

Review

Electrospun fibers for wound healing and treatment of hyperglycemia: A review

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Received 20 March 2016, Accepted 3 June, 2016

The use of electrospun fibers in diabetic wound healing assays represents an extremely important topic for investigation. Electrospun fibers have been applied in the immobilization of drugs, allowing sustained and controlled release of active materials. This review aimed to summarize the state-of-art in the application of electrospun fibers on diabetes, hyperglycemic and diabetic ulcers treatment. Regarding the diabetes control and treatment, electrospinning technique contributes to application of wound healing (*in vitro* and *in vivo* experiments). The glycemic control is favored due to controlled release which has been sustained and improved. The data suggest that the development of encapsulated drugs in electrospun fibers has a promising application in the treatment of diabetes and related complications.

Key words: Electrospun fibers, nanofibers, electrospinning technique, anti-diabetic drugs, hypoglycemic drugs, wound healing.

INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by insufficiency in insulin secretion, insulin action, or both (ADA, 2014) that results in hyperglycemia. The International Diabetes Federation (IDF) estimates that in 2040, 10% of adult population will be diabetics. Considering the South and Central America, this number increases to 65% (IDF, 2015).

Numerous pathogenic processes are consequence of diabetes, due to the several pathologies involving heart, blood vessels, eyes, kidneys and nerves (ADA, 2014;

IDF, 2015; Chen et al., 2015). In addition, diabetic wound healing has been considered one of major complications of diabetes mellitus (Siersma et al, 2014) which results in peripheral neuropathy and/or large vessel disease complicated by trauma (Singh et al., 2005; Boulton, 2008).

The glycemic control is critically important for minimization in the impacts of diabetes and corresponding complications. Recent studies have demonstrated that new therapies can be used in the control of blood

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glucose and the diabetic complications, such as wound healing (Schneider et al., 2009; Arnolds and Heise, 2007; Moura et al., 2014; Nishimura et al., 2012; ITA, 2015).

Electrospinning technique is an extensively studied technology for nanofiber production (FORMHALS, 1934) recently applied in biomedical issues (Yu et al., 2014; Ding et al., 2014) with focus in the development of methods for diabetes treatment and its complications, such as diabetic ulcers (Xie et al., 2013). The action of electrospun fibers is improved due to the unique properties such as high surface area, high loading and simultaneous delivery for diverse therapies and reasonable cost-effectiveness that provided expansion in the use of fibers for drug delivery (Hu et al., 2014). Natural and synthetic polymers can be used in the electrospinning, including soluble and spinnable polymers in water, biocompatible and biodegradable polymers (Agarwal et al., 2009).

Drug-loaded electrospun fibers have been considered as promising strategies to achieve bioactive wound dressings for chronic non-healing wounds (Schneider et al., 2009) and for controlled release in the gastrointestinal tract. The nanoscale multi-agent delivery system has been applied in the drug loading (Yang et al., 2014); thereby the present systematic review summarizes the current studies about the application of electrospun fibers in the treatment of diabetes, hyperglycemic and diabetic ulcers.

Previous work reveals the potential of application of optimized structures for drug-loaded electrospun fibers production (Araujo et al., 2016; da Costa et al., 2015). Corresponding association with natural products (such as *Morus nigra* (Almeida et al., 2011)) represent an important topic of research with the aim of developing new nanostructured systems for application as prototype of wound dressings for non-healing wounds.

DIABETES CONTROL

As consequence of preponderance of individuals with elevation in the plasma glucose that remains untreated and/or undiagnosed (Buysschaert et al., 2015), there is a global trend of increasing diabetes cases. Numerous studies have described new therapies related to the control of glucose, insulin levels and other diabetic disorders (Nacht et al., 2015; Yong et al., 2015; Yang et al., 2016; Du et al., 2016; Chen et al., 2016)

This development requires the use of *in vivo* or *in vitro* models. The diabetes induction in animal models is typically induced by two mechanisms *viz.* alloxan and streptozotocin (Lenzen, 2008). However, streptozotocin-induced diabetes is a more stable model for experimental diabetes and it can be used for both shorter and longer experimental studies (Radenković et al., 2016). Kuricová et al. (2016) recently demonstrated that is possible to simulate *in vitro* culture conditions mimicking human

glycemic variability. The nanotechnology in diabetes research has potential to treat the diabetes complications and to improve the quality of life of the patients (Disanto et al., 2015). Studies have demonstrated that electrospun nanofibers can be used as glucose sensors due to the different mechanisms (Senthamizhan et al., 2016; Ramasamy et al., 2015). In addition, the incorporation of nanostructures promotes the enhanced insulin production in response to glucose stimulation, which enables the development of new diagnostic test for drug development (Blackstone et al., 2014).

PROCESS PARAMETERS FOR ELECTROSPINNING

Relative to electrospun fibers production, the control in the process parameters is a critical parameter in order to obtaining nanofibers with desired morphologies and diameters. The polymer molecular weight, solution concentration and solvent type also affect the diameters and morphologies of the fibers (Cui et al., 2007). According to Jang et al. (2015) pivotal parameters such as polymer concentration, molecular weight, input voltage and gap distance affects the production of nanofibers.

