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Electrospun nanofibres in drug delivery: advances in controlled release strategies

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Emerging drug-delivery systems demand a controlled or programmable or sustained release of drug molecules to improve therapeutic efficacy and patient compliance. Such systems have been heavily investigated as they offer safe, accurate, and quality treatment for numerous diseases. Amongst newly developed drug-delivery systems, electrospun nanofibres have emerged as promising drug excipients and are coming up as promising biomaterials. The inimitable characteristics of electrospun nanofibres in terms of their high surface-to-volume ratio, high porosity, easy drug encapsulation, and programmable release make them an astounding drug-delivery vehicle.

The current review depicts the mechanism of drug release through nanofibres and emphasizes the strategies to tune their drug-release profiles for their applicability in therapeutics. It includes a detailed discussion on their pre- and post-electrospinning adaptation. Further, it discusses the common design criteria for oral, transdermal, topical, and trans-mucosal drug release through nanofibres together with the latest developments. Finally, the review unfolds the future perspectives in nanofibre fabrication to achieve programmable release encompassing the polymer-free approach, green electrospinning, herbal, and combinatorial drug delivery.

1. Introduction: significance of controlled/tuneable release

Conventional drug formulations are often allied with undesired side effects, anti-microbial resistance, and immunocompromised host. For ensuring immediate effects, drugs with a low biological half-life, such as non-steroidal anti-inflammatory drugs (NSAIDs), are delivered as a frequent bulk dosage, which can cause fluctuating drug plasma concentrations, resulting in systemic toxicity, including potentially peptic ulcers, intestinal bleeding, and damage to the gastric mucosa.¹ Improvements in synthesizing technologies have enabled the synthesis of complex drug compounds. Approximately 60–70% of newly discovered drug molecules are poorly water soluble and have low permeability, causing poor absorption in the gastrointestinal (GI) tract. To enhance their bioavailability, they need to be delivered as lipid formulations.² Another important

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The pitfalls associated with conventional drug-delivery systems, such as premature degradation, first-pass metabolism, discomfort or pain during administration, infusion-related toxicity, and systemic toxicity, need to be addressed.⁶ Thus, novel drug-delivery systems aim for controllable, programmed, sustained, or targeted drug delivery as a patient-friendly substitute. The most promising ones involve the polymeric encapsulation of drugs into nanocarriers, which can not only provide temporal control but also protect the therapeutic agent from the harsh physiological conditions.^{7,8}

Nanocarriers, such as liposomes, nanospheres, solid-lipid or metal-based or magnetic or theranostic nanoparticles, dendrimers, micelles, and polymeric nanofibres, have emerged as astounding drug-delivery vehicles.⁹⁻¹² The shape, size, composition, and surface chemistry of these nanocarriers, along with their drug interaction, aggregation, and dissolution, have been found to control the drug-release rate.⁸ However, due to their nano-sized diameters and other surface chemistries, such as zeta potential, most of these nano-drug vehicles are cleared in the GI tract or by the first-pass hepatic metabolism.¹³ In the case of nanoparticles, a high amount of drug is adsorbed on the surface, thereby undergoing a burst release.¹³ For most practical applications, therefore, these nano-drug vehicles further demand another carrier or ligands.⁶ Nanofibres are exceptions to this need due to their interconnected morphology and high drug-encapsulation efficiency, which can also withstand the harsh conditions in the GI tract, and further eliminate the surge from another carrier. Table 1 provides further insights into

The benefits of selecting electrospun nanofibres lie in their scalability, cost, easy programmability, and of course controllability over the morphology.

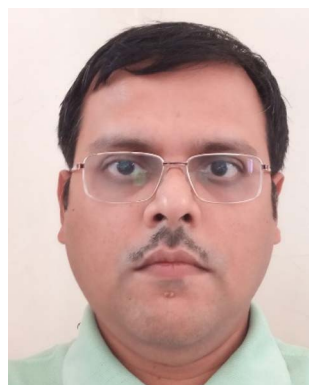
The current review discusses and highlights the role of nanofibres as a therapeutic excipient and their customization to achieve a desired drug-release profile. When it comes to the customization or tuning of their release properties, the most versatile, programmable, and commendable nanofibre-generation technique is electrospinning. The technique is known to provide excellent control and command over the morphology, orientation, size, and the dimension of nanofibres along with various encapsulation strategies for the active pharmaceutical agents (APIs).²⁷ It gives freedom to choose polymers from natural, semisynthetic, or synthetic origins or blends of polymers formed in aqueous or organic solvents or directly spun as a melt. To date, APIs with different bioactivities, such as anti-microbial, anti-inflammatory, cardiovascular, palliative, anti-histamine, anti-pyretic, and anti-cancer, have been successfully loaded into the polymeric nanofibres.⁶ The fact that nanofibres mimic the extra cellular matrix has further expanded their application in translational research and it is believed they may change the impending landscape of the pharmaceutical and biotechnological industries.²⁸ API-loaded electrospun nanofibres are being widely explored and studied in regenerative medicines and tissue culture, skin and osteo-regeneration, enteral drug delivery, pain-relieving transdermal patches, bioactive wound dressings, implants, stents, nerve guides, and in 3D *in vitro* cancer models.^{29–34}

The upcoming section unveils the theoretical background and operation of electrospinning to produce nano/microfibres.

