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Nanofiber in transmucosal drug delivery

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ABSTRACT

Transmucosal route owing to its diverse anatomy and physiology offers numerous advantages for local and systemic delivery of therapeutics. Irrespective of several advantages narrow absorption window and poor retention time of carrier system are the major challenges to achieve desired therapeutic response. Nanofiber due to its unique surface properties provides numerous opportunities to overcome the limitations of conventional vehicles. In this review, the benefits of nanofiber as a carrier system for transmucosal drug delivery are discussed. The aim is to provide detailed understanding of functional features of electrospun nanofiber that make it suitable for transmucosal drug delivery. Review intends to illustrate the potential of nanofibers to deliver drugs via various transmucosal sites like nasal mucosa, intra vaginal and ocular. The review also discusses the current status of nanofiber and explores the benefits of various research works and concludes their results.

1. Introduction

Transmucosal drug delivery refers to the route of drug administration where the drug molecules enter specific tissues through or across the mucosal membrane. These include routes such as buccal, nasal, vaginal, rectal, ocular, sublingual route etc. Transmucosal routes of drug delivery offer distinct advantages for both systemic and local drug delivery. These advantages include possible bypass of first pass metabolism and rich vascular network makes it a potential site for drug administration to systemic circulation. Further transmucosal route is particularly useful in treating mucosal diseases, as it allow direct access to the target tissues, enhance efficacy and reduce systemic toxicity. Apart from the aforementioned advantages, transmucosal route offers formidable challenges like low permeability, limited surface area for absorption, poor retention of the drug and/or delivery systems at the absorption site significantly reduce the performance of drug delivery carrier. In recent years, a significant progress has been made on drug carrier systems for transmucosal drug delivery. Each carrier systems have their own advantages and, limitations. However none of the carrier systems have the potential to overcome the challenges confronting transmucosal route of drug administration. Nanofibers are drug carriers with diameter in nanometer range. Nanofibers with 100 nm diameter offer approximately a specific surface area of 1000 sqm/gram. Nanofibers due to its ultrahigh surface area provide potential advantages for transmucosal drug delivery. Further nanofibers can be made from different biodegradable polymers, natural material via electrospinning and sol–gel process. Wide range of drugs including antibiotics, anticancer drugs, proteins, DNA and RNA can be incorporated into nanofiber scaffold.

Every route has its own advantages and limitations. Buccal route can be used for systemic delivery of various drugs. Drugs administered via buccal route can be rapidly absorbed into the systemic circulation through the deep lingual or facial vein, internal jugular vein, and brachiocephalic vein. Buccal route of drug administration prevents drugs from hepatic first pass metabolism leading to high drug bioavailability particularly serve as an useful alternative to oral administration of drugs [2]. In the recent years nasal route has received a great deal of attention for both local and systemic drug delivery. Apart from hepatic first pass elimination, rapid drug absorption and facilitate the delivery of drug molecules across blood brain barrier [3]. The ocular drug delivery has many limitations like dynamic and static barriers of human's eye. Generally the drugs which are administered through the ocular route shows poor bioavailability. The most commonly used dosage form which is administered through ocular route are eye drops. The limitations of ocular route are poor corneal permeability, preocular retention, narrow absorption window and physiological degradation in the ocular mucosa limits drug absorption. Novel nanotechnology based drug delivery system can be used to overcome these limitations [4].

Polymeric nanofibers owing to their unique functional architect can be used for both systemic and local drug delivery. Recently Joshi and co-workers used nanofiber based systems for the controlled drug delivery in the treatment of periodontitis. It was reported that the developed formulation shows controlled release behaviour with good mucoadhesive strength. The in vivo studies confirmed the maintenance

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of minimum inhibitory concentration over an extended period of time illustrated by significant anti-inflammatory effect. Furthermore, *in-vivo* study confirmed selectivity of the developed therapy with reduced side effects [5]. Electrospinning allow producing composite and multi-layered nanofiber using different polymers to modulate tissue response. In this two different type of polymers are used to make two distinct layer, the inner core and outer shell demonstrated controlled release of entrapped drug helps to modulate the therapeutic efficacy. Huang et al., used co-axial electrospinning process to entrap Resveratrol and Gentamycin sulphate in bioabsorbable polymer i.e. Polycaprolactone. Experimental results demonstrated sustained release of both the drugs [6]. In recent year's electrospun nanofiber have gained great attention for delivering drugs used for treatment of different diseases including inflammation, heart diseases and cancer. Kaplan and co-workers revealing the potential of cisplatin loaded biodegradable polymer nanofibrous mash for post-surgical treatment of lung cancer. They have fabricated a composite nanofiber using Polycaprolactone and poly (glycerol monosterate-co-caprolactone) and observed the sustained release behaviour of cisplatin for extended periods up to 90 days. Experimental outcomes further suggested that local recurrence of cancer was significantly reduced compared to free drugs emphasize the potential of nanofibers in local drug delivery to improve prognosis for lung cancer patients [7]. Drug loading capacity is a key factor determines the potential of drug delivery systems. Previous findings establish the high drug loading efficacy of electrospun nanofibers. However drug loading efficacy of nanofibers depends on physiochemical properties of drug and polymers. In general high drug loading would be expected if both drug and polymers have similar solubility pattern. Recent studies demonstrated that nanofibers exhibits substantial loading efficacy of about 89% of peclitaxel in selected solvent system of cremophor. Moreover electrospinning offers an economically viable alternative to produce continuous nanofibers. Further electrospinning aided by continuous unit operation process makes it simple and easy to sacle-up.

