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Nanofiber for sublingual delivery: A review

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Abstract: Oral drug delivery administration is found as the most appropriate method in drug administration because it is easy to utilize, higher patient compliance along with non-invasive nature. The electrospinning process basically utilized to produce nanofibers by feeding a polymer solution in the high electric field. The electrospinning tools mainly consist of electrical supply to produce more electrical voltage where the syringe is generally filled with the solution of polymer, a pump along with a static or movable collector surrounded in a chamber. Electrospun nanofibers can be produced with natural, semisynthetic along with synthetic polymers. As compared to natural sources of polymers, synthetic polymers are more flexible in modification along with synthesis. In the meantime, natural polymers show more safety as well as biocompatibility. This paper covers a detailed review of all the state-of-art methods used in the field showing promising results.

Key words: Nanofibers, Polymer, Electrospinning, Syringe

Introduction

Oral drug delivery administration is found as the most appropriate method in drug administration because it is easy to utilize, higher patient compliance along with non-invasive nature. Oral preparations could be designed in different methods as it is cost effective. With comparison to another administration methods, oral drug administered require no expertise so can be utilized for chronically diseases having more consumption of dose. Thus, growth of drugs or medicines is preferable in oral medicine products. Nanotechnology is the most appropriate method that was investigated widely in oral drug administration as it has more convenience power as well as more patient compliance connected with this. Electrospinning process is basically utilized to produce nanofibers through feeding a polymer solution in high electric field. From polymer solution a thin jet is created as well as electrostatic field is applied for evaporation to produce micro or nano scale fibers. Different delivery system of drugs having various profiles of drug release like; pulsatile, biphasic along with fast were finally attained which are dependent on electrospun Nanofibers.

Advantages

- The extensively utilised and most convenient drug administration route is the Oral route
- In oral drug delivery, promotional benefits are presented by nanotechnology
- Robust structural characteristics were shown by the polymers utilised for oral drug delivery
- Reduction in fed/fasted variability
- Decreased toxicity
- Increased bioavailability

Disadvantages

- Handling, packaging and shipping is not easy
- Toxic solvents
- Jet instability

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Need of designing Nanofiber

For enhancing the drug delivery along with restricted absorption which results because of weak dissolution/solubility, various methods are developed for improvising the drug molecules, solubility as well as dissolution rates. Such methods comprise of reduction of particle size, dosage form that includes solubility-enhancing agents, development of stable amorphous drug formulations and identifying the parent drugs, water-soluble salts. Thus, for reducing the size of drug particle to a very low range various technologies are developed and applied in the products. Among those technologies, electrospinning is a technology that produces the polymeric Nanofibers incorporated nano sized drugs.

Recent developments in nanofibers

El-Newehy *et al., (2018)* nanofibers mats, mechanical properties can be improved when Green synthesized nanofibers mats use HPC (hydroxypropyl cellulose) or combine with PVA (poly vinyl alcohol) as well as PVP (Polyvinylpyrrolidone). TGA, FT-IR, SEM as well as conventional tools are used to manifest nanofibers mats' physical as well as mechanical attributes.

Illangakoon *et al., (2014)* by electrospinning, prepared rapidly dissolve as well as sustained release mebeverine hydrochlorides' DDS (drug delivery systems) embedded with Eudragit R L 100-55 nanofibers or (PVP) povidone K60. Liquid chromatography (high-performance) along with Nuclear magnetic resonance spectroscopy examined and find a conclusion that MB-HCl has not been destroyed in the spinning process while data collected from Infrared spectroscopy proved that this drug has high compatibility power in the presence of polymer.

Sharma *et al., (2013)* established insulin packed PVA-NaAlg composite nanofiber primarily based a spot/patch for delivery of an anti-diabetes drug. Vivo study had been done on Wistar rats (males) by using sublingual method.

Heo *et al., (2013)* created a mixture of natural along with synthetic polymers nanofiber with utilizing gelatin as well as PU (polyurethane) that had been created by electrospinning technique. SSD (Silver-sulfadiazine) has been combined with mixture of polymer solution to cooperate with nanofibers after electrospinning technique by effects of burn-wound healing test.

Madhaiyan *et al., (2013)* examined that delivery of water-soluble vitamin having hydrophobic polymer nanofiber were suffered the release of vitamin as well as this technique is suitable for transdermal patch functions. Drug loaded fibers have been especially distinguished with porometer, SEM and FT-IR for pore size measurements and to calculate mechanical strength, morphology as well as drug load classification respectively.