2. Electrospinning

Electrospinning is a highly distinguished facile technique to produce polymeric nanofibres. It offers benefits over other nanofibre-generation techniques, such as drawing, phase separation, template synthesis, and self-assembly, for obtaining a controllable morphology, scalability, and ease of handling.^{35,36} This technique is based on the principle of electrohydrodynamics, where the drawing of polymeric threads in the diameter range of 10–1000 nm takes place under the influence of an electric field.³⁷ The simple instrumentation comprises a syringe, syringe pump, voltage supply, and a grounded metallic conductor, as shown in Fig. 1(a). The theory behind nanofibre generation was first given by Sir Geoffrey Ingram Taylor in 1964.³⁷

In the fibre generation process, a syringe is loaded with a polymer-based conducting solution and rested on the syringe pump assembly. As the syringe is pushed at a definite flow rate, a polymer drop exudes from the needle orifice. Under the influence of the electric field on the needle, surface tension and visco-elastic forces try to pull the polymer droplet inwards. The electrostatic forces, however, stretch the droplet outwards, forming a pendant-shaped “Taylor cone”.³⁸ Once the threshold voltage is attained, a highly unstable polymeric jet is generated



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Table 1 Comparison of various drug-delivery systems and their fabrication techniques

Type of nano-carriers and their size	Fabrication mechanism: common techniques	Technological advances	Nature of the carrier	Drug/bio-molecules	Routes	Limitations	Ref.
Micelles, 30–100 nm	Self-assembly: dialysis, solution casting, oil-in-water emulsions	Scalable, (since inexpensive and lower toxicity)	Amphiphilic copolymer	Both	Intravenous, ocular, oral, nasal buccal	Low stability upon dilution in the blood stream, complex characterizations, few clinical trials	14
Liposomes, 30 nm to a few micrometres	Self-assembly: mechanical-dispersion method, solvent-dispersion, detergent-removal method	Scalable, (only a few are approved for <i>in vivo</i> and clinical acceptance)	Phospholipids	Both	Parenteral, ocular, transdermal, intravenous	Low solubility, high cost, short life, leakage and fusion of drug/biomolecules, undergo oxidation and hydrolysis-like reactions	15 and 16
Hydrogel, size in nano/micro/macro as per gel type	Gelation: emulsions and moulding, H-crosslinking, H-bonding, grafting	Scalable	Water-based gel	Both	Oral, topical, transdermal, systemic injectable	Poor drug loading and burst release need to be addressed, low mechanical strength, poor physical stability, very few clinical trials and <i>in vivo</i> studies	17 and 18
Carbon nanotubes, 0.4–3 nm diameter to certain micron length	Top down: chemical vapour deposition, electric arc discharge, laser ablation	Not possible for industrial scale up due to high cost	Carbon	Both	Injected through subcutaneous/abdominal/intravenous route	Non-biodegradable, lack of FDA approval for CNTs, very costly fabrication, environmental impact	19
Quantum dots, 2–10 nm	Top down: molecular beam epitaxy, ion implantation, e-beam and X-ray lithography, bottom up: precipitation, sol-gel, microemulsion	Not possible for industrial scale up due to high cost	Semiconducting crystal	Both	Active and passive transport	Toxicity, poor body clearance, synthesis protocol, manufacturing cost, environmental impact	20
Nanoparticles, 1–100 nm	Bottom up: hydrothermal route, chemical reduction, green synthesis, evaporation–condensation, sol-gel, and colloidal methods	Limitations for scalability	Organic or inorganic or hybrid material	Both	Intravenous, subcutaneous, inhalation spray	Toxicity, needs testing protocols, only iron oxide nanoparticles are clinically proven and FDA approved; also, biocompatibility, drug targeting, transport and release, and interaction with biological barriers need to be investigated	21–23
Nanofibres, 50–1000 nm	Drawing: electrospinning	Scalable (since cost effective, easily programmable, continuous process)	Polymers/blend with inorganic materials	Both	Oral, transdermal, topical, buccal, and intravenous (injectable hydrogel), implantable	Need to investigate controlled-release strategies, few only clinical trials, more focus needed for <i>in vivo</i> studies	24–26

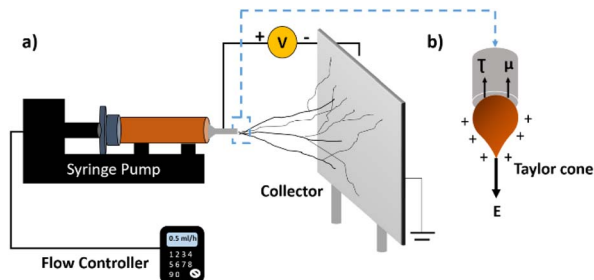


Fig. 1 (a) Basic set up and (b) working principle of electrospinning, where μ is the visco-elastic force, τ is the surface tension, and E is the electrostatic force.

due to the repulsive-like charges. This polymeric jet travels towards the lower potential region, and during the process, the solvent gets evaporated. One-dimensional dried nanofibres are then deposited on the oppositely charged collector. This whole theory is also known as the *jet instability theory*.³⁹ Though this theory looks comprehensible, several factors impact the size, orientation, and morphology of the nanofibres. The fibre formation and morphology are governed by the solution properties, electrospinning or process parameters, and ambient conditions.^{36–38} A brief description of the effect of these parameters on electrospinning was provided by Seeram Ramakrishna *et al.* (2005), and is mentioned below.²⁵

2.1. Solution parameters

2.1.1. Molecular weight and viscosity. The molecular weight of the polymer depends on the length and entanglement of the polymer chain. A higher degree of entanglement presents more drag and intermolecular attraction, imparting a high resultant viscosity. As the solution viscosity increases, the diameter of the fibre increases. If the solution is highly viscous, then it cannot be pumped out from the syringe. The low viscous solution forms beads under high surface tension.

