NANOFIBER PATCHES FOR ENHANCED SUBLINGUAL DRUG DELIVERY: A REVIEW

Ms. Amandeep Kaur[1] , Prof.(Dr.)Naresh Singh Gill[2],Mr. Sahil Chandel[3] ,Ms. Kanika[4]*

Associate Professor LTSU[1] , Executive Dean/ Director LTSU[2] ,Department Of Pharmaceutics[3] ,Assistant Professor LTSU[4]

[1]ranaji.kaur@gmail.com,[2] rip.director@rgi.ac.in ,[3]sahilchandel497@gmail.com

[4]kanikapharma1993@gmail.com

Abstract

Nanofiber-based drug delivery systems have gained significant attention in recent years, particularly for sublingual administration, due to their potential for rapid absorption, improved bioavailability, and enhanced patient compliance. Traditional oral formulations often face challenges such as first-pass metabolism and delayed onset of action, limiting their therapeutic efficacy. Nanofiber patches, produced via electro spinning, provide a high surface area, facilitating quick dissolution and efficient drug release through the sublingual mucosa. Additionally, their flexible and ultra-thin structure ensures ease of application and improved patient comfort. Despite these advantages, several formulation challenges must be addressed. including taste masking, uniform drug distribution, and stability under physiological conditions. This review explores the fabrication techniques, physicochemical properties, drug loading strategies, and potential applications of nanofiber patches for sublingual drug delivery. Furthermore, current challenges and future perspectives in the development of these systems are discussed to highlight their role in advancing non-invasive and efficient therapeutic approaches.

Keywords- Nanofiber patches, sublingual drug delivery, electro spinning, bioavailability. sustained release.

1. Introduction

One new and exciting paradigm in biomedical research is nanotechnology, or the utilization of nanomaterials for biomedical purposes. In order to accomplish the intended therapeutic efficacy, nanomaterials with remarkable physiochemical characteristics, biocompatibility, and low biological toxicity can detect their local biological surroundings and start cellular level reprogramming. Current applications for diagnosis, imaging, and therapy include a variety of zero-dimensional (quantum dots, carbon dots, graphene quantum dots), one-dimensional (Nano rods, nanowires, nanotubes, Nanofiber), and two-dimensional (graphene oxide, transition metal dichalcogenides, transition metal oxide, MXens, etc.) nanomaterial and Nano sized particles. Nanofibers are nanostructures that resemble fibre and usually have two nanoscale dimensions. Nanofibers are easily functionalized with biological molecules and have a high surface area-to-volume ratio with adjustable porosity. Nanofibers are a strong and appealing option for many cutting-edge biomedical applications because they may be made from a wide range of materials, including natural and synthetic polymers, inorganic nanomaterials, composites, and biomolecules as medications [1]. Because of their exceptional qualities, nanofibers are the perfect nanomaterial for applications in biomedical engineering, healthcare, water and environmental treatment, and energy generation and storage. A novel and adaptable method, electrospinning continuously extracts nanofibers from viscoelastic fluids by using the electrostatic repulsion between surface charges. Nanofibers are produced using a variety of various materials, including small molecules, polymers, ceramics, and their mixtures [2]. A secondary structure of nanofibers, such as porous, hollow, or core-sheath structures, has been produced in addition to solid ones. During or after the electrospinning process, the surface of the structure can be functionalized with various molecular moieties. Because of its variable diameter, ease of handling, low solution consumption, and affordability, electrospinning is the primary technique of choice for producing nanofibers on a wide scale. Numerous biomedical uses for electro spun Nanofiber exist, including wound dressings, medication and gene delivery devices, sensors, and catalysts. For effective loading,

release, and accumulation of the therapies into the target region, a variety of therapeutic delivery methods have been studied. But when it comes to choosing various substances, medications, and genes (DNA, RNA, etc.) for therapeutic uses, electrospinning offers a great deal of freedom [3].

