing and regulates infections by the controlled discharge of Linezolid. The scaffolds showed a pleasant favorable impact with tissue healing on a rat model of a tibia fracture through their smooth adjustment of the composition. The antibiotic loading also provided more effective therapeutic and prophylaxis effect with two times a day of commercial linezolid than intraperitoneal therapy. With a 37-fold reduction in antibiotic treatments in contrast to traditional therapy, the effectiveness of the electrospun meshes removes the requirement for two shots every day for one single usage. The strategy might avoid an increase in antibiotic resistance and enable cost-effective therapy (Eren Boncu et al., 2020).

Topical antibacterial treatment can also be synthesized by electrospinning Chitosan (CTS) nanofibers with Silver nanoparticles (AgNPs). This has demonstrated antibacterial action against gram-negative *Pseudomonas aeruginosa* (*P. aeruginosa*) and gram-positive Methicillin-resistant cocciaureus MRSA (S. J. Lee et al., 2014). In addition, core nanofibers containing Gentamycin and Resveratrol in the core of PCL were observed. Moreover, the presence of pseudomonas lipase in the PCL biodegradation causes the release of the core drug. Sustained release without initial burst impact for 7 days is reported (Z. M. Huang et al., 2006).

Ciprofloxacin based transdermal patches fabricated with sodium alginate (NaAlg) – polyvinyl alcohol (PVA) is helpful to transport the drug locally and give swift action to regulate infections. These patches demonstrate both sustained and controlled release in accordance with the Higuchi model and Korsmeyer-Peppas Model (Kataria et al., 2014).

5.2.2 Smart -Antibiotics

Electrospun nanofiber grounds are often employed in the smart antibiotic delivery system for controlling the release of medications to several biological factors, like pH factor, temperature also

UV-light sensitivity (Figure-8). Deterioration of antimicrobial Neomycin was studied in respect to UV-light and pH- reacting photolytic action of Tungsten disulfide (TDS), TDS-chitosan along with TDS-polycaprolactone nanofibers. At pH 3, the antibacterial medication Neomycin coupled with TDS-chitosan and TDS-polycaprolactone nanofibers demonstrated a rather excellent breakdown proportion as well as antimicrobial effectiveness (Fakhri et al., 2018).

Figure 8: Smart delivery systems (stimuli responsive) (*adapted from* Shahriar et al., 2019)

A study on pH- based antibiotic release from Eudragit nanofiber mesh developed by co-axial electrospinning demonstrated drug discharge rate of Tetracycline from Tetracycline-loaded Eudragit nanofiber mesh relies on the physiological pH value also the molar ratio of pure Eudragit and Eudragit L100 in an Eudragit nanofiber mesh. Tetracycline release rate coming through the fabricated nanofiber mesh was substantially quicker at pH 6, while it was very sluggish at pH 2. Furthermore, Tetracycline release was optimal at both pH levels at greater molar ratio of the Eudragit nanofiber mesh (Son et al., 2015). Nanofiber scaffolds have greater potential uses for antibacterial medication delivery with sustained release features than other drug nanocarriers (Shahriar et al., 2019).

5.2.3 Anti-Hypertensives

Anti-hypertensive medicines are used to treat high hypertension. Their difficulties such as reduced bioavailability, shorter half-lives, limited permeability and unwanted side effects can be waived off by employing suitable polymers for the electronic spinning of medicines (Nangare et al., 2020). A linear oral Nifedipine delivery has been achieved from a compressed tablet with Nifedipine and Polyvinylpyrrolidone (solubility enhancer) coated with nanofibrous Poly (lactic-co-glycolic acid) base sheet. An increase in sheet thickness has been noticed, resulting in more delayed release of