2.1.2. Surface tension. Surface tension decreases the surface area per unit mass of fluid, causing bead formation in fibres. Generally, surfactants are added to encourage smooth fibre formation.

2.1.3. Solution conductivity. Conductivity increases the charge-carrying capacity, stretching the polymer jet, and the high bending instability. An increase in conductivity decreases the diameter and increases the area of deposition of the nanofibres.

2.1.4. Dielectric effect of the solvent. The bending instability of the electrospinning jet increases with the dielectric constant. A greater dielectric property reduces the diameter of the nanofibres and bead formation, and increases the area of deposition.

2.2. Processing parameters

Processing parameters are external factors that act on the electrospinning jet and that are less significant than the solution parameters. The key ones are described below.

2.2.1. Voltage. A higher voltage will lead to greater coulombic forces and a stronger electric field. High voltage effectively reduces the fibre diameter and facilitates fast solvent evaporation to yield dry fibres. When a less viscous solution is used under a high electrostatic field, a secondary jet emerges from the orifice, forming fine fibres. At low voltage, the reduced acceleration of the jet and weaker electrostatic field will increase the flight time and may facilitate finer fibre formation.

2.2.2. Feed rate. As the feed rate increases, the greater volume of solution is drawn from the tip of the needle and the less flight time is available to dry the solution. An increase in feed rate increases the fibre diameter and bead size. Since less flight time is available, therefore wet fibre webs are formed because of the lower solvent evaporation. Generally, a low feed rate is favourable.

2.2.3. Temperature. An increase in temperature of the solution increases the evaporation rate and decreases its viscosity, ultimately reducing the fibre diameter. The use of high temperatures causes the biopolymers, like proteins and enzymes, to lose their functionality.

2.2.4. Effect of the collector. Generally, a conducting collector, like aluminium foil, is used because it helps in dissipating charges on the fibres and hence, allows accumulating more fibres, thus increasing the fibre packing density. In the case of a non-conducting collector, the like charges will repel each other, leading to less deposition and sometimes 3D fibres. A porous collector induces faster solvent evaporation, while a patterned collector changes the texture of the fibre mat, and a rotating collector gives an improved morphology as there is more time to evaporate the solvent.

2.2.5. Diameter of the orifice. A smaller internal needle diameter reduces clogging, the bead size, and ultimately the diameter of the fibre. However, if the diameter is too small, it will be difficult to extrude a single drop out of the needle.

2.2.6. Distance between the tip and the collector. The distance affects the flight time as well as the electric field. Decreasing the distance has the same effect as increasing the voltage.

2.3. Ambient conditions

The effects of the surrounding conditions on electrospinning have been poorly investigated. These include the following.

2.3.1. Humidity. High humidity causes the development of circular pores on the fibres. The reason behind this is because electrospinning water drops will condense on the polymer surface, leaving pores after drying.

2.3.2. Type of atmosphere. The composition of air will affect the electrospinning. Different gases behave differently under high electrostatic fields.

2.3.3. Pressure. A low pressure does not support electrospinning. If the pressure is below atmospheric pressure, the solution will flow out of the needle, causing an unstable jet initiation. As the pressure decreases, a rapid bubbling of the solution will occur.

Table 2 summarizes the parameters controlling the morphology and performance of electrospinning.



Table 2 List of the parameters controlling the morphology and performance of nanofibres

Category	Parameter	Effect on the morphology and performance
Solution property	Molecular weight and solution viscosity	• The threshold values of both parameters need to be met to commence the electrospinning or else the solution is not spinnable • Molecular weight ↑ solution viscosity ↑ fibre diameter ↑ • Area of deposition ↓, continuous and smooth fibres obtained (<i>vice versa</i>)
	Surface tension	• Threshold value of surface tension needs to be met for Taylor cone initiation • If surface tension ↑ and viscosity ↑ fibre diameter ↑ continuous and smooth fibre formation ↑ • If surface tension ↑ and viscosity ↓, fibre formation is discontinuous and bead formation ↑ • Surface tension ↑ fibre diameter ↓
	Solution conductivity and dielectric constant	• Solution conductivity ↑ dielectric constant ↑ fibre diameter ↓ area of deposition ↑ • Solution conductivity ↓ dielectric constant ↓ bead formation ↑
Processing conditions	Voltage	• Voltage ↑ fibre diameter ↓ • Voltage ↑ surface tension ↑ bead formation ↑ or fibre thickness ↑ • If voltage ↑ and flight time ↑, fibre order ↑ crystallinity of fibre ↑
	Feed rate	• A lower feed rate is desired to obtain finer fibre formation • If feed rate ↑ and solvent–evaporation rate ↓, web formation ↑
	Temperature	• Feed rate ↑ fibre diameter ↑ • Temperature ↑ viscosity ↓ fibre diameter ↓ • Temperature ↑ biofunctionality of active molecules ↓
	Effect of the collector	• Conductive collector: dense and packed nanofibres • Non-conductive collector: 3D and loosely packed nanofibres • Patterned collector: same patterned nanofibres with the same orientation
	Diameter of the needle	• If too small a needle diameter, the solution cannot ooze out • Diameter of needle ↓ fibre diameter ↓ bead formation ↓
	Distance between the needle tip and collector	• Distance ↓ then interconnected wet fibre formation ↑ • Distance ↑ fibre diameter ↓
Ambient condition	Humidity	Humidity ↑ pore formation in the fibre ↑
	Pressure	Pressure below atmospheric: electrospinning is not possible

Although the electrospinning set-up is simple to operate, the science behind fibre generation is highly complex. An understanding of the electrostatics, solution rheology, and solution properties is of utmost importance. The solution properties, process parameters, and ambient conditions discussed above are interdependent and influence each other during the electrospinning process.