1.1. Nanofiber: an approach to overcome limitations of transmucosal route

1.1.1. Surface area

Regardless of certain potential advantages, transmucosal sites have certain potential barriers like keratinized tissue, high blood flow, low patient acceptability and small absorbing surface area limits the absorption of drug. Further drugs with low therapeutic window and selective physio-chemical properties seem to play a very critical for the prediction of in-vivo performance. In addition to above, the entire transmucosal site interfaced with mucus lined cellular barrier. Taking above parameters into consideration, residence time of drugs at the site of absorption may prove to correlate with treatment outcome. Nanofiber due to their high surface area to unit volume, and interconnected nonwoven architect provide large surface area for better mucoadhesion. The surface area generated by nanofiber directly depends on fiber diameter. Nanofiber with smaller fiber diameter generates higher surface area and vice versa.

Further presence of sialic acid and fucose moieties in mucus makes the mucosal surface negatively charged. Therefore optimum mucoadhesion might be based on the positive charges and critical degree of hydration. Electrospinning due to its simple fabrication technique allow fabricating nanofiber from a number of natural and synthetic polymers. Nanofiber owing to its unique surface properties ensures a higher proportion of charged groups on their outer surfaces; allow strong electrostatic interaction between the cationic polymer and the anionic mucus. Electrospinning is capable of fabricating fibers with nanometer range, hence allow an increase available surface area for mucoadhesion. Samprasit et al., demonstrated chitosan thiolated nanofiber shows high mucoadhesive behaviour (approx22) then CS/PVA nanofiber (approx11). Higher mocoadherent property of thiolated chitosan nanofiber could be attributed to net content of chitosan. Chitosan as a cationic polyelectrolyte increases the net charge density leading to higher mucoadhesivity [8].

1.1.2. Solubility

The drug performance via transmucosal route depends on several factors such as aqueous solubility and permeability. Further it becomes more important for drugs with narrow absorption window. Nanofiber due to its unique fabrication technique and surface properties offers various advantages over other drug delivery systems to improve drug solubility and permeability. Electrospinning in particular because of its flash evaporation and sudden expansion of the product helps to convert drugs from a crystalline state to amorphous, thereby helps to improve drug solubility and increase the possibility to improve bioavailability of drug with poor aqueous solubility. Further electrospinning allows fabricating nanofibers from number of amphiphillic polymers like PVA, PVP and PEO, which further helps to improve the solubility of poorly water soluble drugs. Recently Malik et al., reported higher solubility of Diacerein in PLLA nanofiber. Results indicated that solubility of drug in nanofibers was increased by 3 folds compared to plain drug. Higher drug solubility can be attributed to the dispersion of drugs in nano size in PLLA fiber matrix. Nano dispersion of drug increases the available surface area, helps to improve both solubility and permeability of drug [9]. Further liquid polymeric jet during electrospinning undergoes a transition from the crystalline to amorphous state leading to higher drug solubility. Moreover presence of polymeric surfactant increases membrane fluidity thereby facilitates paracellular transport of hydrophilic drug, which facilitate the transcellular uptake of lipophilic drugs.

1.1.3. Controlled drug release

Considering the narrow absorption window of transmucosal absorption sites, controlled drug delivery systems account to be a key factor for bioavailability. The drug release kinetics from nanofibers can be easily modulated by the choice of polymer and nanofiber fabrication techniques. Two basic rate controlled drug delivery system includes reservoir matrix systems, monolithic matrix systems which are commonly employed to control the release of encapsulated therapeutics, can be easily produced by modified co-axial electrospinning process. In a study conducted by Kaur and co-workers reported an extended release of antimicrobial from PLLA nanofiber. The extended drug release behaviour primarily is a function of polyelectrolyte behaviour of PLLA which remains in non protonated state at the acidic pH of vaginal fluid, controlled the release of therapeutic agent governed by diffusion mechanism [10]. Similarly, another classic study conducted by Malik et al., validated the delayed release behaviour of Diacerein from PLLA nanofiber followed by oral administration at gastric pH. Results shows that approximately 61.3% of drug was released in 30 h, found particularly beneficial for localized drug administration [9]. Apart from the intrinsic property of polymer, morphology of nanofiber also contributes to a large extent to control the release of therapeutic agent.

In a recent study conducted by Siafaka and co-workers have demonstrated a controlled release of Teriflunomide from the nanofiber formulation consisting of poly(lactic acid)/poly(butylenes adipate) blends. Results revealed that drug release kinetics not only depends on the ratio of polymeric blends but also largely affected by fiber diameter [11]. Advancements in electrospinning of polymeric nanofibrous scaffolds make it possible to fabricate core-shell nanofiber with co-axial electrospun process to achieve desired drug release kinetics. Sultanova and co-worker studied the release behaviour of ampicillin from co-axially electrospun PCL nanofiber. Drug release studies shows that formulation prepared without core shell exhibit significant burst release. While the formulation prepared from a 10% PCL core fluid and 4% w/v PCL shell fluid demonstrated extended drug release behaviour with a zero order rate kinetics [12]. Similarly in another attempt made by Zupancic and co-workers demonstrated the extended release behaviour of Ciprofloxacin from core shell nanofiber with monolithic or blended core. Results shows sustained release of Ciprofloxacin for 2–4