the medicines with signs of lag phase (Park et al., 2011). Biodegradable polyesters such as poly (l-lactic acid) (PLLA), poly (lactic-co-glycolic acid) (PLGA) and poly(β-caprolactone) (PLCL) have been investigated as filament forming matrix polymers for sustainable sublingual Captopril (CPL) delivery from nanofibers and drug release-controlled diffusion has been found (H. Zhang et al., 2012). The use of Polyvinylpyrrolidone (PVP) K90 as the first matrix and hydroxypropyl β-cyclodextrin has been developed for rapid release of lipophilic nano- and microfibers to prevent local supersaturation (Vigh et al., 2013). Polymeric patches containing Timolol maleate and Dorzolamide Hydrochloride have been recommended in the treatment of glaucoma, which exhibited a considerable reduction in intraocular tension compared to commercial eye drops (Gagandeep et al., 2014b).

5.2.4 Antiretroviral

For biomedical experts, HIV is another issue, and several preventive efforts are under way to avoid infection, while the complexities in combating the virus are known (Rizvi & Saleh, 2018). It has been shown that the practicality of Cellulose Acetate Phthalate (CAP) electrospun nanofiber and Tenofovir (TFV) a Disoproxyl-fumarate inhibitor as anti-HIV medicaments is greater. Due to the pH-dependent solubility of CAP, the drug release rate was controlled. The presence of modest quantities of human semen with a pH of 7.4 - 8.4 leads to a quick disintegration of the nanofibers in healthy vaginal fluid (acidic circumstances) and to the subsequent release of the integrated medication. This enables HIV transmission to be effectively inhibited by releasing antiviral medication combined with the innate antibacterial capabilities of CAP (C. Huang et al., 2012). Thus, these nanofibers have major implications for the manufacture of fiber-based medical textiles for the treatment of HIV in the pharmaceutical sector (Krogstad & Woodrow, 2014).

5.2.5 Anti-inflammatory:

Anti-inflammatory medications (NSAIDS) are distinguished from steroids and widely popular for their anti-inflammatory properties. They are also an often-given drug as they are well-known for pain relief, antipyretic and blood coagulation (Shahriar et al., 2019). The NSAIDs are a group linked to several negative consequences of ulcers, abdominal disorders, and vascular problems. Usually, the medicine does not show a rapid beginning of action and an extended pharmacological

impact. This can be due to problems such as low bioavailability, low porousness, shorter half-lives, etc (Conte et al., 2017).

Ibuprofen is the NSAID class, usually recommended for the treatment of pain, fever, inflammation, migraines, arthritis, and unpleasant menstrual problems. According to one research, demonstration of the dissolution rates of this loaded medication may be improved by ibuprofen-laden PCL nanofibers in such a biological setting whereby about 100 percent ibuprofen is released through manufactured nanofibers within 4 hours (Potrč et al., 2015).

Sublingual administering of migraines that display quick and mutually independent release of medicines has been effectively electrospun in flexible and physically resistant membranes containing Sumatriptan sucinate and Naproxen. The release rate of both medicines was doubled utilizing these fibers. Drugs subsequently infiltrate as non-ionized moieties through sublingual mucosa (Vrbata et al., 2013b).

For delivery of ketoprofen (KET), core-sheath nanofibers were generated utilizing coaxial electrospinning which offered biphasic drug release profile. The initial burst effect of electrospun poly (vinyl alcohol) (PVA)fiber mats was abolished after treatment by stability against disintegration in water by treatment with methanol. PVP and Zein were utilized respectively as sheath polymer and core matrix. Remote drug release followed by long-lasting release for more than 10 hours from these nanofibrous sheets was observed (Y. N. Jiang et al., 2012).

5.2.6 Wound Healing

Wound healing is a complex physiological process that involves tissue regeneration and restoration and is influenced by both internal and external aspects. Despite significant progress over the last decade, developing more effective wound covering patches and skin replacements remains a difficult issue (Augustine et al., 2014).