Macri *et al., (2012)* "electrospun tyrosine-derived polycarbonate terpolymers" fulfil the requirement of biomaterials which may erode, degrade as well as deliver a therapeutic agent in time along with controlled way. The mixture of electrospinning along with terploymers gives chance to fabricate devices with same drug loading as well as diameter but having low performance (that is degradation along with drug delivery).

Meng *et al., (2011)* fabricated Drug (Fenbufen, FBF) loaded PLGA/gelatin nanofibrous along with PLGA scaffolds through electrospinning strategy. The impacts of gelatin material, crosslinking time, fibre agreement, as well as buffer solution pH valuation on FBF discharge conducting of ensuing nanofibrous scaffolds have been examined.

Kenawya *et al., (2009)* produced a new system of electrospun fibers to deliver ketoprofen as NSAID (non-steroidal anti-inflammatory drug). The fibers have been generated from either PU (polyurethane) as a non-biodegradable polymer or PCL (polycaprolactone) as biodegradable polymer or might be from mixture of these two.

Yu *et al., (2009)* produced oral FDMs (fast-dissolving drug delivery membranes) which were poorly soluble in water by using electrospinning method with PVP (polyvinyl pyrrolidone) along with ibuprofen as the drug carrier or filament-forming polymer as well as model drug respectively. Results obtained from Morphological observations, X-ray diffraction as well as various scanning calorimetry verified that ibuprofen has been distributed in a nanosolid dispersions form in the ultrafine fibers and drug was physically present in form of molecular or amorphous.

Maretschek *et al., (2008)* produced organically poly (L-lactide) solution as well as an aqueous protein-solution yielded protein with NNs having 350nm fiber diameter by using electrospinning technique. For encapsulation, C (Cytochrome) has been selected as a hydrophilic model protein. Gas adsorption as well as SEM imaging measurements have been taken to find out morphology along with surface attributes of various nanofiber nonwovens.

Wang *et al., (2006)* produced electrospunPLGA-based micro- and nanofibers in vitro to inserts sustained delivery of anticancer drug for the treatment of C6 glioma. From electrospinning method nanofibers as well as PLGA-based micro 30 nm to 10 mm diameters were obtained. In fibers anticancer drug V paclitaxel model has been encapsulated whereas the efficiency of encapsulation was found more than 90%.

Methods of preparation

Electrospinning process is basically used for producing Nanofibers through feeding a polymer solution in more electric field. From polymer solution, basically thin jet is created as well as electrostatic field is applied for evaporation to produce micro or Nanoscale fibers. In 1934, for the first time the mechanism of Nanofiber production by Electrospinning method was reported.

Basics of electrospinning

The electrospinning tools mainly consists of an electrical supply to produce more electrical voltage where syringe is generally filled with solution of polymer, a pump along with a static or movable collector surrounded in a chamber. With the start of procedure, solution is emitted from syringe by a pump. Subsequently the droplet1is put through a higher voltage as well as distinction in electric voltage contained among collector along with nozzle with the counter cost as well as the resulted electric voltage will cause a cone shaped1deformation of1the droplet recognized as a Taylor cone. If the1voltage outperforms a threshold value, droplets' surface tension will overcome by electric force as well as solutions charged jet is removed from needle of syringe.

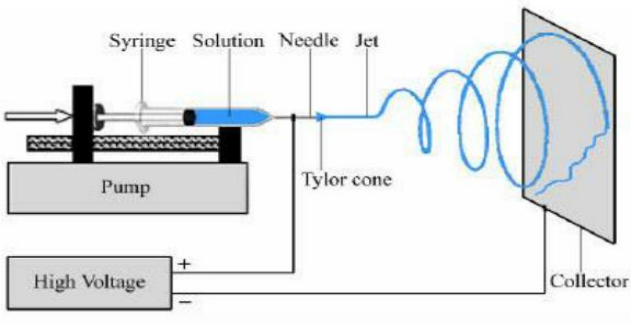

Figure 1: Flow diagram of electro spinning process

After that charged jet of solvent occurs as well as solid material is gathered in the form of small solid fiber, Braghirolliet *et al., (2014)*. Electrospinning along with dissolution are significantly conducted at ambient temperature under given atmospheric conditions (**Fig. 1**).

Advantages

Electrospinning has a distinctive advantage that if calcination is controlled, complicated hierarchical designs may be produced. These complicated designs are ought to fabricate by utilizing techniques such as CVD (chemical vapour deposition), self-assembly, template-based synthesis, along with other techniques based on solution. A wet-chemistry technique like sol-gel synthesis, hydrothermal technique, Polyol technique was also approved towards synthesizing. Out of these techniques, hydrothermal technique was proved as the efficient and best fabrication technique to produce inorganic nanomaterials. Specially, this technique is utilized to produce TiO_2 NWs(nanowires) due to its controllable and fine crystal form as well as better dispersibility. Nevertheless, when compared with electrospun NWs synthesized through hydrothermal technique normally have a reduced aspect ratio that is essential to transfer in power systems for example hydrogen generators as well as LIBs (lithium ion batteries).