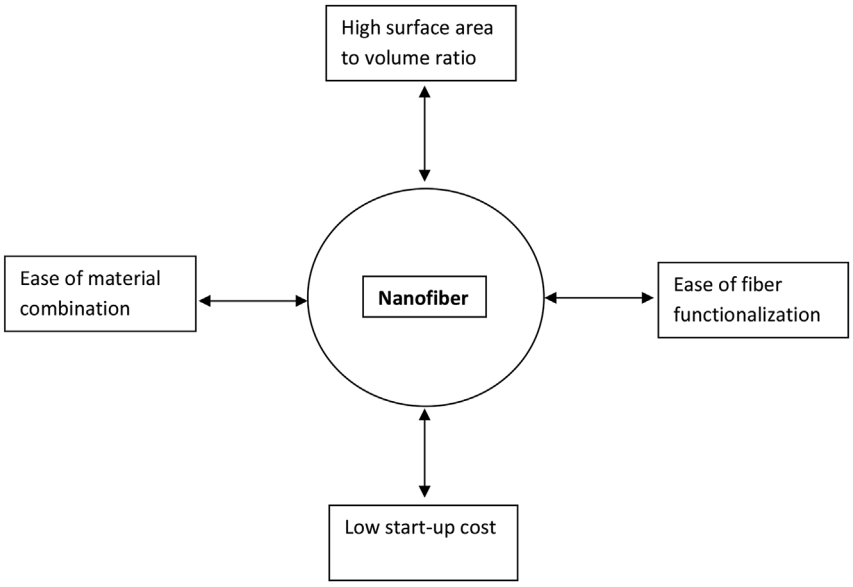

Fig. 1. Advantages of nanofiber as a drug delivery system.

weeks from PMMA shell and PVA core nanofiber. The controlled drug release is mainly governed by diffusion mechanism through the PMMA shell membrane [13].

1.1.4. Drug loading

The effectiveness of nanofiber as drug carrier depends on its loading efficacy. High drug loading capacity is very beneficial, because it can precisely control the release rates and provide an efficient alternative to control the size of the final dose. Many current novel drug delivery systems have limited drug loading efficacy with respect to the excipients ratio making it expensive and difficult for the transition from concept to clinical application. Simple fabrication process and high surface areas involved in nanofiber enable high drug loadings. Meng et al., achieved high loading efficacy of Fenbufen in a composite PLGA/gelatin nanofiber scaffold [14]. Several factors appear to affect the drug loading efficacy of electrospun nanofibers. In general drug solubility in the selected solvent system, polymer density, method of electrospinning and drug loading technique are among the major factors influence drug loading capacity of nanofibers. Recently Xu and co-workers demonstred that 89% drug loading capacity of paclitaxel in prepared nanofibers could be related to higher solubility of prepared paclitaxel succinic acid complex in the selected solvent system chremophor [15]. Similarly Paskiabi and co-workers reported 100% drug loading efficacy of Terbinafine in PCL nanofibers, could be related to high drug solubility in the selected solvent system. Passive equilibration technique yields greater loading efficacy than active loading technique [16].

1.1.5. Mechanical properties and flexibilities

Mechanical properties of nanofibers make significant contributions which influence drug loading, drug release, and overall stability. The tensile strength and Young's modulus are usually considered for measuring the mechanical properties and deformation of electrospun nanofiber. Tensile strength is a very important parameter which determines for how long the formulation will maintain its integrity. Nanofibers due to their nonwoven fibrous membranes structure and ultrafine fibers exhibit excellent mechanical properties. Thomas et al., fabricate PCL nanofiber by electrospinning technique and check its tensile strength by adjusting different rotational speed of the collector (0, 3000, 6000 rpm), results increase in tensile strength of nanofiber from 2.21 ± 0.23 MPa at zero rpm, 4.21 ± 0.35 MPa at 3000 rpm and 9.58 ± 0.71 MPa at 6000 rpm. Experimental outcomes suggested that both collector geometry and speed affect the fiber diameter. In addition to mechanical strength, flexibility also plays a key role in determining the pharmaceutical function of the drug carriers. Formulation which is non-flexible can cause irritations at the site of administration. Thomas and co-workers in his study also reported that fiber prepared at 6000 rpm is more flexible as compared to fiber prepared at zero rpm [17].

1.1.6. Sterility

Sterilization of drug carrier has its own importance in pharmaceutical industry. Formulations that are prepared for the biomedical application should be sterile to prevent any kind of problem which can occur due to contamination. In most of the formulation terminal sterilization is used which can affect the overall efficacy or yield of the formulation. Further sterilization methodology could affect the stability of the formulation. Electrospinning process allows the operator to maintain the aseptic environment during the nanofiber which eliminates the need of terminal sterilization. Further electrospinning allow fabricating nanofiber under UV irradiation to eliminate terminal sterilization. Garg et al., in their study prepare nanofiber patch under UV irradiation for the ocular delivery of Timolol maleate and dorzolamide hydrochloride to produce sterile nanofibers [18].