Wound healing is a progressive and engaging method that requires dermal cells (fibroblasts, endothelial cells), growth factors (EGF, FGF-2, and VEGF), cytokines, etc. The whole method also consists of hemostasis, inflammation, proliferation and remodeling/ maturation (Janis, 2006). Furthermore, the great likeness to ECM and practicality for multifunctionalization make electrospun drug-loaded scaffolds promising in the treatment of skin damage also illnesses,

particularly for some chronic skin illnesses with no therapeutic treatments (Ding et al., 2019). Aside from wound covering, an ideal wound dressing should promote wound healing by acting as a barrier for germs, absorbing wound exudates, providing and maintaining a moist environment, allowing gas exchange, and being easily removed from the site (Yanzhong Zhang et al., 2005).

By employing double electrospinning process a wound dressing membrane was developed which relied on customized Polybutylene adipate-co-terephthalate and Gelatin nanofibrous structures loaded with Doxycycline. The use of gelatin allows for the incorporation of a water-soluble component in the scaffold for controlling release as well as create improved ECM mimicking. Within three days after starting the therapy, the fibers showed significant wound healing in vivo, with minimal cytotoxicity (Varshosaz et al., 2020).

Through the use of side-by-side electrospinning technique PVP and Ethyl cellulose nanofibers were synthesized with interdependent discharge of Ciprofloxacin and Silver Nanoparticles which possess antibacterial characteristics. Because of the Janus method, the fibers can burst and release ciprofloxacin within 30 minutes. The persistent release of silver nanoparticles then continues the antibacterial activity for up to 72 hours, resulting in significant suppression of bacterial growth. Because of this characteristic, this scaffold is a viable technique for avoiding infections throughout the wound healing process. To demonstrate their potential, however, toxicity data also cell adherence investigations are required (J. Yang et al., 2020).

A dual drug discharge matrix was developed by electrospinning of Two Polylactic acid formulation mixed with Lidocaine HCL or Mupirocin. The separate loaded fibers were gathered at the same time to produce an integrated matrix (2-stream electrospinning). This configuration enabled the instant release of lidocaine HCl for pain relief, as well as the continuous release of mupirocin over many days to avoid bacterial infection (Thakur et al., 2008b).

For obtaining faster diabetic injury healing a number of angiogenic factors (VEGF, bFGF, PDGF, and EGF) were co-loaded to Collagen/Hyaluronic acid combination scaffolds to quickly raise the production of blood vessels and make way for faster assimilation with surrounding tissues. Alternate angiogenic agents include Epigallocatechin-3-O-gallate, Desferrioxamine, had also been incorporated into Hyaluronic acid/PLGA and PVA/Chitosan scaffolds, correspondingly, to drastically accelerate neovascularization and collagen accumulation thereby accelerate diabetic wound healing. Bioactive drug 20(R)-Ginsenoside RG3 was incorporated into PLGA fibers

through pDA coating immobilizing the bFGF to a greater extent to stop the production of hypertrophic scars while the wound healing method undergoes (Ding et al., 2019).

Tissue engineering is indeed a multifaceted topic that combines materials, chemistry, and biology. In order to achieve in situ tissue regeneration or organ restoration, cells are expected to adhere, spread as well as differentiate while being supported by 3D scaffolds that would progressively decay in the meantime (Griffith & Naughton, 2002). Another critical connection in this technique is the use of appropriate pharmacological and physicochemical parameters that influence or guide cellular responses on a molecular level. Because of their strong physical similarity to ECM, electrospun scaffolds are commonly used as scaffolds for tissue regeneration. Furthermore, further research is being conducted on the use of active ingredient-loaded fibrous scaffolds in the search of enhanced therapeutics results (Ding et al., 2019).