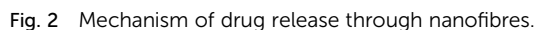
3. Insights into the drug-release mechanism

Electrospun polymeric nanofibres are known to enhance the therapeutic efficacy of drug molecules through polymeric encapsulation and tuning of the drug-release rate. For instance, sustained drug release ensures a constant drug plasma level and maximum time in systemic circulation for the efficient absorption of drugs, thus enhancing the therapeutic index and

ultimately, patient compliance.⁸ In literature, electrospun nanofibres have been employed to achieve various kinds of release profiles, including a fast or immediate release, sustained release, prolonged release, delayed-release, on-demand release, the release of multiple phases, and the co-delivery of multiple components based on the disease obligation.⁴⁰ Such release profiles can be achieved by implementing one or more controlled-release strategies during electrospinning or post electrospinning. Before that, it is important to understand the drug-release mechanism through nanofibres.

There have been numerous attempts to understand the mechanism of drug release through nanofibres. Y. Fu *et al.* summarized that the release mechanism is an intricate process and a function of multiple factors.⁴¹ The factors that significantly contribute to drug release are: (a) the physico-chemical properties of the drug, (b) the structural characteristics of the polymeric matrix, (c) the release environment, and (d) the possible interactions among all these factors. To elaborate in

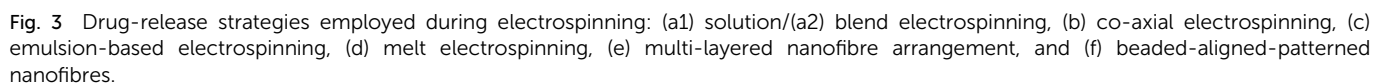




The controlled release of a drug is important since it is economical, environmentally friendly, and patient compliant as it avoids drug level fluctuations, toxic accumulation, multiple dosages, and restricts material losses. In order to control the drug release, one needs to investigate and understand the fundamentals behind drug diffusion through nanofibres. In general, drug diffusion, the polymer-matrix swelling, and material degradation are the key mechanisms involved in the drug release from polymeric nanofibres. However, all three mechanisms do not need to exist together.

The details of the pre- and post-electrospinning strategies to encapsulate the drug into the polymeric matrix and the understanding of its release behaviour are disseminated in the following section.

In another study, tri-axial electrospinning was introduced by Liu *et al.* (2019) to obtain electrospun ferulic acid/gliadin nanofibres.⁴⁷ Two non-electrospinnable solutions were placed in the middle (solvent) and outer layers (dilute CA), while the core solution was made up of electrospinnable ferulic acid/gliadin. After electrospinning, a thin coat of CA was formed



4.1.4. Melt electrospinning. In conventional electrospinning, mostly the organic and mixed volatile solvent system is specially selected to dissolve the drug and polymer. However, the drug loading is limited by its solubility in the solvent and also by the ratio of the solvent in the mixed system.⁵¹ It has been

Compared to solvent-based electrospinning, melt-based electrospinning is economically and environmentally friendly,

and hence it is termed a “green process.” In the future, reducing the fibre diameters from microns to the nano level is desired.

4.1.5. Multi-layered arrangements. Diffusional barriers in electrospun mats can be created by fabricating a multilayer assembly, as shown in Fig. 3(e).⁵⁷ In one such report, a multi-layer assembly of inner and outer ethyl cellulose nanofibres over curcumin-loaded gelatin nanofibres aided the sustained release of curcumin for 96 hours.⁵⁸ The outer hydrophobic nanofibre coating restricted fluid penetration by imparting water-contact resistance to the inner hydrophilic curcumin–gelatin mat, which delivered all the curcumin in only 30 min when tested alone.⁵⁸ The drug release could be effectively controlled when focusing on the transdermal and transmucosal routes.

4.1.6. Aligning or patterning of nanofibres. Aligning or patterning nanofibres can help control the interfibrous spacing and overall porosity, facilitating penetration and occupancy of the release media inside the nanofibrous matrix. Further, the spacing between the nanofibres changes the surface wettability too.

Aligned nanofibres can be produced using a rotating mandrel as a collector (as shown in Fig. 3(f)), or by a unidirectional patterned collector or parallel electrodes.⁵⁹ The patterned nanofibres can be generated by collecting fibres on patterned templates (mesh, grids, complex architecture), as shown in Fig. 3(f), or by employing patterned electrodes.⁶⁰ M. Saadatmand *et al.* prepared different templates for the non-conducting polymer with a pentagon and tetragon geometry.⁶¹ When cetirizine (anti-histamine drug)-loaded PCL nanofibres were deposited on these non-conducting templates, patterned cavities with random deposition were formed. The transdermal drug-release studies demonstrated a burst and immediate release profile, since the spacing between the pattern was more, *i.e.* in the millimetre scale. However, in a study by Adepu *et al.* (2017), micropatterned drug-loaded nanofibres with 100 μm spacing and a cup-like geometry in a mesh gave a zero-order release for 12 h (65% release),¹ showing spacing of the patterns matters.