1.2. Nanofibers for transmucosal drug delivery

The nanofiber patch is synthesized by the electrospinning process. In electrospinning the nanofibers are prepared by applying the high voltage to the polymer filled in the syringe [19]. The applied voltage creates an electric field, which results into a jet stream of polymer solution by creating a force greater than the surface tension of the solution. The jet then bends and elongates due to electrical instability, causing a spiralling motion and smaller-diameter jet. The solvent then evaporates, leaving only a charged polymer nanofiber. The nanofiber is attracted to a grounded collector, where it solidifies into a non-woven mat. The collector can be rotated to produce a desired fiber orientation [20].

1.2.1. Buccal route of drug delivery

Among the various routes of transmucosal drug delivery, buccal route perhaps the most commonly used site for both conventional as well as novel drug delivery systems. In buccal route the drug is applied to the buccal cavity from where the drug diffuses through the oral mucosa directly into the systemic circulation (see Fig. 1). The benefits of the buccal route include enhanced bioavailability and rapid onset of action. The buccal route is categorised into two main categories i.e.

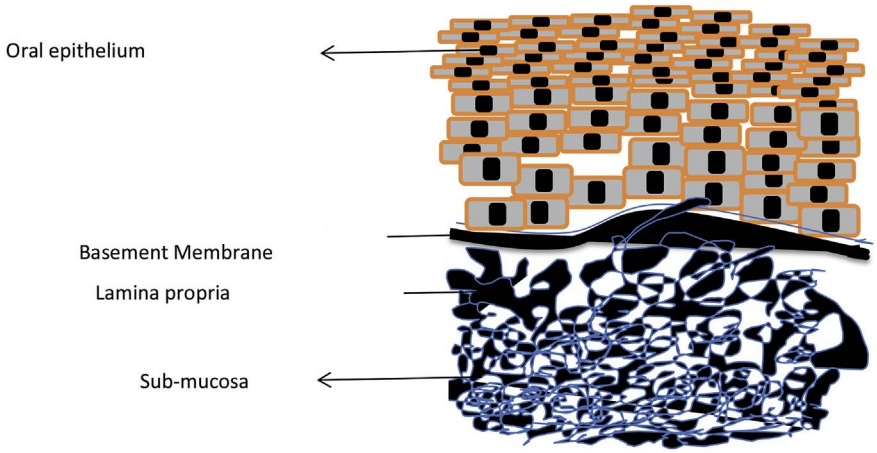

Fig. 2. Schematic diagram of buccal mucosa.

Table 1
Summary of the oral mucosa anatomy and physiology.

Absorptive site	Estimated surface area	Percent total surface area	Local pH	Mean fluid volume(ml)	Relative enzyme activity	Relative drug absorption capacity
Oral cavity	100 cm^2	0.01	5.8–7.6	0.9 ml	Moderate	Moderate
Stomach	0.1–0.2m^2	0.20	1.0–3.0	118	High	Moderate
Small intestine	100m^2	98.76	5.0–7.0	212	High	High
Large intestine	0.5–1.0m^2	0.99	6.0–7.4	187	Moderate	Low
Rectum	200-400m^2	0.04	7.0–7.4	–	Low	Low

sublabial and sublingual. Sublabial route, where the drug is administered under the lips where in case of sublingual route the drug is placed under the tongue. The buccal route is preferred because it prevents the drug from gastric degradation in stomach and also bypasses the first pass metabolism and pre systemic elimination. Various mucoadhesive polymers and permeation enhancers are used for the development of buccal drug delivery formulation, which leads to better bioavailability and controlled release of drug. This route is most preferred route used for anti-psychiatric drugs, opioid drugs, cardiovascular drug and nicotine as smoking cessation aid. The schematic diagram of the buccal mucosal membrane is illustrated (Fig. 2): The above given diagram is of buccal mucosa, the mucosal membranes available at other transmucosal sites are almost similar the general difference is in the vascularisation of the mucosa at the various sites. So the transmucosal site is selected on the basis of anatomy and physiology. The comparison of the oral mucosa is given the table given below(Table 1) [21].:

The mucoadhesion is a very important property which must be considered to prepare an effective buccal drug delivery system. Various mucoadhesives polymers are used in the formulations of buccal drug delivery systems. These mucoadhesive polymers enhances the retention time of the formulation at the application site, leads to the increased bioavailability, and also helps to attain the controlled release of the formulation [22].

1.2.1.1. Advantages of nanofiber scaffold in buccal route.

1. The advantage of the nanofiber as a drug delivery system is its high surface area to volume ratio.
2. It can be utilized directly to the site of infection to provide localized as well as systemic action of drug.
3. It is very easy to remove the scaffold nanofiber in case of any adverse drug reaction.