2. Electrospinning

Methods For creating the nanofibers of polymers, composites, and inorganic materials such as carbides, oxides, nitrides, and hybrid composites, electrospinning is regarded as a promising, extremely effective, and straightforward technique. The electrospinning method creates nanofibers from a polymer solution by using electrostatic forces [4]. Figure 1 illustrates the three primary components of the electrospinning setup, which are (i) a high voltage power source, (ii) a spinneret, and (iii) a conductive collector. A voltage (kV) is placed between the spinneret and the collector during the electrospinning process. These components are optimally spaced apart and conduct electricity. A charged jet of polymer solution may be released from the tip of the droplet when the supplied electric field exceeds the droplet's surface tension. The polymer solidifies as a result of solvent evaporation as the jet gets thinner and longer with an increasing high diameter loop. On the target, the cemented nanofibers are subsequently gathered. Random and aligned nanofibers are the two broad categories into which electro spun Nanofiber fall [5]. A basic plate collector may be used to create random nanofibers, while a disc or cylinder that rotates quickly along its rotational path can be used to create aligned nanofiber mats or uniaxial fiber bundles. The molecular weight of polymers and the properties of polymer solutions (such as viscosity, conductivity, dielectric constant, and surface tension); (ii) the processing parameters (such as the electric potential, flow rate, feeding rate, distance between the capillary and collection, and the use of coaxial or triaxial needles for hollow, core–shell, or multi-sheathed structures); and (iii) controlled post processing parameters (such as heating rates and heating temperatures, especially for inorganic materials) can be changed to modify the distinctive physical properties of electro spun Nanofiber, including their high surface-to-volume ratio, controllable fiber diameters, and fibrous structures [6]. Nanomaterials 2019, 9, x FOR PEER REVIEW 3 of 32 are generated using a straightforward plate collector, while aligned nanofiber mats or uniaxial fiber bundles can be created with a disc or cylinder that spins at high speeds, serving as the collector in the direction of its rotation. The distinctive physical properties of electro spun Nanofiber, including a high surface-to-volume ratio, adjustable fiber diameters, and various surface morphologies (such as dense, hollow, and porous) along

with fibrous structures, can be modified by varying certain parameters, for instance: (i) the molecular weight of polymers and characteristics of the polymer solution (viscosity, conductivity, dielectric constant, and surface tension) [7]; (ii) the processing conditions (including electric potential, flow rate, feeding rate, and the distance between the capillary and the collector, as well as utilizing coaxial or triaxial needles for hollow, core-shell, or multi-sheathed configurations); and (iii) controlled post-processing conditions (like heating rates and temperatures, particularly for inorganic substances) [8].

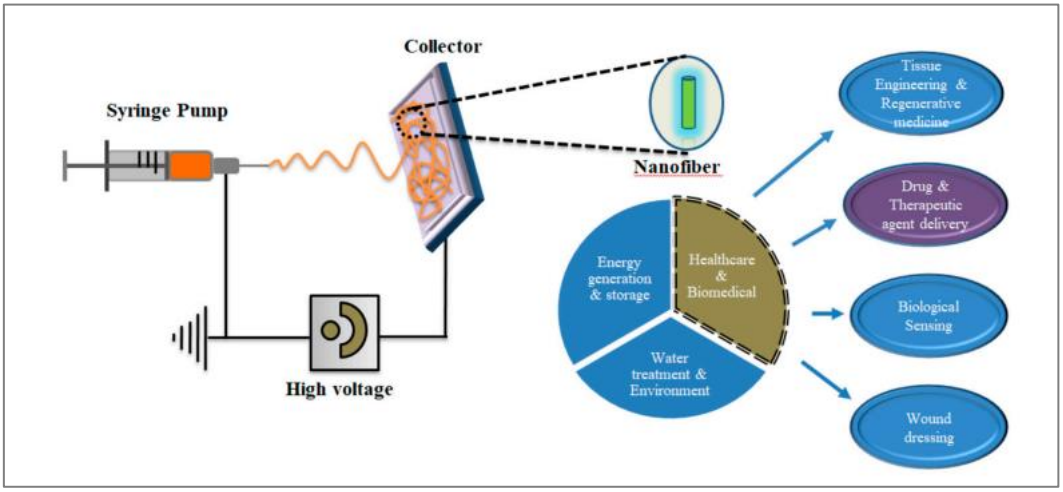

Figure 1. Schematic representation of a traditional electrospinning process and various healthcare and biomedical applications of nanofibers

2.1 Types of Electrospinning

While fibers created through various electrospinning techniques have garnered growing interest in biomedical applications, difficulties remain in choosing the right method and fine-tuning several parameters to produce sturdy cargo-loaded nanofibers [9]. Electrospinning methods can be divided into five distinct categories: Blend electro spinning;

- Coaxial electrospinning;
- Emulsion electrospinning;
- Melt electrospinning; and
- Gas jet electrospinning.

Blend electrospinning is capable of producing nanofibers that enable burst release, whereas co-axial and emulsion electrospinning techniques are utilized to create core-shell nanofibers that facilitate sustained drug release. Melt electrospinning is recognized as a more environmentally friendly fabrication technique, widely employed to create highly organized electro spun Nanofiber. Nonetheless, melt electrospinning tends to yield fibers with a greater

diameter [10]. The fundamental principles of each electrospinning configuration and the process variables influencing fiber morphology are detailed in the following sections.