4.1.7. Beaded nanofibres. Often undesirable and rejected during the fabrication of drug-loaded nanofibres, beads can act as a drug reservoir too. Tingxiao Li *et al.* (2019) explored and validated the potential of beads on string nanofibres made up of PLGA, as an excipient for micro-level solid drug particles of tetracycline hydrochloride (antibiotic drug).⁶² As per the study, the bead number and bead diameter were crucial factors in drug release. The bead number defines the encapsulation capability or drug loading capability, whereas the bead diameter or size majorly contributes in determining the drug-release kinetics.⁶² Bigger sized beads were found to lower the initial burst release, whereas, an increased number of beads increased the total drug release. Thus, a uniform-sized bead distribution is desired to estimate the drug-release mechanism. Regarding the uniform fabrication of beads, Tugba Eren Boncu *et al.* (2020) illustrated the interdependency of the solution parameters (*i.e.* a low viscosity, low conductivity, high surface tension, and low polymer concentration) and process parameters (*i.e.* a lower voltage, high flow rate, and small distance between the collector and needle orifice).⁶³ For a less viscous solution with lower

conductivity, uniform circular beads were formed in one of the studies due to an insufficient elongation of the polymeric jet by an electrical force.^{44,63} However, when the viscosity gradually increased, then spindle-shaped beads were formed (refer to Fig. 3(f)).⁴⁴

The most engaging feature of beads on string nanofibres is the formation of 3D nanofibres with macro-pores, which paves a way for regenerative medicine.⁶² Tingxiao Li *et al.* (2020) successfully encapsulated bovine serum albumin with growth factors in the core side into beaded nanofibres of polylactic acid- ϵ -caprolactone (shell side). The as-prepared scaffold showed good attachment and the spread of human mesenchymal stem cells onto the surface of the core and shell nanofibres with the sustained release of growth factors.⁶⁴ Compared to the bead-free nanofibres, the mechanical strength of beaded fibres is less due to the decreased cohesive force between the nanofibres.⁶³ This can be significantly resolved by using polymer blends.

4.2. Post electrospinning

The post-electrospinning operation involves the immobilization of the drug or biomolecules or enzymes onto the pristine polymeric nanofibres and surface modification of the drug-loaded polymeric nanofibres. Fig. 4 shows the post-electrospinning operations that can be employed to immobilize the active molecules and control their release.

4.2.1. Surface immobilization. As electrospinning utilizes an organic solvent system that may be toxic, it can be a challenge to incorporate a few drug molecules, such as solid drug particles, natural or bioactive drugs, and biomolecules such as polypeptides, proteins, vitamins, enzymes, and antibodies. Those biomolecules that may lose their activity during solution preparation can be incorporated into the nanofibres in three different ways: encapsulation, adsorption, and covalent bonding,^{65,66} refer to Fig. 4 for further insights.

4.2.1.1 Encapsulation. This is the process in which drugs or biomolecules are entrapped in the polymeric matrix. The biomolecules are suspended uniformly into the spinning solution and get immobilized after electrospinning. For instance, Xiaobo Chen *et al.* (2019) loaded gentamicin (antibiotic drug) into mesoporous silica nanoparticles and suspended them in PCL solution before electrospinning. The entrapped drug could be released steadily, and a $\sim 20\%$ release was achieved after 24 h compared to $\sim 65\%$ without immobilization.⁶⁷

4.2.1.2 Adsorption. Adsorption is the most common way to immobilize drugs and biomolecules. It involves a two-step process. First, the drug/biomolecule and electrospun mat are dipped in a solution for a fixed time. Due to the high surface area and porous structure of the mat, the solution penetrates in to the innermost fibres and then surface adsorption of the drug/biomolecule occurs. In the second step, the mat is rinsed with buffer solution to remove unadsorbed molecules. The weak van der Waals forces or hydrophobic and electrostatic interactions hold the adsorbed molecules.⁶⁶ Although adsorption is inexpensive, reagent-free, and easily reversible, weak bonding also lets it gets desorbed fast with a change in the temperature, pH,

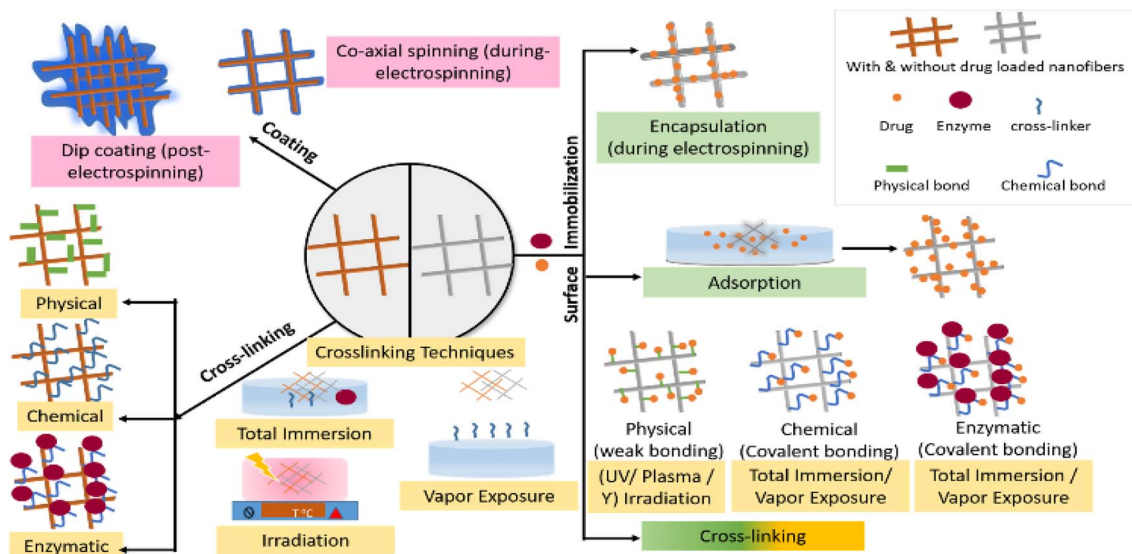


Fig. 4 Post electrospinning strategies involving drug/enzyme immobilization and controlled release, comprising surface immobilization, crosslinking, and coating.

or surface energy. Thus, for rapid delivery, adsorption is the easiest immobilization technique.