1.2.1.2. Nanofiber as buccal transmucosal patch. Nanofiber system owing to its unique surface properties was shown to have great potential for both local and systemic drug delivery via buccal route. Nanofibers due to its flexibility, viscosifying, mucoadhesive and ease of application provide a good alternative to other mucoadhesive films used in buccal drug delivery. Aduba et al., prepared a nanofiber scaffold using gelatine and PEG-DA for oral candidiasis treatment using Nystatin. They found the nanofiber structurally stable in aqueous solution in oral mucosa. The release profile of the nanofiber scaffold was studied and shows promising results [23]. Nanofiber because of its high surface to volume ratio can also be intended for rapid transmucosal drug delivery. Tyagi et al., prepared an oral transmucosal nanofiber scaffold using electrospinning technique. In-vitro release profile indicated a quick dissolution of the drug and fast absorption from the prepared nanofibers [24]. Similarly Zamani et al., explored the localized effect of metronidazole benzoate in periodontitis using poly e-caprolactone nanofiber scaffold [25]. In addition to above, nanofiber scaffold can also be utilized to improve the solubility of poorly aqueous soluble drugs. Yu et al. reported a hydrophilic Polyvinylpyrolidone (PVP) nanofiber using sodium dodecyl sulphate as a transmembrane enhancer. The composite nanofiber shows the enhanced drug solubility up to 26 folds faster dissolution than plain drug and 10 fold increased permeation across the epithelial layer of the oral mucosa, compared to the parent drug [26]. Nanofiber can also be used to mask the taste of the bitter drug. Coaxial electrospinning technique often used and prove effective to mask the bitter taste of drug. In coaxial electrospinning technique, the drug containing nanofiber (with unpleasant taste) is encapsulated within another polymer which helps in taste masking. Illangakoon et al., in his study successfully masked the unpleasant taste of paracetamol and caffeine using polymeric nanofiber. Apart from the taste masking, the prepared formulation stimulates the saliva secretion to facilitate the fast dissolution of experimental drug. These fast dissolving oral films can be easily used in case of children and for the patients who can't swallow [27]. In addition to said application, nanofiber can also be used to promotes wound healing [28].

1.2.2. Ocular route of drug delivery

The ocular route of drug delivery is used for various eye disorders. Drug absorption following ocular delivery mostly occurs through the penetration through the sclera and conjunctiva into intra-ocular tissue of the eye. Several factors need to be considered for designing an ophthalmic formulation that it must be sterile and free of gritty

particles [29]. The ocular drug delivery systems can be generally divided into two categories i.e. conventional drug delivery systems and the novel ocular drug delivery systems. Since electrospinning process allows fabricating nanofibers under the aseptic environment therefore eliminates the need of terminal sterilization. Further nanofibers owing to its unique nanoscale properties reduce contact irritations.

1.2.2.1. Advantages of ocular drug delivery system.

1. Can be used to attain the sustained and controlled release by using novel ocular drug delivery systems
2. To provide the targeted and localized effect in the eye globe.
3. To enhance the therapeutic efficacy of the drugs by protecting them from first pass hepatic metabolism.
4. Various drugs which get degraded in the GIT can be preferably administered through the ocular route to get instant absorption into the systemic circulation.

1.2.2.2. Recent perspectives in ocular drug delivery. The conventional drug delivery system for ocular route includes the eye drops and ointments, contributes approximately 90% of the current marketed ocular drug delivery systems [30]. The most common problem with the conventional ocular drug delivery system is poor bioavailability, due to naso-lachrymal drainage and dilution with tears. Due to quick elimination of the drug from site of administration, frequent dosing is required. To overcome these problems various novel ocular drug delivery systems are developed [31]. Various micro level and nanotechnology based ocular drug delivery systems are prepared to enhance the bioavailability and improve the retention time of the drug in the ocular region. The concept of prodrug is also used to enhance the permeation and bioavailability of the drug from ocular region. Drug absorption across the ocular mucosa and subsequent layers require appropriate lipophilicity and solubility in the aqueous medium. Generally the amino acids and peptides are used to make pro drugs due to the presence of various amino acid and peptide transporters on biological membrane. Dipeptide (glycine–valine and tyrosine–valine) monoester prodrugs of ganciclovir (GCV) shows superior corneal absorption and bioavailability as compared to parent drug [32].

Microemulsion is another novel technique used for ophthalmic preparations; these are biphasic system which is stabilized by the use of surfactant and co-surfactants. The microemulsions are thermodynamically stable and clear in appearance [33]. Chemical stability studies on microemulsion performed by Vandamme et al., demonstrated that selection of dispersed phase, dispersion medium and surfactant/cosurfactant systems are key parameters which can affect stability of the microemulsion. Optimization of these parameters results in improvement in solubility of the drug. e.g. chloramphenicol, indomethacin [34]. In addition to above, appropriate selection of surfactant helps to increase the drug permeability across the mucosa and cornea. Vandamme shows that oil-in-water emulsion consisting of pilocarpine using lecithin, increase the permeability in which they use propylene glycol, PEG 200 as surfactant/co surfactants, and isopropyl myristate as the oil phase. The developed system was non-irritating to the rabbit animal model. The main problem of the microemulsion is the retention time of the formulation at the site of absorption.

Nanosuspension is another submicron colloidal system which is used to administer the poorly soluble drugs and are stabilized by the use of surfactants. Nanosuspensions are also used in the ophthalmic preparation and are non-irritant in nature. The charge on the surface of the nanoparticles is responsible for their adhesion with cornea [35]. Ocular inserts are also used for ocular drug delivery, the ocular inserts can also be used to achieve the sustain release of the drug. Mahajan and Deshmukh makes an polymeric gel film as ocular insert of thickness 0.20 ± 0.07 μm, the percent release of the drug from the film over 24 h was 98.85 [36]. The problem with the ocular inserts is the thickness. As the ocular insert are solid dosage forms so they can cause irritation with the increase in the thickness of the insert.