2.1.1 Blend Electrospinning

Blend electrospinning is capable of producing nanofibers that enable burst release, whereas co-axial and emulsion electrospinning techniques are utilized to create core-shell nanofibers that facilitate sustained drug release. Melt electrospinning is recognized as a more environmentally friendly fabrication technique, widely employed to create highly organized electrospun nanofibers. Nonetheless, melt electrospinning tends to yield fibers with a greater diameter [10]. The fundamental principles of each electrospinning configuration and the process variables influencing fiber morphology are detailed in the following sections. [12]

2.1.2 Co-Axial Electrospinning

Co-axial electrospinning is an advancement over traditional mix electrospinning, which uses two nozzles instead of one to connect to the high voltage source. To create nanofibers with core-shell morphologies, two distinct solutions are fed into each nozzle and pushed out [13]. Core-shell nanofibers with enhanced physiochemical and biological characteristics may be created using both natural and synthetic polymers. The ability to both protect and overcome the denaturation of pharmaceuticals or biomolecules in the biological system makes this technology superior than the mix electrospinning method. The biomolecules or medications are located in the inner jet of co-axial electrospinning, and they co-spread with the polymers in the outer jet. As a consequence, the cargo is protected, and it also helps to sustain them in the biological environments. For instance, Merkle et al. created core-shell nanofibers using gelatin and polyvinyl alcohol (PVA) [14]. By adding more gelatin to the shell, the core PVA phase's mechanical strength was increased. In contrast to PVA fibers, the authors asserted that the gelatin shell increased fibroblast and cell adherence to the PVA/gelatin fiber surface. Furthermore, biomolecules can be added to the surface of coaxial fibers to increase their biofunctionality and improve interactions between cells and surfaces [15]. In addition to the design complexity, core-shell nanofibers from coaxial electrospinning require careful monitoring of the viscoelasticity and interfacial tension of the core and shell polymers.

2.1.3 Emulsion Electrospinning

In order to create core-shell nanofibers, emulsion electrospinning necessitates a setup akin to mix electrospinning, which involves spinning two immiscible liquids concurrently. In this

case, surfactants and active bioactive compounds are first permitted to produce W/O emulsions before being combined with the polymer matrix solution [16]. The emulsion droplets are stretched into an oval form along the fiber trajectory. The viscosity gradient and droplet enrichment in the axial area are also caused by the rapid evaporation of the continuous phase solvent [17]. The core material is guided to settle inside the fiber matrix rather than on the polymer surface by the viscosity difference between the elliptical droplet and the polymer matrix. In comparison to co-axial electrospinning, this technique is comparatively straightforward and provides a sustained release of the loaded cargo materials [18]. The diameters of the nanofibers are significantly impacted by the applied voltage. A lower diameter of nanofibers is produced as a result of higher applied voltage. Fiber shape can also be influenced by other factors including flowrate and spinning distance. Nevertheless, the bioactive molecules included in the emulsion electrospun fibers may be harmed by the interface tension between the organic and aqueous phases of the emulsion [19].

2.1.4 Melt Electrospinning

In the realm of electrospinning, where toxicity and solvent build up are issues, melt electrospinning has drawn increased interest. Instead of using solvent evaporation to produce the desired result, this approach uses a polymer melt, which turns from a liquid to a solid upon cooling [20]. To create high-quality fibers with a wide variety of diameters and consistent shape, the flow rate and homogenous polymer melt conditions must be regulated. The average fiber diameter has been decreased by the use of polymer mixes and additives. The structure and functionality of medications, proteins, and bioactive compounds put into fibers can be impacted by the melt temperature. The properties of the final fibers can be affected by the melt electrospinning process's flow velocity and melt viscosity. By employing oxygen and ammonia plasma to create hydroxyl or peroxyl and N-containing functional groups, respectively, the surface wettability of melt electrospun fibers has been enhanced [21].

2.1.5 Gas Jet Electrospinning

The traditional melt electrospinning method is improved by gas jet electrospinning, which involves adding a gas jet device to the traditional electrospinning setup. Melt electrospinning's primary drawback is that method necessitates precise temperature control, necessitating the placement of many heating zones in order to maintain the polymer melt. In

contrast to the solutions, thicker nanofibers are produced as a result. This method can delay the polymer solidification process by providing enough heat close to the nozzle by enclosing the co-axial jet in a tube that feeds the heated gas. For instance, Zhmayev et al. spun polylactic acid (PLA) and shown that, in contrast to conventional electrospinning, the diameter of the nanofibers produced by gas jet electrospinning was reduced. It's interesting to note that the diameter of the nanofiber was significantly impacted by the hot gas flow rate. Thinner nanofibers may form as a result of the greater drag force that the higher gas flow rate can provide to the jet surface. The results of Zhmayev et al. shown that increasing the gas flow rate from 5.0 L/m to 15.0 L/m resulted in a considerable drop in the diameter of the nanofiber, from 350 nm to 183 nm. [22]