4.2.1.3 Covalent bonding. The interactions between the functional groups of biomolecules with the functional groups of polymers can produce stable complexes. Mostly, biopolymers with -amino, -carboxylic, -thiol, -imidazole, -indole, and -hydroxyl groups are involved in covalent bonding.⁶⁶ The bonding can be done either by direct reaction or by activation through a crosslinker. In one study reporting the immobilization of bromelain enzyme onto cellulose triacetate, the enzyme was immobilized on nanofibres through glutaraldehyde. For comparison, the enzyme was also blended with the polymer in an organic solvent system of acetone and di, methyl formamide, and it was found that 90% enzymatic activity was lost due to exposure to the organic solvent system post-electrospinning.⁶⁸ Thus, covalent bonding has benefits over surface immobilization; however, use of inappropriate chemical crosslinkers can also reduce the bioactivity.

4.2.2. Crosslinking. Mostly, nanofibres derived from natural-based polymers require crosslinking to enhance their water resistance and thermo-mechanical characteristics. Crosslinking means linking polymer chains, which alters the functionality of the polymer. It can be done in three distinct ways: physical, chemical, and enzymatic crosslinking.^{69,70} Physical crosslinking involves using a high-energy electron beam, UV/ γ irradiation, plasma exposure, or de-hydrothermal treatment.⁷¹ For example, de-hydrothermal treatment of drug-loaded PVA nanofibres causes a condensation of water molecules and crystallization of drugs.⁷² This aids in the slow release of drug molecules. Plasma exposure generates an oxygen radical that reacts with water and removes it from the polymer.⁷³ To determine the most suitable strategy, it is significant to understand the structure and functional groups of the polymer. Chemical and enzymatic crosslinking are similar to covalent

bonding in the presence of a crosslinker/enzyme, as explained in Section 4.2.1.

4.2.3. Coating. An applied coating can act as a diffusional barrier to control the initial drug release. Yaoyao Yang *et al.* (2019) demonstrated that a cellulose acetate coating of 11.6 μm could prolong ibuprofen release from core (ibuprofen-gliadin) and shell (cellulose acetate) nanofibres, from 23.5 to 44 h.⁷⁴ As mentioned earlier, the thickness of the coating plays an important role.

Apart from this, the coating can protect the bioactivity of drugs and also provide sliding/flexibility while passing through the GI tract. Tao Hai *et al.* (2019) demonstrated that a lipid coating on berberine hydrochloride-loaded ethyl cellulose nanofibres could reduce the burst release of the drug from 65% to 40% in the initial 4 h, while also enhancing the anti-microbial activity of berberine compared to the case without the coated nanofibres.⁷⁵

As we are aware, most polymers do not possess any specific functional groups, so they must be functionalized for successful specific applications. The current section highlights the techniques to functionalize polymeric nanofibres, such as, by using particular encapsulation techniques to load the active molecule or by employing surface modifications after nanofabrication. These specific techniques, such as blending, coating, grafting, crosslinking, or plasma exposure, need to be properly controlled to prevent the nanofibre morphology being distorted. Moreover, the functionalized nanofibres should not be toxic to the user or the environment.

5. Drug delivery through nanofibres in different routes

In any route of drug administration, the drug has to cross biological membranes before entering the systemic circulation or