1.2.2.3. Nanofiber as ocular drug delivery system. The nanofiber is a good approach to deliver the drug through the transmucosal (ocular) route. Nanofibers form. 50–1000 nm in diameter can be readily produced from both natural and synthetic polymers using electrospinning. The nanofiber film can be applied to the mucosal membrane at various transmucosal sites [37]. Limitations in recent drug delivery system include loss of the drug with tears and limited space in the ocular region to retain the drug carriers. Several investigators attempts mucoadhesive nanoparticles and polymeric ocular inserts to improve the retention time. However that can cause blurred vision, irritating and have a watery discharge. Considering the aforementioned problems, nanofiber can be a good option for the various ocular drug delivery systems. In a recent study Garg et al., prepared a nanofiber patch to treat glaucoma by using a biodegradable mucoadhesive polymer to improve carrier retention and provide the controlled release of the drug. Further the diameter of the nanofiber is in nanometer makes it easy for administration and biodegradability of polymer avoids the need for patch removal. Results demonstrated that the prepared nanofibers formulation shows excellent bio-adhesive properties and a high fraction of drug was recovered at the target site, ensure the controlled drug release behaviour of the prepared dosage form [18]. In ocular region the nanofiber can also be used for tissue engineering. Sharma et al., prepared a surface modified poly (epsilon-caprolactone) nanofibrous scaffold with good physical, pharmaceutical andmechanical properties, suitable for ocular surface reconstruction [38]. Electrospun nanofibers due to its unique surface properties and appropriate mechanical properties serve as an appropriate scaffolds material suitable for cell growth, thus can support growth, proliferation, and differentiation of cells. Zajicova et al., grows limbal stem cells and mesenchymal stem cells on nanofibrous scaffold prepared from polyamide 6/12. Experimental finding demonstrated that the conditions were favourable for the growth of limbal stem cells and mesenchymal stem cells and polyamide 6/12 can be used in treatment of various ocular injuries [39].

1.2.3. Nasal route of drug delivery

Nasal route is another transmucosal route where the drug is administered into the nasal cavity to get systemic or localized effect of the drug. The advantages of nasal route includes: rapid onset of action of drugs acting systemically, bypasses hepatic first pass metabolism, avoids parenteral administration for systemically acting drugs, self-administration or good patient compliance, lower dose leads to reduction of dose. Nasal drug administration is very good option in case of

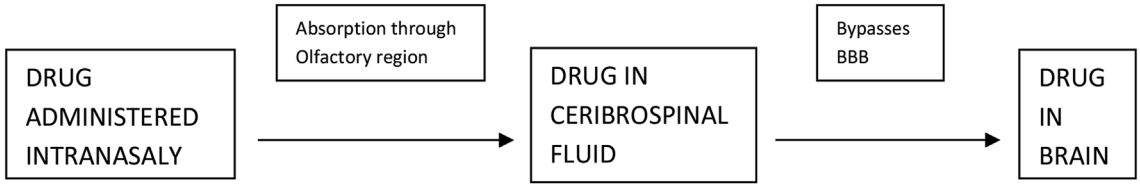

Fig. 3. Nasal drug administration for Drugs acting on Central Nervous System.

drugs which are acting on Central Nervous System (CNS) [40] (Fig. 3). The main disadvantages of the Nasal route are instability of the peptide drugs and, rapid muco-ciliary clearance mechanism, leads to poor bioavailability. This bioavailability can enhanced by using the novel drug delivery systems like microspheres, nanofiber etc. where any mucoadhesive material can be used and also attain the controlled release of the drug by using suitable polymer [41]. There are various formulations which are administered intra-nasally. The limitations further includes the small volume of intra nasal cavity, allows instillation of small amount of volume i.e 25–200 μl. Moreover drug molecules with molecular weight grater then 1000 Da are not suitable for intra nasal administration.

1.2.3.1. Nanofiber in nasal route of drug delivery. Nanofiber is a novel drug delivery system, where fibrous structure containing drug. Nanofibers are recently used in various applications. The extremely large surface area of nanofibrous polymeric matrix allows longer retention times and slow release of encapsulated drug, hence serve as a potential carrier for nasal drug delivery. Nanofiber can be used to deliver the drug directly to brain because it bypasses the BBB. Kaur et al., worked in this direction and make an intranasal gel formulation loaded antidepressant drug for direct administration into brain. Nasal route enhances the drug bioavailability in brain leading to administration of a low dose. In their study they found promising results [42]. Nanofiber scaffold can also be used in the tissue engineering, particularly beneficial in case of injury to the nasal epithelium or to respiratory epithelium. Rabiatul et al. make an effort to make an in vitro model of respiratory epithelium model by electospinning of poly(methyl methacrylate) (PMMA) [43]. Nanofiber is also analysed for its potential of tissue engineering in various traumatic injuries of central nervous system and olfactory region. Rochikind et al. explored the potential of nanofiber in regenerating axon through nasal olfactory mucosa [44].

1.2.4. Sublingual route of drug delivery

Sublingual route of drug administration refers drug administration under the tongue. Drugs with desired physio-chemical properties rapidly absorbed through the sublingual mucosa up to 10 folds grater then oral route. The sublingual route shows rapid absorption but problem is short duration of action. Sublingual route is a good option for cardiovascular diseases like angina. In terms of permeability, the sublingual route have high permeability as compared to other regions of the mouth [45]. John et al., compared oral and sublingual formulations of Verapamil in healthy volunteers and found good absorption and bioavailability in sublingual as compared to oral formulation [46].