5.2.7 Delivery of Anticancer Agents

Despite major progress in treatments, prevention and detection, cancer is among the world's worst ailments to torment mankind up to this day, remaining singular among the world's top sources of mortality (Siegel et al., 2019). It is very difficult to discover a possible new cancer treatment strategy because of several inconveniences with anti-cancer therapies such as imperfect solubility, blood circulation irresistibility, poor cancer cell buildup, highly toxic to normal cells, poor tumor functionality and an excessive elimination profile (Torres-Martinez et al., 2018). Due to the changeable surface morphology for drug pharmacokinetics modulation, electrospinning has been developed in cancer research as a method which is extremely competitive (Chen et al., 2018).

Doxorubicin Hydrochloride (DOX) is one of the most essential and commonly used drugs in chemotherapy. Through consolidation of water-soluble DOX into a hydrophobic or amphiphilic Poly (ethylene glycol)—Poly (*l*-lactic acid) (PEG-PLA) Di block copolymer, a nanofiber drug delivery system can be developed through emulsion electrospinning. The three-stage diffusion regulated mechanism of drug release from these nanofibers demonstrates that the release rates for the first step were lighter than for the second. This shows that the rate of release of drugs reduces with the growing drug content inside the fibers is as a reservoir delivery mechanism (Xu et al., 2008). Likewise, Paclitaxel electrospun fibers were fabricated with Poly (lactic-co-glycolic acid) (PLGA) polymer. Due to their fact that the drug resides in a solid solution condition and continuous

release of the drug in fibers, a significant reduction in cytotoxicity was possible for more than 60 days. With more than 90 percent improvement in the encapsulation effectiveness of biodegradable PLGA microfibers and nanofibers PLGA is promising to provide an alternate drug delivery tool for the treatment of brain tumor (J. Xie & Wang, 2006).

A scaffold made up of Poly (D, L-lacticco- glycolic acid), gelatin, and Pluronic F127 was synthesized for the ailment of breast cancer treatment along with Prodigiosin (Akpan et al., 2020). A number of core-shell nanofibers relying on Eudragit S100, a copolymer of methacrylic acid and methyl methacrylate, as shell and polyethylene oxide as the core was fabricated where the fibers core were ingrained with 5- fluorouracil or ferulic acid or Cyclodextrin as antitumoral agents. In addition, as a contractor for magnetic resonance imaging the core includes a Gadolinium complex. This strategy might combine treatment of the tumor with monitoring of the fiber activity (Luraghi et al., 2021a).

Much has been learnt about drug activity as well as attempts for clarifying the molecular grounds of resistance have shown many different mechanisms that either prohibit a drug from attaining its goal, implement compensating survival mechanisms, or produce dormant lull cancer cells. These are known as multi-medication resistance (Komarova & Wodarz, 2005). A combination of medicines with many targets may avoid drug resistance treatment failure however, at the expense of higher side effects owing to numerous long-term medication regiments (Szakács et al., 2006). An implantable hierarchical-structured ultrafine fiber device was produced through microfluidic electrospinning to locally co-transport Doxorubicin and Apantinib. Afterwards of 21 days increased survival rates, the tumor mass was investigated which showed that the mice undergoing treatment had 4 times less than the untreated mice. The synergistic impact of doxorubicin and apatinib has a high capacity for developing devices with low systemic toxicity which can produce tremendous therapeutic effects (Luraghi et al., 2021a).

Table 9: Recent research on electrospun scaffold-based techniques for anticancer medication and gene delivery in cancer therapy (modified from Ding et al., 2019)