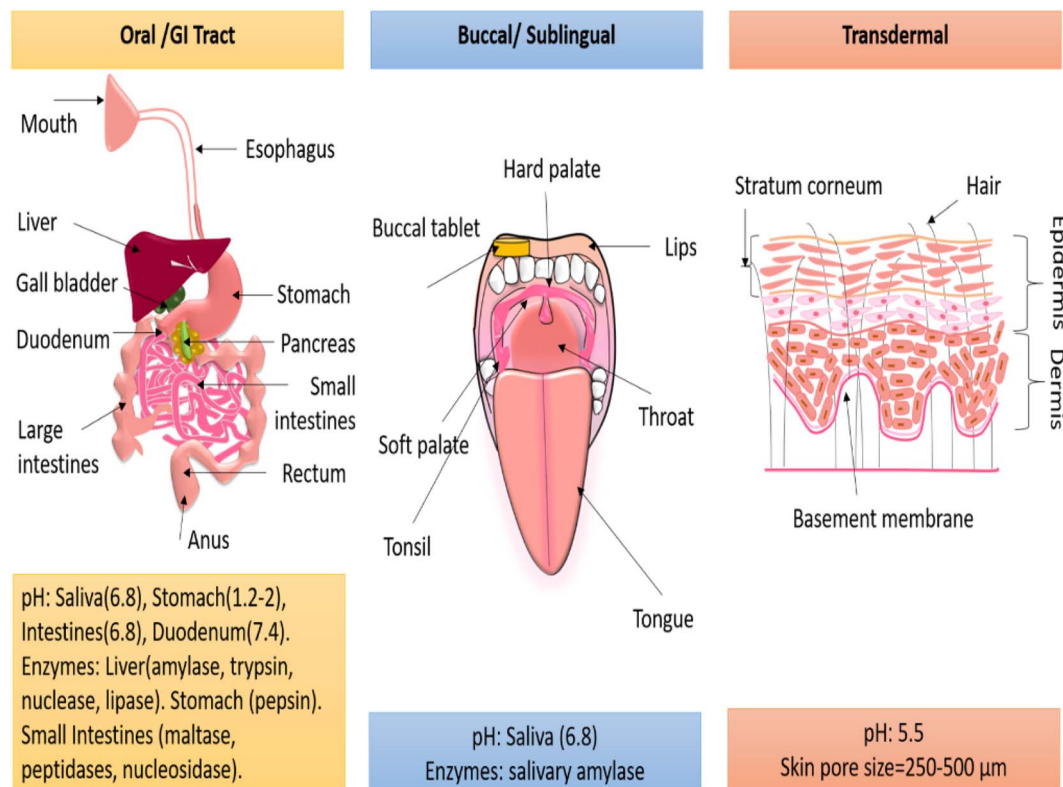


Fig. 5 Physiological conditions in the oral or GI tract, buccal/sublingual, and transdermal routes.

getting into the direct diseased site. While targeting specific routes, the physiological conditions must be considered, and accordingly, the properties of the nanofibres should be tuned to fit these conditions. Fig. 5 highlights the physiological conditions in the oral, transdermal, and buccal routes. The following section delineates the suitability of nanofibres for a particular route and the further customization required to achieve controlled release.

5.1. Buccal or sublingual route

In the buccal or sublingual region, the moist environment, flexible tissues, and slippery texture cause a lower retention of conventional formulations.⁷⁶ However, drug-loaded nanofibres, by virtue of their high specific surface area and mucoadhesive properties, can effortlessly deliver drugs in the buccal or sublingual regions.⁷⁷ The drug absorbed by the highly vascularized buccal mucosa and sublingual region can directly enter into the systemic circulation, eliminating the need for passage through the GI tract and therefore bypassing the influence of enzymes, gastric acids, and the first-pass effect.^{40,77} This route is especially suitable for delivering drugs with poor solubility and low bioavailability. Jinghan Li *et al.* (2020) delivered the carvedilol (beta-blocker used to treat heart failure and hypertension) drug, which is known to have poor aqueous solubility and 25% bioavailability, by the sublingual route immediately from polyvinyl pyrrolidone PVP/PEG-400 nanofibres.⁴⁰ The amorphous nature and hydrophilicity of the nanofibres could ensure the

release of 80% carvedilol in 30 min from nanofibres, while only 10% of the drug was released from the physical mixture alone.⁴⁰

Emese Sipos *et al.* (2019) fabricated the oral-dissolving nanofibrous web-releasing aceclofenac (an anti-inflammatory drug with a low biological half-life) within a minute from trolamine/PVP nanofibres.⁷⁷ The improved wettability and high dissolution of trolamine-PVP aided immediate drug release.⁷⁷ Thus, buccal or sublingual drug delivery provides a plausible way to deliver poor-water-soluble drugs, non-steroidal anti-inflammatory drugs, antibodies, and peptide-based formulations, either for systemic drug delivery or for treating oral diseases. Further, buccal or sublingual delivery can be used for old-aged people and children who face difficulties swallowing.

5.2. Oral/GI tract route

The oral route is the most preferred route for drug administration but has a highly complex physiology. In the GI tract, the drug must penetrate through the epithelium and the innermost lining of the entire lumen. The epithelial cell barrier selectively permeates the drug to the underlying tissue compartments *via* three mechanisms: transcellular diffusion, para-cellular diffusion, and receptor or carrier-mediated diffusion.⁷⁸ Furthermore, after an oral administration, the drug has to survive through variable pH conditions and enzymatic degradation, as shown in Fig. 5. Polymeric encapsulation, a high surface-to-volume ratio, and a nano topography aid systematized drug diffusion along with their biostability in gastric acids and enzymes. For

hydrogel, the composite displayed a higher modulus and compressive strength along with improved cell proliferation.⁹⁸

Nanofibres can be loaded into the hydrogel in various steps. Juliana Ribeiro *et al.* (2020) first fabricated ciprofloxacin- β -cyclodextrin nanofibres and then cryo-cut the mat and freeze-dried it in polydioxanone to obtain short nanofibres. Later, these short nanofibres were dispersed into a gelatin methacrylol hydrogel. The injectable hydrogel delivered the loaded antibiotic at a sustained rate for treating periodontal disease and pulpal pathology.⁹⁷

This section discusses the design considerations with respect to the physiological conditions in the oral, buccal, transdermal, topical, and parenteral routes. Their smaller size, easy drug encapsulation, ability to mimic the extra cellular matrix, and biodegradability make polymeric nanofibres as an interesting carriers for different administration routes. However, the drug interaction with the biological barriers, and its absorption, solubility, and bioavailability determine its fate for clinical acceptance.

6. Future challenges and state of the art

Although numerous strategies are being executed and have been formulated to attain customized drug delivery, the focus is on achieving inexpensive, biocompatible, patient-friendly, and environmentally friendly drug-delivery systems. The following are the neoteric aims being explored in this direction.

6.1. Green electrospinning

When it comes to large-scale production, the material and production cost, and societal and environmental concerns need to be considered.^{104–106} Basically, a “green” approach is anticipated. Earlier, melt electrospinning was described as a “green process”. Other alternatives with probable pros and cons are discussed below.