1.2.4.1. Advantages of sublingual route.

- Rapid onset of action and patient compliance.
- First pass hepatic metabolism is bypassed and drug is protected from enzymatic degradation.
- Good absorption results into dose reduction which minimizes the side effects of drug.
- Highly vascularised surface area results into faster absorption.

1.2.4.2. Nanofiber in sublingual drug delivery. The limitation associated with the sublingual drug delivery is that it is not suitable for prolonged drug administration. The sublingual drug delivery systems are not suitable for sustained release delivery systems because drug does not reside at sublingual site for longer time periods [47].

As we know that the nanofiber is a novel concept of drug delivery systems and the applications of nanofiber in various fields are yet to be explored. Nanofiber in drug delivery system is a point of interest for researchers. Nanofiber due to its high surface area to volume ratio can release the huge amount of drug instantly. Further depending on the polymer used in the nanofiber can also control the release of drug for extended period of time. Vrbata et al., makes nanofiber with Sumatriptan succinate and naproxen, both these drugs are used in migraine treatment. The nanofiber exhibit instant release and high permeability of the drug through sublingual mucosa [48]. The drug loading capacity was 40% to the nanofiber volume. Nanofiber can also be used to provide the sustained and controlled release of drug through sublingual site. Sharma et al., makes a nanofiber using biodegradable polymer Poly(vinyl alcohol) and sodium alginate for sublingual delivery of insulin. In vitro release study demonstrated insulin release follows first order kinetics after initial burst release [49]. Yu et al., make an attempt to incorporate solid dispersion of ferulic acid into composite nanofiber of polyvinylpyrrolidone and Sodium Dodecyl sulphate and sucralose in ethanol(75%), they found 13 fold increase in the permeability across the sublingual mucosa [50]. Singh et al., make nicorandil loaded nanofiber for angina pectoris through sublingual route in an attempt to reduce the mucosal ulceration. In their histopathological studies they found no sign for mucosal ulceration. The nicorandil loaded nanofiber also shows the prolonged time of action [51].

1.2.5. Vaginal route of drug delivery

Vaginal route of drug delivery is very complex and dynamic route for drug delivery. In earlier days this route of drug administration was used for sustained release. The advantage of the vaginal route of drug administration is that it bypasses the hepatic first pass metabolism of the drug, and allows self-administration of the drug. While talking about sustained release, single administration can provide the drug release for weeks and even up to months. In earlier studies it was found that vaginal route is very potential route than others for some drugs like morphine, Atropine and potassium iodide. Vagina is very complex route for drug delivery due to alteration in pH and presence of microbial flora. Further the rate of drug absorption and bioavailability was found to be altered with the change in thickness of epithelial layer during menstrual cycle. All these things make the vaginal route a very complex route for drug administration [52].

1.2.5.1. Nanofiber in vaginal drug delivery. Nanofiber can be a very useful drug delivery system for vaginal drug delivery. Now a day a lot of work has been conducted on mucoadhesive nanofibers for vaginal drug delivery. Nanofiber can be used for localized action as well as to attain the desired therapeutic level of drug in blood. Zong et al., worked with cisplatin loaded poly(ethylene oxide) polylactide composite nanofiber for localized effect in cervical/vaginal cancer. They found that toxicity reduces in peripheral organs like kidney and liver when drug is administered through vaginal route [53]. Nanofiber can also be used for targeted delivery of drug in vagina. Various antimicrobial agents are administered through vaginal route. Kaur et al., prepared a poly lactic acid nanofiber containing antimicrobial agent for targeted and controlled release of encapsulated pharmaceuticals in urinary tract infection. In this work promising results were obtained [54]. In an another example Sharma et al., prepared fluconazole loaded nanofiber of polyvinyl alcohol(PVA) for treatment of vaginal candidiasis and they found good antimicrobial activity of fluconazole in nanofiber compared to parent drug with sustained release pattern up to 6 h [55]. Ball and Woodrow prepared an electrospun solid dispersion containing anti-human immunodeficiency virus (HIV) microbicides i.e. Maraviroc for pre exposure prophylaxis of HIV and intended for Intravaginal administration. Maraviroc prevents the entry of the virus into the host cell. In this 28% Maraviroc loaded electrospun solid dispersion in polyvinyl pyrrolidone and poly(ethylene oxide) nanofiber is prepared which shows instant release of drug i.e. within 6 min which is very good as compared to other formulations like films and tablets that require 15 min to dissolve [56]. Nanofiber can also be used to control the release of drug at different pH conditions Jiang et al., prepare polydopamine coated poly(ε-caprolactone) nanofiber containing anticancer agent which shows different release pattern of drug at different pH conditions [57]. This pH-responsive release pattern can be

Table 2
Application of nanofibers in mucosal drug delivery.