Anticancer Reagents	**Polymer Matrix**	**Cancer Cell Lines**	**Highlights**

Camptothecin	PCL PLA	C2C12 cell, in vitro HepG2 cell, in vitro and in vivo	Sustained release for more than 6 days; 25% greater reduction in cell growth than free drugs after 72 hours After 72 hours, the cytotoxicity was 20 times more than that of free drugs; there was more necrosis and apoptosis.
Paclitaxel	PLGA	C6 glioma cells	Sustained release >80 days 44 percent fewer tumors on day 24 as compared to free drug control;
Cisplatin	PCL/PGC-C18	Lewis Lung carcinoma cell	Superhydrophobic Sustained release in a linear profile for more than 90 days; significant increase in median recurrence-free survival to more than 23 days
Doxorubicin	PEG-PLA PEG-PLA	Murine mammary carcinoma EMT6 cell, in vivo SMMC7721 cell, in vitro and hepatocarcinoma H22 cell, in vivo	12 days of continuous release; After 10 days, cell growth was reduced by 40% as compared to free drugs.
Paclitaxel and Doxorubicin	PEG-PLA	C6 Glioma cells	Synergistic inhibition effects on tumor cell
Plasmid DNA encoding for Cdk2 shRNA	PCL	MCF-7 breast cancer cell	Cell inhibition increased by 40% in contrast to the control scaffold. Sustained release for more than 21 days;
Paclitaxel and MMP-2 RNAi	PLGA	U87MG-luc2 cell	Anticancer action that is synergistic;

Fibers containing core-loaded Hydroxycamptothecin (HCPT) and 2-hydroxypropycyclodextrinbound HCPT were created, and it was discovered that the inclusion

complex had greater anticancer efficacy and fewer side effects than the free drug (Luo et al., 2012c).

5.2.8 Cardiovascular Agents

The cardiovascular regime allows the circulation of the blood and the transfer of key nutrients. Coronary artery diseases, stroking, cardiac arrest, hypertension related heart ailment as well as the main reason for mortality all over the globe are among the most frequent (Luraghi et al., 2021a).

Because of its agonistic effects on both ATP-sensitive K + and polyatomic ion, nitrate, channels, nicorandil is commonly employed in the treatment of angina or angina pectoris. Nicorandil as an anti-anginal drug is restricted by its low bioavailability and delay starting activity and the main adverse effects, including increased turnover rates and mucosal ulcers (Bhattarai et al., 2019). To address these constraints, Nicorandil had been electrospun to provide a sublingual dose for Angina pectoris using polymer nanofibers consisting of Riboflavin, Hyaluronic acid, and PVA. Riboflavine was predicted to heal mucosal ulceration in the nano-fibre scaffolds, whilst hyaluronic acid would assure fast inflammation healing in injured tissue by lowering pro-inflammatory cytokines Moreover, a histological analysis at the site of administration for the formulated formula had not shown any mucosal ulceration (Im et al., 2010b).

Carvedilol is also a cardiovascular drug that latches to and suppresses both alpha and beta-adrenergic receptors in order to treat congestive cardiac insufficiency (Bhattarai et al., 2019). The use of PCL nanofiber scaffolds to deliver poorly water-soluble carvedilol for oral administration was studied. The average size of the medicinally loaded PCL nanofiber has been noted to be precisely related to the loaded medicine and the Carvedilol crystallinity has reduced in the PCL nanofiber following encapsulation. In only 4 hours, about 77 per cent of carvedilol was discharged from PCL electrospun nanofibers, indicating that this weakly water-soluble medicine improved significantly (B. Gupta et al., 2007).

To improve therapeutic benefits nanofibers of polylactic acid as covering stents were fabricated (Bakola et al., 2018). Fibers have been incorporated in the blood clot formation inhibitor Dipyridamole to aid with thrombosis showing consistent dispersion of drug in the artery which typically happens afterwards of stent installation.

Chapter 6: Discussion

The technology of electrospinning may overcome certain barriers in conventional medication delivery methods. For example, the low solubility of several regularly used APIs (such as ibuprofen and ketoprofen) limits their usage and leads to problems in administration. Electrospun nanofibers were employed to overcome drug hydrophobicity as well as to stabilize APIs in amorphous conditions. Throughout general, the API is disseminated in the fibre on a molecular scale; it is driven to assume an amorphous condition. This distribution is stabilised by favorable secondary contacts between the API and the carrier polymers (for example, hydrogen-bonding, hydrophobic and electrostatic interactions). Electrospun fibers are capable of alleviating some of these challenges by offering an API with a stable storage matrix. The presence of the API in a fiber might also help protect it from heat and light processes and keeps the API away from reacting and degrading molecules. One of the major benefits of electrospun nanofibers is their ability to restrict the periphery. The drug's side effect is directly applied to a particular place of action (Shahriar et al., 2019).