6.1.1. Green solvent. In electrospinning, a suitable solvent system is required to dissolve API and polymers. Often these volatile solvents are toxic, hazardous to the environment, and difficult to recover. During electrospinning, solvent vaporization takes place, and the vapours accumulate in the closed compartment. These vapours can corrode the metallic set-up, entrap into the pores of drug-loaded nanofibres, and can harm the operator after opening the doors.¹⁰⁶ Considering these issues, water-based solvent systems have the potential to offer the least environmental hazards most economically.¹⁰⁷ The noted green solvents, apart from DI water, are acidic PBS, skimmed milk, and limonene, which is an extract obtained from orange peels.¹⁰⁷ Water-soluble polymers, such as PVA, PEO, PVP, gelatin, polyamic acid, hydroxypropyl cellulose, kefir, dextran, and many more, can be considered for electrospinning.^{72,107} These polymers with fast water-dissolution properties could be ultimately utilized in the immediate or fast release of drugs, preferably in the buccal or sublingual routes.¹⁰⁶

A few water-soluble polymers, such as polyelectrolytes, are not spinnable. In such cases, additives and salts can help. Songnan Li *et al.* (2020) fabricated nanofibres from an aqueous dispersion of modified starch and octenylsuccinated, and introduced pullulan polysaccharide to improve the adhesive/blending properties of the solution.¹⁰⁸ Furthermore, the water-soluble polymers face poor mechanical and thermal characteristics, which need to be improved. For tissue engineering of scaffolds and wound dressings, the mechanical strength is a decisive parameter. Daqian Gao *et al.* (2020) implemented a “green crosslinking” approach to improve the water resistivity and mechanical strength of PVA nanofibres loaded with epidermal growth factor derivatives as a wound-dressing biomaterial.¹⁰⁹ Before the loading of the growth factor, the PVA nanofibrous mat was crosslinked in ethanol solution for 24 h and later heated at 120 °C for 2 h.¹⁰⁹ Another approach is the blending of water-soluble polymers with synthetic polymers. Dalila Miele *et al.* (2020) blended collagen and PCL using an acidic aqueous solvent system as a green approach for improving the mechanical strength.¹¹⁰

6.1.2. Green polymer. The future of sustainable nanotechnology is feasible only with the best use of green materials. Here, biopolymers can serve as an affordable, easily available, non-toxic, biocompatible, biodegradable, and environment-friendly polymer source. To mention a few, these encompass alginate, chitosan, hyaluronic acid, kefir, pullulan, tree gum, gellan gum, zein, soy protein, and wheat protein, which are derived from natural sources.¹⁰⁵ In recent times, polysaccharides and protein-based polymers have received abundant attention. However, these biopolymers have poor conductivity and mechanical properties, and hence they are mostly blended with synthetic polymers. In blended nanofibres, a combination of the properties exhibited by the individual polymers is observed. Wherein, the addition of synthetic polymers can improve the water stability and thermo-mechanical characteristics of a final nanofibrous matrix, biopolymers provide biocompatibility and controllable biodegradability. In a study carried out by Meera Moydeen Hameed *et al.* (2020), core-shell nanofibres were fabricated with cephalixin (antibiotic), and corn oil as the core and PVA were blended in 90 : 10 ratios with four kinds of biopolymers, namely chitosan, carboxymethyl cellulose, carboxymethyl starch, and hydroxypropyl cellulose, respectively. After thermal crosslinking at 120 °C for 6 h, crystallization occurred. The *in vitro* release studies demonstrated that the nature of the biopolymer blend and its inherent interaction with the second polymer could significantly control the drug-release kinetics.⁷²

6.1.3. Crosslinker-free approach. In drug delivery and tissue engineering, biopolymers are exploited as drug excipients or scaffolds, owing to their cytocompatibility and non-toxic degradation in the system.^{111,112} However, FDA-approved biopolymers, such as gelatin, chitosan, and alginate, often face limitations due to the use of chemical crosslinkers, such as glutaraldehyde, which is toxic. Although a few works have reported minimizing the use of crosslinkers either by lowering their concentration or time of exposure, a crosslinker-free approach would always be welcomed.^{57,81} We can exclusively



6.4. Polymer-free drug release

As a polymer-free system, it may undergo first-pass metabolism and a decayed bioactivity; hence, cyclodextrin-based nanofibres can be used in buccal or sublingual administration.

Due to an upsurge in the complexities associated with synthetic drugs, such as anti-microbial resistance, lethal side effects, inappropriate systemic clearance, and cytotoxicity, it is high time to develop phytochemical-based drug delivery.^{117–119} As evidenced by various studies, herbal drugs are easily adaptable to the human body and offer minimum side effects. The numerous components in herbal extracts can act synergistically and offer a complete solution to a disease, unlike synthetic drugs.¹²⁰ The polymeric encapsulation of herbal drugs into nanofibres in the form of extracts, active components, and essential oils have been investigated for varied applications, such as wound-healing mats, drug-delivery systems, and implants.^{26,121} In recent times, phytochemical-loaded nanofibrous patches have been explored and tested for effectual chemotherapy after cancer surgery to prevent relapse. Rasouli *et al.* (2020) encapsulated the plant antioxidants curcumin and chrysin simultaneously into a PLGA/PEG blend. The obtained nanofibres exhibited enhanced anti-cell proliferative activity against breast cancer cells compared to only curcumin-loaded nanofibres.¹²² Thus, phytochemical-based drug delivery can offer the safest alternative to chemotherapy and radiotherapy, which traditionally can cause adverse side effects and affect the life quality of cancer patients.

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