Drug	Polymer	Application	In-vitro performances	Biological outcomes	References
Nanofibers in oral, buccal and sublingual drug delivery					
Nicorandil	Poly vinyl alcohol	Angina pectoris.	Fiber diameter ranging from 200 to 450 nm and shows controlled release behaviour	Pharmacokinetic studies established the preclinical safety and showed the maintenance of an effective therapeutic level for a prolonged period.	[58]
Ibuprofen or Carvedilol	Poly caprolactone	Oro-mucosal drug delivery system	The average fiber diameter increased with a higher drug loading	The incorporation of both model drugs into the PCL nanofibers significantly improved their dissolution rates.	[59]
α-mangostin	Citosan and Poly vinyl alcohol	Oral hygiene	The prepared formulation shows suitable tensile strength, swelling, mucoadhesive properties and rapid release behaviour of the drug	The mats exhibits less cytotoxic after 72 h and instant antimicrobial activity	[60]
Docitaxil	Poly vinyl alcohol	Buccal cancer	prepared fibers were smooth and shows excellent mucoadhesive potential	Prepared formulation demonstrate good anticancer activity in in-vitro cell lines study	[61]
Sumatriptan succinate and naproxen	Chitosan, poly vinyl alcohol, poly acrylic acid and poly caprolactone	Migraine	Thermal analysis proved that the resulted membranes contained noncrystalline drug forms.	Drug in nanofibers shows good sublingual permeability	[48]
Nanofibers in ocular drug delivery					
Dexamethasone	Poly-lactic acid (PLA) and poly-vinyl alcohol (PVA)	Anterior segment ocular diseases	Fiber thickness increases with increasing drug concentration from 50 to 93 μm and exhibit extended drug release pattern	No cytotoxicity was observed in corneal endothelial cells for up to 24 h	[62]
Ofloxacin	Poly(ε-caprolactone) (PCL) and PCL: poly (butylene succinate) PBS	Ocular application	Fiber diameter decreased with decreasing polymer amount. Drug release behaviour depends on the ratio of PCL and PBS	Exhibits excellent antimicrobial activities against *P. aeruginosa*, S. epidermidis, S. Aureus and *E. coli* strains	[63]
Voriconazole (VRC)	Polyvinyl alcohol (PVA)/ hydroxypropyl-β-cyclodextrin (HPβCD)	Ocular application	The nanofibers exhibited bead-free average fiber diameters of 307 ± 31 nm. Shows sustained drug release pattern	Nanofibers significantly prolonged the half-life, and increased the bioavailability of VRC in rabbit tears with no sign of irritation	[64]
ciprofloxacin	Poly vinyl alcohol	Mucosal permeability	Smooth nanofibers with fiber diameter ranging from 200 to 300 nm.	Intestinal tissue shows maximum permeability followed by eye, trachea, sublingual, rectal, and skin.	[65]
Timolol maleate and dorzolamide hydrochloride	Poly vinyl alcohol	Glaucoma	Bead free ultrafine nanofibers results in 12% PVA	Demonstrated significant fall in the intraocular pressure compared to commercial eye drops	[18]
Nanofibers in nasal drug delivery					
Collagen	Poly (methyl methacrylate) PMMA	In vitro respiratory epithelium model	The amount of collagen was significantly higher in PMMA group cross linked with genipin	Degree of cell adherence was significantly higher in PMMA cross linked with UV	[66]
Nanofibers in vaginal drug delivery					
Cisplatin	Poly-caprolactone/ Chitosan	Cervical cancer	Prepared nanofibers had shown the sustained release pattern up to one month	Prepared formulation exhibited superior anti-tumor activity in animal model	[67]

(*continued on next page*)

Table 2 (*continued*)

Drug	Polymer	Application	In-vitro performances	Biological outcomes	References
Tenofovir	Thiolated hyaluronic acid (HA-SH) polymer	HIV vaginal transmission	Papered nanofiber shows a mean diameter of 85 nm and about 87% drug release in 1 h	The anti HIV activity of drug remains unchanged in nanofiber. Prepared formulation exhibited enhanced drug retention and bioavailability in vaginal tissue	[1]
Cisplatin	Poly(ethylene oxide)/polylactide	Cervical cancer	Prepared formulation shows good mucoadhesive property and in vivo vaginal retention evaluation	In vivo trials showed that a better balance between anti-tumor efficacy and systemic safety	[68]
Nitrofurantoin	Polylactic acid	Urinary tract infection	Ultrafine nanofibers shows sustained drug release behaviour	A major fraction of drug was recovered from the kidney after 32 h results in a significant reduction in colony forming unit (CFU)	[69]
Fluconazole	Poly vinyl alcohol	Vaginal candidiasis	prepared nanofibers were found to be uniform, non-woven, with the diameter ranging from 150 to 180 nm	Prepared formulation exhibit superior anti-microbial activity against *Candida albicans*, when compared to the plain drug	[70]

used for oral delivery or for vaginal delivery of anticancer agent or antimicrobial/anti-inflammatory agents respectively. Table 2 summarizes the application of nanofibers in mucosal drug delivery.

2. Conclusion

Nanofibers due to its unique surface and functional properties can overcome many of the obstacles of conventional drug-delivery systems used for transmucosal drug administration. Nanofibers due to its multi layered structure helps to mask the bitter taste of drugs, makes electrospun nanofibers highly suitable for buccal and sublingual application. Closed cycle electrospinning process maintaining a sterile environment throughout the fabrication process makes it suitable for ocular drug delivery. Further nanofibers can be prepared from a variety of polymers to achieve desired physiochemical and pharmaceutical properties suitable for transmucosal drug delivery. Moreover special kind of nanofibers such as core shell of multi-layered fibers can be produced using modified fabrication technique like coaxial technique to control the release of entrapped therapeutics thus proven to be effective in local and systemic delivery of drugs via mucosal route. Recently electrospun Fibers has been extensively studied for tissue engineering, drug delivery and wound dressing established their safety and effectiveness for biological application.

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