3. Therapeutics Delivery Systems

In addition to having poor bio distribution, solubility, and stability in the biological system, the majority of traditional medications are hydrophobic. Furthermore, many medications lack the intended active targeting properties, which may lead to non-specific systemic toxicity or quicker bodily excretion without producing the intended therapeutic effect. Approaches, formulations, and technologies for delivering therapeutic agents to the intended therapeutic location in the body are known as drug delivery systems (DDS) [23]. In addition to encapsulating the target drug or biomolecule, the developed DDS technologies optimize its absorption, distribution, release, and elimination with increased loading effectiveness and safety. Drug release from DDS carriers is dependent on processes based on diffusion, degradation, swelling, and affinity [24]. Electro spun nanofibers are receiving a lot of interest as prospective therapeutic Nano carriers, as was previously indicated. Furthermore, their remarkable qualities—such as high therapeutic payload capacity, biocompatibility, and biodegradability—meet the requirements for a promising therapeutic delivery candidate [25]. Various routes of administration (ROA) are being studied using electro spun Nanofiber scaffolds as a medicinal Nano carrier. Many common routes, including oral, parenteral (subcutaneous, intramuscular, intravenous, and intrathecal), sublingual/buccal, rectal, vaginal, ocular, nasal, inhalation, and transdermal, can be used to administer drugs or therapeutics to any part of the body using electro spun nanofibers (Figure 2). Here, we outline the typical drug delivery methods using electro spun nanofiber [26].

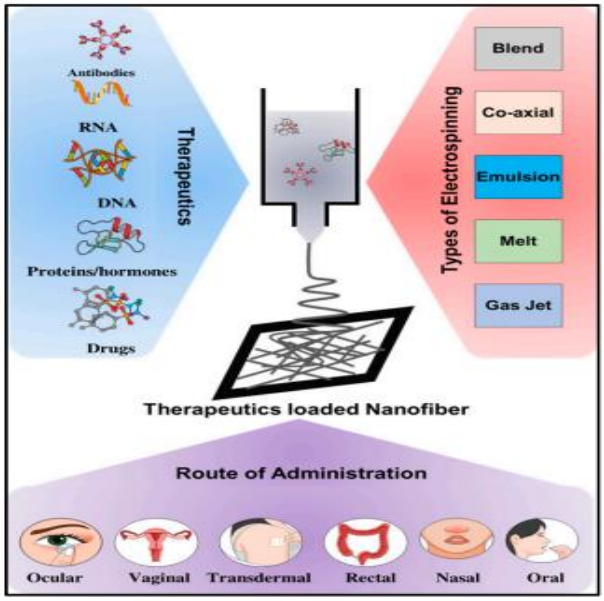

Figure 2. Types of electrospinning, different therapeutics-loaded nanofibers and their route of administrations

3.1 Oral

The oral route of administration is seen to be the most convenient and preferred of all delivery methods, and it can solve the issues that other routes of administration may present [27]. Nonetheless, it is challenging to provide medications that target the oral route of delivery successfully. Before creating a successful oral delivery system, researchers should take into account the main obstacles that can prevent drug delivery systems from being absorbed into the body, such as the stomach's acidic gastric juice, proteases, mucosal barriers, and intestinal retention. Targeting the oral route, electrospun nanofiber scaffolds present a fantastic opportunity to load and distribute both macro and micro molecules [28]. The ability to construct any desired release features, such as regulated, rapid, biphasic, or delayed drug releases, is another exciting benefit of employing electrospun nanofibers. Poly (lactic-co-glycolic acid) (PLGA), polyvinylpyrrolidone (PVP), poly(ethyleneoxide) (PEO), PVP/cyclodextrin, PVA, polycaprolactone (PCL), PVP/ethyl cellulose, PVP/zein, cellulose acetate, Eudragit L, hydroxypropyl methylcellulose (HPMC), Eudragit S, Eudragit S/Eudragit RS, and shellac are among the polymers used to design oral drug delivery systems using electrospun nanofibers. [29].

3.2 Rectal

Typically, children less than six months are unable to ingest any medication or dietary supplements. The rectal route could be the most effective substitute for oral medication

delivery methods in certain situations. Furthermore, the rectal route works well for individuals who are vomiting or asleep. Rectal medication delivery systems based on electro spun nanofibers are becoming more and more well-liked. Electro spun nanofibers may be a safe, biocompatible, and biodegradable sealing fiber for the treatment of post-operative peritoneal effusion after rectal or pelvic surgery. 2014 saw the publication of the first clinical study examining the sealing capabilities and safety of electro spun nanofibers in treating lymphorrhea after pelvic surgery [30]. The authors created self-assembled nanofibers using a synthetic substance called PuraMatrix, which is made up of sixteen amino acid peptides. The clinical trial involved 20 individuals with colorectal cancer. Following a follow-up period of two to three months, the experimental group's post-operative drainage volumes were significantly lower than those of the control group. In a different investigation, Modgill and colleagues looked into how easily penicillin may pass through various cellular membranes from an incredibly thin nanofiber scaffold. The authors created ultra-thin nanofibers loaded with ciprofloxacin using PVA. Studies on in vitro permeability demonstrated the electrospun nanofibers' efficacy in comparison to the unmodified medication. The rectal mucosal membrane's maximum ciprofloxacin permeability was found in PVA nanofibers. In contrast to the control group, which displayed significant oscillations, the drug release investigation demonstrated the regulated release behavior of ciprofloxacin from nanofibers in the rectal mucosal membrane. [32].