Disadvantages

Currently, there are many limitations of Electrospinning. Firstly, organic NFs needs more polymer variety but in electrospinning it is used in limited amount as well as NFs performance along with structure are also not examined.Next, the functionality as well as

assortment of electrospun inorganic NFs software were restricted because of its friability afterward calcination, though inorganic NFs have many possible applications in numerous areas including power systems, large temperature purification, effective catalysis, and biological tissue engineering.

Polymers used in electrospinning nanofibers

Electrospun nanofibers can be produced with natural, semisynthetic along with synthetic polymers. As compared to natural sources of polymers, synthetic polymers are more flexible in modification along with synthesis. In the meantime, natural polymers show more safety as well as biocompatibility. Copolymers along with Synthetic polymers like PEO (Poly Ethyleneoxide), PVP (Poly Vinyl Pyrrolidone), PLGA (Poly Lactic-co-Glycolic Acid), PCL (Poly ε- CaproLactone), and PLA (poly lactic acid) were utilized in tissue engineering to produce drug delivery, in drug delivery area, various polymers parameters like; polymer composition, weight and polymer ratio of crystalline to amorphous segments can also affect drug release rate in nanofibers. Many polymer as well as its solvents utilized to produce electrospun nanofibers especially for drug delivery system. In drug delivery system, polymer behavior plays an essential part either it is polycationic or polyanionic. Different synthetic as well as natural polymers are present such as; chitosan, pectin, xyloglucan, guar gum, alginic acid and etc. Synthetic polymers like; HPMC, poly-caprolactone, poly (DL-lactidecoglycolide), PLA and etc. were utilized to produce suitable1nanofiber especially for drug delivery system.

a) **Polyvinyl alcohol (PVA):** PVA was examined because of its film forming capability, tremendous mechanical properties, high chemical resistance as well as high hydrophilicity. These types of properties leads it to use in various area such as biomedical along with biotechnology fields. Therefore, PVAfibers of electrospun are utilized in biocatalysts immobilization, nanosensors, tissue engineering, drug delivery and filtration.

b) **Almond gum as Nanofibers:** Almond gum basically got in an exudates form that is biodegradable, natural as well as non-toxic in nature. It exudates generally from almond1trees (*Prunus communis*L, *Prunus dulcis*L.,) which belongs to Rosacea family. Structurally it1is consist of1arabinogalactan as well as it has 2 main fractions such as water soluble as well as water insoluble fraction.

c) **Chitin-Chitosan Nanofibers:** Chemically chitin is β-(1-4)-poly-N-acetyl-D-Glucosamine. Most polysaccharide is distributed widely in1the nature. Majorly this is representing in an exoskeleton structural component of insects, shrimp shells, crab, yeast and fungi's cell wall. Chitin's flexibility as well as strength makes it essential for surgical operations along with biodegradability.

d) **Starch as nanofibers:** Starch is basically a biocompatibility and inexpensive biopolymer that exists widely in plant tissues like; leaves, rubbers, roots, seeds and stems. It may be linked and cross linked with few elements subject to enzyme, pH and redox agents as they have several hydroxyl groups. Therefor so many efforts were devoted in this research work for drug delivery system based on ST. Starch-based carriers are able to attain precise medication distribution and controlled medication discharge, and may lessen the revitalizing consequences of medications on the gastrointestinal along with other digestive organs.

Nanofiber in the targeting field

a) **Fast release:** Several scientific researchers along with pharmaceutical companies have lately formed novel dosage which quickly split in an oral cavity. These are known as FDDDSs (Fast-Dissolving Drug Delivery Systems) or orodispersible. FDDDSs drugs have ability to disintegrate or dissolve quickly having no need of water to swallow. Hence, more bioavailability along with quick drug action may be attained by these drugs.

b) **Controlled release:** CDDS (Controlled Drug Delivery Systems) were also have capability to treat several drugs. In many fields such as oral and topical drug delivery, Electrospun

nanofibers has capability to utilized due to its unique properties like cost effectiveness, flexibility, long surface area, more loading efficiency, high porosity, versatility. In oral drug delivery field, they were utilized as controlling drug system such as sustained release, biphasic, burst and delayed.