The exciting potential of nanofibers in clinical studies is now not very widely explored. At now, most research are limited to the pre-clinical phase by biochemical characterization. Although numerous works show considerable outcomes in in vitro or in vivo models, this methodology is still limited by the creation of translation studies for patients (Goonoo et al., 2014). Clinical development of novel instruments needs more time and cost-effectiveness than the preclinical phase, which might interfere with initial investment. The manufacturing of the unit should also satisfy particular criteria to satisfy the criteria of ISO 10993 and should be manufactured under GMP circumstances (Luraghi et al., 2021b).

Although the advantages of electrospinning have mainly been shown in numerous disciplines of research, manufacturing still has to be efficiently implemented. Various issues related to the process of electrospinning must yet be resolved. Among them are: (i) the large-scale manufacturing process; (ii) precision also repeatability throughout the production process; as well as (iii) the environmental and safety elements of electrospinning. In large-scale, electrospinning using solvents for biomedical and pharmaceutical purposes, accurate control of solvent residues becomes crucial. The use of solvent-free spinning should nevertheless reduce the possibility of solvent residues and solvent recovery. Due to the absence of dependable and economical

technology, the usage of several different active polymer materials, nanofibers are currently restricted to manufacture. It is also tough to achieve the consistency of fibers with certain morphologies and qualities using customized electrospun fibers (Bhattarai et al., 2019).
Currently, few electrospun products have gained authorization by FDA and very few clinical studies to further demonstrate the function of the platforms for the supply of drugs have been published. Although nanofibers are multifunctional, more development and study are necessary for effective application of nanofibers, particularly for biomedical treatments. A detailed study is needed to make the scaling of nanofibers broadly accessible.

Although in vivo investigations to validate the healing effectiveness under complicated in vivo conditions have previously been undertaken, the enormous disparity of in vivo differences in size also metabolism between humans and tiny animals' investigations might create startling outcomes at the time of clinical trials. In addition, both cost costs and manufacturing rate constraints impeded large-scale human clinical studies. In this respect, enormous efforts are still required. Another barrier for real marketing is the poor efficiency of the electrospinning laboratory equipment. Although high fiber output may already be increased by high throughput spinning systems like needleless electrospinning and multi-needle spinning, drug loading systems from these equipment were hardly studied. Quality control and high replicability in high-performance electrospinning also challenge the huge buildup of charges over the long-term process. By optimizing qualities, nanofibrous mats may be examined for more particular applications in terms of fiber diameter, orientation, shape, porosity, mechanical characteristics and electrofibrous products. As an interdisciplinary subject in the field of materials science, pharmaceutical engineering and life science, further dialogs between researchers among different fields needs initiation, therefore, mutual cooperation promoted and accelerated in order to further solve the missing enigmas in this design chain -creation-laboratory verification-clinical trials -marketing (Ding et al., 2019).