3.3 Vaginal

Recently, researchers have looked into electrospun nanofiber scaffolds that target vaginal passageways. However, before developing vaginal drug delivery systems with nanofibers, it is important to take into account the acidic state of the vaginal mucosa (~pH 4). Brako et al., for instance, created progesterone-encapsulated nanofibers that are intended to be administered vaginally. The authors created electrospun nanofibers using carboxymethylcellulose, a mucoadhesive chemical. Electrospun progesterone/carboxymethylcellulose nanofibers as generated demonstrated sustained release characteristics [33]. A research employing the anti-HIV medication maraviroc, in which the authors spun the drug using either PVP or PEO and showed that it dissolved quickly when it came into contact with moisture, is another illustration of nanofiber-based vaginal drug delivery [34].

4.5. Nasal

Nowadays, electro spun nanofiber scaffolds are created using supramolecular peptides. The potential of electro spun supramolecular peptide nanofibers for intranasal vaccination administration has been demonstrated. For instance, Si and colleagues used peptide nanofibers made by viral polymerase to create an influenza vaccine that is administered intranasally. Both humoral and cell-mediated immune responses against the influenza virus may be triggered by this self-assembled nanofiber. Specifically, antigen-presenting cells in lung-draining mediastinal lymph nodes first swallowed the nasally administered nanofiber vaccine particles, which then triggered both Th1 and Th2 to create an antibody against the target antigen. Additionally, without the addition of a vaccination adjuvant, a strong immunological response was generated. [35].

3.4 Ocular

For eye infections or inflammation, different drops or ointments are often utilized. These medications are readily and swiftly removed from the eye in these situations. Therefore, nanofiber-based ocular inserts have been investigated and contrasted with eye drops or comparable dosage techniques in order to enhance therapeutic efficacy and get around the need for repeated administration of a defined ocular dose. It is possible to insert drug-loaded nanofiber scaffolds into the ocular mucosa to enable the regulated release of integrated medications. For instance, as detailed in Section 5.1.9, brimonidine tartrate (BT)-loaded electro spun nanofibers were employed as ocular inserts to treat ocular inflammation and infection. [36]

3.5 Transdermal

Transdermal drug delivery systems (TDDS) provide superior skin permeability and administer a medication locally, preventing unwanted drug dispersion. Electro spun nanofibers have been evolved into TDDS because of its high solubility, excellent shape, and prolonged drug release kinetics. According to reports, electrospun nanofibers have the potential to improve solubility and create a transdermal patch for medications classified as systems II in biopharmaceutics. These pharmaceuticals have a high therapeutic efficacy and no cytotoxicity. The strength of TDDS is hydrophilic polymers with high permeability, and a number of in vitro and in vivo analyses point to the potential use of drug-loaded electrospun nanofibers in TDDS establishment [37].

3.6 Sublingual/Buccal

The buccal, sublingual, and gingival areas are the three distinct divisions of the oral mucosa. A few years ago, scientists were also interested in creating drug delivery systems based on nanofibers for administration via the buccal (between the gums and teeth) or sublingual (under the tongue) routes. The drug-loaded electrospun nanofibers in the sublingual or buccal delivery systems often disintegrate in the presence of mucus, allowing the medication to enter the tiny blood arteries directly. It's interesting to note that these oromucosal routes of administration are the most researched locations for nanofiber-based treatments, which provide flexible and multipurpose medications, growth factors, DNA, RNA, proteins, peptides, or vaccine delivery systems. [38].

When a medication is administered sublingually, it is positioned beneath the tongue and enters the bloodstream through the floor of the mouth and the ventral surface of the tongue [39]. The reticulated vein, which is located beneath the mouth mucosa, quickly absorbs the medication solutes. They are then carried via the internal jugular vein, the brachiocephalic vein, and the facial veins before being emptied into the systemic circulation. Direct systemic administration is made possible by the substance's more direct access to the blood circulation through the highly vascularized buccal mucosa's absorption pathways. [40].

Sublingual drug delivery is used in medicine for some barbiturates, enzymes, hormones, and cardiovascular medications. The administration of several vitamins and minerals has been a growing subject, and this approach is shown to be easily and completely absorbed. [41].

3.6.1 Mechanism of sublingual absorption

Three separate layers make up the mucosal lining. The epithelial membrane, which is made up of stratified squamous epithelial cells and serves as a protective barrier, is the outermost layer. The basement membrane, which resupplies the epithelium, is the deepest layer of the epithelial membrane. The submucosa and lamina propria are located under the epithelium. Collagen and elastic fibers are found in the lamina propria, a moist and less dense layer of connective tissue [42]. Additionally, the oral submucosa has a strong blood artery supply [43].