c) **Biphasic release:** Several drugs like NSAID (Non-Steroidal Anti-Inflammatory Drugs) are good to managed in a biphasic release system form as it has many effects. For this particular reason, coaxial electrospinning process was utilized for the preparation of sheath/core ketoprofen-loaded nanofibers which can give biphasic drug release profiles with use of PVP in a form of sheath polymer along with ethyl cellulose in a form of core matrix.

d) **Delayed release:** Drug encapsulation in a polymer was examined for oral delivery of proteins along with peptides as well as to treat ulcerative colitis diseases. Electrospunmebeverine hydrochloride-loaded nanofibers was produced by PVP polymers as well as drug was delivered by Eudragit R L100-55 to GI tract in protected along with sustained manner particularly in human stomach.

e) **Colon drug delivery:** Currently, for oral drug delivery various techniques were investigated to colon such as timed-release systems, prodrugs, matrix system utilized for controlling release rate as well as pH-based sensitive polymers. In another research electrospinning process was utilized to produce Eudragit L100-55 nanofibers having diclofenac sodium. Results also showed that Drug release nanofibers has been basically pH-dependent, hence nanofibers demonstrated diclofenac colonic drug delivery.

f) **Dual drug delivery:** A good example of utilizing electrospun nanofibers as two medication distribution methods was eudragit/zein composite nanofibers tricked with pantoprazole and aceclofenac. Eudragit S 100 was insoluble in acidic solutions therefore its drug release rate was near about 8 hours. As a general result, a dual drug delivery system has been effectively produced having less side effects.

g) **Nanofibers in advanced wound care:** In comparison to conventional wound treatment, advanced wound treatment dressings work in hydrated locations, needless regular changing as well as simply help to decrease the ache of dressing modifications and decrease scars.

h) **Topical drug delivery:** In tissue engineering Electrospun" Nanofibers for gene along with drug delivery application were utilized to enhance therapeutic efficacy. Additionally, mucous layers faces some strong adhesiveness by the fibrous surface structure due to their nano-porous structures that rapidly absorbs the mucous layers via nano-void volumes. The better adhesiveness to word natural surfaces enables Nanofibers to become the most perfect candidate for topical drug delivery products.

i) **Nucleic acid:** Luu *et al*., basically defined plasmid DNAin a PLA-PEG block co-polymer nanofibrous matrix generally for tissue engineering reasons. β-galactocidase receptor gene basically released near about 80% in 20days.Transfection tests done on the osteoblastic cells line MC3T3-E1 show elevated transfection effectiveness of the fiber-encapsulated DNA over naked plasmid put into the moderate, but less than that with a business transecting reagent. DNA stability was enhanced during electrospinning procedure.

j) **Delivery of chemotherapeutic agents:** Nowadays Nanofibers are utilized widely as an anti-neoplastic drug delivery. This is related to fibrous scaffolds characteristics that permit drug delivery just after medical implantation and tumour resection. Mostly nanofiber was operated widely to treat malignant tumours.

Recent advancement

The following table presents the recent formulated nanofiber products along with their formulations as well as brand name.

Table 1: Markedly available Nanofibre products

Product	Formulation	Brand Name
Dermafuse	Bioactive borate glass nanofibrous dressing	Mo-sci corporation U.S.A
Kerlix AMD	Nanofibrous PHMB gauge	Kendall
Apligral	Bovine collagen nanofibrous sponge with neonatal foreskin fibroblasts and keratinocytes	Novartis
Nanocell	Nanofibrous microbial cellulose masks	Thaionano cellulose
Integra	Nanofibers bovine type1 collagen/glycosaminoglycons/syntheticpolysiloxane based dermal analog	Integra life sciences
Trans type	Electrospun Nylon Mesh/Collagen/Silicone dermal substitute embedded with allogenic fibroblasts	Advanced Tissue Sciences
Tegaderm	Eletrosun poly(caprolactone) (PCL)/gelatin/polyurethane/scaffold	3M company
Chito flex	Fabricated chitosan Nanofibrous dressing	Hemcon Med Tech.Inc.
Permacol	Dermal matrix of procine Nanofibers	Covidien
AlloDerm	Condaners a cellular matrix Nanofibersautograft	Life cell corporation

Conclusion

In present investigation we have reviewed the Nanofibers for sublingual delivery. Various literature forms has been reviewed and studied for more clarity. It is concluded that the method of preparation of nanofiber was found to be simple, reproducible, provides good loading capacity. In this particular work we studied for generating a fast-dissolving drug delivery system successfully for immediate release of drug mixture. This technique involved electrospun fibers utilizing PVA as a form of filament forming agent. The collected data information in this study clearly shows that electrospun fibers can include exceptional applicants for oral fast dissolving films that may be especially helpful for patients having swallowing problems.

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