Chapter 7: Conclusion and Future Perspective

7.1 Conclusion

The limitless potential of electrospinning provides a spectacular foundation for the creation of new drug delivery systems capable of maximizing therapeutic advantages while avoiding undesirable side effects. Drug- polymer choices can be fine-tuned solely for a specific application or need. Electrospun drug delivery has obtained growing interest due its variable use in different sectors. It has already been used industrially in several forms like mats, composites etc. Drug delivery by electrospinning has become one of its most significant application in the biomedical sector. It is being studied extensively for drug delivery applications due to its flexibility in synthesis, variation in fiber morphology and great surface area. The drug delivery devices can be adjusted through altering the source of materials, several drug loading techniques which can regulate the morphological, physiochemical and biological activities of the drug loaded device. By selecting a specific polymer matrix drugs can be released at any interval of time by incorporating proper materials and also implementing smart approaches to developing the system. The medicine's minimum necessary dose can be reduced by employing electrospun fiber for local drug delivery, which not only results in less systemic absorption but also decreases undesirable side effects. By implementing different techniques of electrospinning, it is also possible to develop rapid, sustained, biphasic, or zero-order fashion release of drugs for overcoming various challenges that linger in the traditional drug delivery devices for specific conditions. Multiple drug release or timed release of drugs release due to certain stimuli (pH, temperature, light and electric/ magnetic field) can now be thought of and developed by this magnificent method. In contrast to conventional drug formulations, electrospun drug loaded formulations can boost the solubility of drugs that do not dissolve in water through greater solid dispersion that is possible for the extensive surface to volume ratio of the electrospun fiber. Thus, fast dissolving drugs that can be used in oral cavity or higher dispersion by the skin is also possible through electrospinning. Furthermore, electrospun scaffolds can also be used to treat infections and wounds effectively and also can aid in wound healing. Since these electrsopun nano scaffolds can mimic the Extracellular Matrix (ECM) it can be implied for cell proliferation and differentiations which in turn plays a major role in Tissue regeneration. Anticancer therapies can also be revolutionized by the use of multidrug loading through electrospinning along with targeted application and regulation of its release. The

electrospinning method also is very economic and has the capability to scale up for the betterment of pharmaceutical sector. Nevertheless, electrospun frameworks have certainly evolved into multifunctional platforms containing active components that have the potential to solve existing critical medical issues.

7.2 Future Perspective

Electrospun scaffolds might open up new avenues for customized treatment by modifying mechanical characteristics or release kinetics. Nonetheless there is still an enormous void between lab rectification and clinical trials and then commercialization. Only a handful of electrospun products have got approval from FDA and not much clinical trials have been concluded to verify functions of designed drug delivery devices(Stoddard et al., 2016). Although in vivo studies have already been done to validate the curative efficiency in complicated in vivo situations, the enormous disparity in size as well as metabolic systems among human and small animals utilized in vivo investigation may result in surprising findings during clinical trials. Furthermore, both cost restrictions and production rate constraints hampered large-scale human clinical studies(Persano et al., 2013). Massive efforts are still required in this regard. The poor yield of the experimental electrospinning equipment is another barrier to commercialization. Despite the fact that High throughput electrospinning technologies, such as needleless electrospinning and multi-needle electrospinning, are currently competent of increasing fiber synthesis, studies regarding drug loading system using such setups have been rare(M. Yu et al., 2017). Several problems limit scaling-up and future uses in biological sectors. Quality control and good reproducibility is also a hurdle as due to storing up of charge when electrospinning is done for a long amount of time(M. Yu et al., 2017).As a multi-disciplinary field that has associations with material science, pharmaceutical science and life science in general more studies with scientists from diverse fields should be carried out to develop and connect the missing pieces of the puzzle that remain in the design-synthesis-laboratory-authentication-clinical trials and commercialization of such innovative drug delivery devices. The Continuous technological advancement and the development of more complex integrated systems may also aid in the development of novel smart devices capable of precisely modulating the amount of medication released from the scaffold in response to bodily inputs. Such advancements might also pave the way for electrospun nanofibers to be used in areas where they are now underutilized, such as diabetes, hormone treatments, or

even autoimmune disorders, which are currently characterized by few, if any, studies (A. Sharma et al., 2013b). Overcoming such constraints might result in an even more potent tool for fast and noninvasive tissue creation, as well as a step closer to customized treatment. Although a lot has been accomplished by the use of this unique technique there still remain a huge opportunity for more varied implications of electrospinning the pharmaceutical field for drug delivery usage.

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