The medication immediately diffuses into venous circulation after being absorbed via the mucous membrane in the sublingual area. The venous blood from the mouth cavity's sublingual area empties into a common trunk, which then empties into the superior vena cava through the internal jugular vein, subclavian vein, and brachiocephalic vein. In contrast to

oral administration, venous return from these areas enters the systemic circulation and avoids the pre-systemic drug clearance. The medicine becomes immediately available throughout the body and acts quickly when it drains directly into the systemic circulation. It should be mentioned that smoking can alter the absorption of drugs since it induces vasoconstriction [44].

3.6.2 Drugs for sublingual administration

Direct nutritional benefits are achieved through sublingual absorption, which circumvents exposure to the liver and stomach. This is especially crucial for people with gastrointestinal issues like ulcers, hyperactive gut, celiac disease, impaired digestion, the elderly, and invalids.The nutritional advantage is unaffected by gastrointestinal factors [45].

3.6.3 Factors affecting the sublingual absorption [46]

- **Thickness of oral epithelium:** As the thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to the thinner epithelium and also the immersion of drug in smaller volume of saliva.
- **Lipophilicity of drug:** For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
- **pH and pKa of the saliva:** As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- **Oil to water partition coefficient:** Compounds with favorable oil to- water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.
- **Solubility in salivary secretion:** In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of the drug is necessary for absorption.
- **Binding to oral mucosa:** Systemic availability of drugs that bind to oral mucosa is poor.

3.6.4 Advantages [47]

- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
- Low dosage gives high efficacy as hepatic first-pass metabolism is avoided and also reduces the risk of side effects.
- Due to rapidity in action, these sublingual dosage forms are widely used in emergency conditions e. g. asthma.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

3.6.5 Disadvantages [48]

- Sublingual medication cannot be used when a patient is uncooperative.
- Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- The patient should not smoke while taking sublingual medication because smoking causes vasoconstriction of the vessels. This will decrease the absorption of the medication.

Conclusion

Nanofiber patches have emerged as a promising platform for sublingual drug delivery, offering several advantages over conventional dosage forms, including rapid drug absorption, improved bioavailability, and enhanced patient compliance. Their high surface-area-to-volume ratio facilitates faster dissolution and efficient mucosal absorption, making them ideal

for drugs requiring a rapid onset of action. Additionally, their thin, flexible nature ensures ease of administration and patient comfort.

Despite their potential, several challenges must be addressed to optimize their clinical application. Key issues include achieving uniform drug distribution, enhancing stability under sublingual conditions, and addressing taste masking concerns. Furthermore, scalability and regulatory compliance remain critical hurdles in transitioning these systems from research to commercial production.

Future advancements in polymer science, electrospinning technology, and nanomaterial engineering will play a vital role in overcoming these challenges. Continued research and clinical validation will be essential to establish nanofiber patches as a viable and widely significant promise for improving therapeutic outcomes and expanding non-invasive drug administration options.

References:

1. Tiwari, J.N.; Tiwari, R.N.; Kim, K.S. Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. Prog. Mater. Sci. 2012, 57, 724–803.
2. Yong, K.T.; Yu, S.F. AlN nanowires: Synthesis, physical properties, and nanoelectronics applications. J. Mater. Sci. 2012, 47, 5341–5360.
3. Lim, C.T. Synthesis, optical properties, and chemical-biological sensing applications of one-dimensional inorganic semiconductor nanowires. Prog. Mater. Sci. 2013, 58, 705–748.
4. Hassanzadeh, P.; Kharaziha, M.; Nikkhah, M.; Shin, S.R.; Jin, J.; He, S.; Sun, W.; Zhong, C.; Dokmeci, M.R.; Khademhosseini, A.; et al. Chitin nanofiber micropatterned flexible substrates for tissue engineering. J. Mater. Chem. B 2013, 1, 4217–4224.
5. Behrens, A.M.; Casey, B.J.; Sikorski, M.J.; Wu, K.L.; Tutak, W.; Sandler, A.D.; Kofinas, P. In situ deposition of PLGA nanofibers via solution blow spinning. ACS Macro Lett. 2014, 3, 249–254.
6. Shah, S.; Yin, P.T.; Uehara, T.M.; Chueng, S.T.D.; Yang, L.; Lee, K.B. Guiding stem cell differentiation into oligodendrocytes using graphene-nanofiber hybrid scaffolds. Adv. Mater. 2014, 26, 3673–3680.
7. Yang, X.; Zou, W.; Su, Y.; Zhu, Y.; Jiang, H.; Shen, J.; Li, C. Activated nitrogen-doped carbon nanofibers with hierarchical pore as efficient oxygen reduction reaction catalyst for microbial fuel cells. J. Power Sources 2014, 266, 36–42.

8. Shang, M.; Wang, W.; Sun, S.; Gao, E.; Zhang, Z.; Zhang, L.; O'Hayre, R. The design and realization of a large-area flexible nanofiber-based mat for pollutant degradation: An application in photocatalysis. Nanoscale 2013, 5, 5036–5042.
9. Cheng, L.; Ma, S.Y.; Wang, T.T.; Li, X.B.; Luo, J.; Li, W.Q.; Mao, Y.Z.; Gz, D.J. Synthesis and characterization of SnO2 hollow nanofibers by electrospinning for ethanol sensing properties. Mater. Lett. 2014, 131, 23–26.
10. Wu, Q.; Tran, T.; Lu, W.; Wu, J. Electrospun silicon/carbon/titanium oxide composite nanofibers for lithium ion batteries. J. Power Sources 2014, 258, 39–45.
11. Liu, Y.; Zhao, L.; Li, M.; Guo, L. TiO2/CdSe core-shell nanofiber film for photoelectrochemical hydrogen generation. Nanoscale 2014, 6, 7397–7404.
12. Shi, H.; Zhou, M.; Song, D.; Pan, X.; Fu, J.; Zhou, J.; Ma, S.; Wang, T. Highly porous SnO2/TiO2 electrospun nanofibers with high photocatalytic activities. Ceram. Int. 2014, 40, 10383–10393.
13. Xue, J.; Xie, J.; Liu, W.; Xia, Y. Electrospun Nanofibers: New Concepts, Materials, and Applications. Acc. Chem. Res. 2017, 50, 1976–1987.
14. Thenmozhi, S.; Dharmaraj, N.; Kadirvelu, K.; Kim, H.Y. Electrospun nanofibers: New generation materials for advanced applications. Mater. Sci. Eng. B Solid-State Mater. Adv. Technol. 2017, 217, 36–48.
15. Hu, X.; Liu, S.; Zhou, G.; Huang, Y.; Xie, Z.; Jing, X. Electrospinning of polymeric nanofibers for drug delivery applications. J. Control. Release 2014, 185, 12–21.
16. Sridhar, R.; Lakshminarayanan, R.; Madhaiyan, K.; Barathi, V.A.; Limh, K.H.C.; Ramakrishna, S. Electrosprayed nanoparticles and electrospun nanofibers based on natural materials: Applications in tissue regeneration, drug delivery and pharmaceuticals. Chem. Soc. Rev. 2015, 44, 790–814.
17. Niu, C.; Meng, J.; Wang, X.; Han, C.; Yan, M.; Zhao, K.; Xu, X.; Ren, W.; Zhao, Y.; Xu, L.; et al. General synthesis of complex nanotubes by gradient electrospinning and controlled pyrolysis. Nat. Commun. 2015, 6, 1–9.
18. Ren, X.; Ying, P.; Yang, Z.; Shang, M.; Hou, H.; Gao, F. Foaming-assisted electrospinning of large-pore mesoporous ZnO nanofibers with tailored structures and enhanced photocatalytic activity. RSC Adv. 2015, 5, 16361–16367.
19. Peng, S.; Li, L.; Hu, Y.; Srinivasan, M.; Cheng, F.; Chen, J.; Ramakrishna, S. Fabrication of Spinel One-Dimensional Architectures by Single-Spinneret Electrospinning for Energy Storage Applications. ACS Nano 2015, 9, 1945–1954.
20. Ma, F.; Zhang, N.; Wei, X.; Yang, J.; Wang, Y.; Zhou, Z. Blend-electrospun poly(vinylidene fluoride)/polydopamine membranes: Self-polymerization of dopamine and the excellent adsorption/separation abilities. J. Mater. Chem. A 2017, 5, 14430–14443.

21. Bhattarai, R.S.; Bachu, R.D.; Boddu, S.H.S.; Bhaduri, S. Biomedical Applications of Electrospun Nanofibers: Drug and Nanoparticle Delivery. Pharmaceutics 2018, 11, 5.
22. Muerza-Cascante, M.L.; Haylock, D.; Hutmacher, D.W.; Dalton, P.D. Melt Electrospinning and Its Technologization in Tissue Engineering. Tissue Eng. Part B Rev. 2014, 21, 187–202.
23. Steyaert, I.; Van Der Schueren, L.; Rahier, H.; De Clerck, K. An alternative solvent system for blend electrospinning of polycaprolactone/chitosan nanofibres. Macromol. Symp. 2012, 321–322, 71–75.
24. Schoolaert, E.; Steyaert, I.; Vancoillie, G.; Geltmeyer, J.; Lava, K.; Hoogenboom, R.; De Clerck, K. Blend electrospinning of dye-functionalized chitosan and poly(ε-caprolactone): Towards biocompatible pH-sensors. J. Mater. Chem. B 2016, 4, 4507–4516.
25. Nikmaram, N.; Roohinejad, S.; Hashemi, S.; Koubaa, M.; Barba, F.J.; Abbaspourrad, A.; Greiner, R. Emulsion-based systems for fabrication of electrospun nanofibers: Food, pharmaceutical and biomedical applications. RSC Adv. 2017, 7, 28951–28964. [CrossRef]
26. Kai, D.; Liow, S.S.; Loh, X.J. Biodegradable polymers for electrospinning: Towards biomedical applications. Mater. Sci. Eng. C 2014, 45, 659–670. [CrossRef]
27. Liao, I.C.; Chew, S.Y.; Leong, K.W. Aligned core–shell nanofibers delivering bioactive proteins. Nanomedicine 2006, 1, 465–471.
28. Yu, D.G.; Chian, W.; Wang, X.; Li, X.Y.; Li, Y.; Liao, Y.Z. Linear drug release membrane prepared by a modified coaxial electrospinning process. J. Membr. Sci. 2013, 428, 150–156.
29. Merkle, V.M.; Zeng, L.; Slepian, M.J.; Wu, X. Core-shell nanofibers: Integrating the bioactivity of gelatin and the mechanical property of polyvinyl alcohol. Biopolymers 2014, 101, 336–346.
30. Vaidya, P.; Grove, T.; Edgar, K.J.; Goldstein, A.S. Surface grafting of chitosan shell, polycaprolactone core fiber meshes to confer bioactivity. J. Bioact. Compat. Polym. 2015, 30, 258–274.
31. McClellan, P.; Landis, W.J. Recent Applications of Coaxial and Emulsion Electrospinning Methods in the Field of Tissue Engineering. BioRes. Open Access 2016, 5, 212–227.
32. Luo, X.; Xie, C.; Wang, H.; Liu, C.; Yan, S.; Li, X. Antitumor activities of emulsion electrospun fibers with core loading of hydroxycamptothecin via intratumoral implantation. Int. J. Pharm. 2012, 425, 19–28.
33. Zhang, X.; Wang, M. Effects of Emulsion Electrospinning Parameters on the Morphology and Structure of Core-Shell Structured PLLA Fibers. Adv. Mater. Res. 2011, 410, 386–389.

34. Wang, C.; Tong, S.N.; Tse, Y.H.; Wang, M. Conventional Electrospinning vs. Emulsion Electrospinning: A Comparative Study on the Development of Nanofibrous Drug/Biomolecule Delivery Vehicles. Adv. Mater. Res. 2011, 410, 118–121.
35. Yoon, Y.I.; Park, K.E.; Lee, S.J.; Park, W.H. Fabrication of microfibrous and nano-/microfibrous scaffolds: Melt and hybrid electrospinning and surface modification of poly(L-lactic acid) with plasticizer. BioMed Res. Int. 2013, 2013, 309048.
36. Dalton, P.D.; Klinkhammer, K.; Salber, J.; Klee, D.; Möller, M. Direct in Vitro Electrospinning with Polymer Melts. Biomacromolecules 2006, 7, 686–690.
37. Hutmacher, D.W.; Dalton, P.D. Melt Electrospinning. Chem. Asian J. 2011, 6, 44–56.
38. Kim, S.J.; Jeong, L.; Lee, S.J.; Cho, D.; Park, W.H. Fabrication and surface modification of melt-electrospun poly(D,L-lactic-co-glycolic acid) microfibers. Fibers Polym. 2013, 14, 1491–1496.
39. Zhmayev, E.; Cho, D.; Joo, Y.L. Nanofibers from gas-assisted polymer melt electrospinning. Polymer 2010, 51, 4140–4144.
40. Ishikawa T, Koizumi N, Mukai B. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem Pharm Bull 2009;49:230-2.
41. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta-estradiol. Obstet Gynecol 2007;89:340-5.
42. KL Moore, AF Dalley, Anne MR. Agur. Eds. Clinically Oriented Anatomy. 6th ed. Lippincott Williams and Wilkins, Philadelphia, PA; 2009. p. 944.
43. CA Squier, PW Wertz. Structure and function of the oral mucosa and implications for drug delivery," in oral mucosal drug delivery. MJ Tathbone. Ed. (Marcel Dekker, New York, NY; 2006. p. 1-26.
44. Kurosaki Y, Takatori T, Nishimura H, Nakayama T, Kimura T. Regional variation in oral mucosal drug absorption permeability and degree of keratinization in hamster oral cavity. Pharm Res 2011;8:1297-301.
45. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Pharm Sci 2010;3:18-22.
46. Richman MD, Fox D, Shangraw RF. Preparation and stability of glyceryl trinitrate sublingual tablets prepared by direct compression. J Pharm Sci 2015;54:447-51.
47. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies, tastemaking and clinical studies. Crit Rev Ther Drug Carrier Syst 2014;21:433-76.
48. Katz M, Barr M. A study of sublingual absorption I. Several factors influencing the rate of adsorption. J Am Pharm Assoc Am Pharm Assoc (Baltim) 2015;44:419-23.