Therefore, there was the broad range in the characteristic fiber diameters and fiber morphologies in different studies due to the use of different process parameters, polymers and solvents.

The definition of appropriate polymer represents a key component for development of sustained release electrospun fibers (Chou et al., 2015). Polymers used in these studies are all biocompatible and may be employed for applications involving the development of control drug delivery systems (Li et al., 2000; Zong et al., 2003; Yao et al., 2003; Li et al., 2003; Zhou et al., 2003) (Table 1).

LOADED AND CONTROLLED RELEASE OF DRUGS

The encapsulation efficiency contributes to improve the absorption and prolonged release of components (corresponding data is summarized on Table 1). In all reported data, there were enhancements on resulting release. Sustaining drug release from electrospun nanofibers shows regular release kinetics that depend upon material surface chemistry, drug loading, and processing parameters (Chou et al., 2015).

In these studies, the electrospun fibers show improved activity of the substances followed by controlled release of drugs and/or substances. The profile of *in vitro* assays shows sustained and controlled release of drugs, substances and natural product (Lee et al., 2015, 2014; He et al., 2014; Sharma et al., 2013; Merrell et al., 2009; Yang et al., 2011, 2012; Choi et al., 2008), while for different systems the drug release is order of hours (Sharma et al., 2013), days (He et al., 2014; Merrell et al., 2009; Choi et al., 2008) or weeks (Lee et al., 2015, 2014;

Table 1. Electrospun fibers: production and characterization.

Authors, year	Polymer	Solvent	Process parameters			Characterization			Mechanical properties		Encapsulation / entrapment efficiency
			Voltage applied to polymer solutions(kV)	Flow rate	Work distance (cm)	SEM	TEM	AFM	Tensile strength	Elongation at breakage	
Lee et al., 2014	PLGA	HFIP	17	3.6 mL/h	12	Yes	No	No	Yes	Yes	-
Lee et al., 2015	Collagen and PLGA	HFIP	17	3.6 ml/h	12	Yes	No	No	Yes	Yes	-
Merrell et al., 2009	PCL	Methanol and chloroform	25	2mL/h	10	Yes	No	No	No	No	-
Choi; Leong and Yoo, 2008	PCL and PCL	Methanol and chloroform	15	-	15	No	No	No	No	No	-
Yang et al., 2011	PELA	Chloroform	19	1.6 ml/h	-	Yes	No	No	No	No	79.2 ±14.8%
Yang et al., 2012	PELA	Chloroform	20	1.6 mL/h	-	Yes	No	No	No	No	87.7 ± 16.5 and 79.3 ± 11.6%
He et al., 2014	PGC and PCL	HFP	30	3 mL/h	25	Yes	No	No	No	No	-
Sharma et al. 2013	PVA and NaAlg	Deionized water	15	0.5 ml min ⁻¹	15	Yes	No	Yes	Yes	No	99%

PLGA, Poly-D-L-lactide-glycolide; PCL, Poly(ϵ -Caprolactone); PEG, Poly(ethyleneglycol); PELA, Poly(ethylene glycol)-poly(DL-lactide); PGC, Protected Graft Copolymer; PVA, Poly(vinyl alcohol); NaAlg, sodium alginate; HFIP, 1,1,1,3,3,3-hexafluoro-2-Propanol; HFP, 1,1,1,3,3,3-Hexafluoro-2-propanol); SEM, Scanning Electron Microscopy; TEM – Transmission Electron Microscopy; AFM – Atomic Force Microscopy.

Yang et al., 2011, 2012).

WOUND HEALING ACTIVITY

The absence of reepithelialization requires the development of acute or chronic non-healing wounds, in which the use of electrospun nanofibers accelerate wound healing rates in diabetic rats (Lee et al., 2015, 2014; Merrell et al., 2009; Yang et al., 2011, 2012; Choi et al., 2008) from

sustained release of substances that increase the re-epithelialization and regeneration of the skin by various mechanisms which depend on the substance/drug, the polymer and the process parameters applied in the production of the fiber (Table 2).

On the other side, the metformin is used in the treatment of type 2 diabetes. It represents the first-line pharmacological therapy associated with low weight gain and a reduced amount of hypoglycemic occurrence (UKPDS, 1998). In spite

of this application, no trials about the effect of metformin on wound healing in diabetic patients (Salazar et al., 2015) were performed. Studies have demonstrated that metformin acts in wound healing around oral implants (Inouye et al., 2014) and promotes nerve regeneration after sciatic nerve injuries in diabetes mellitus, providing its therapeutic values for peripheral nerve injury repair in diabetes mellitus (Ma et al., 2015).

The use of metformin-loaded electrospun fibers

Table 2. Glycemic control and healing diabetic wounds provided by electrospun fibers.

Authors, year, country	Substance / natural product	Animals	Concentration	Release pharmaceutical of	Design	Parameters assessed	Results and conclusions
Lee et al. 2014 China	Metformin	Sprague–Dawley rats	40 mg	<i>In vivo</i> and <i>In vitro</i> by HPLC	Wound repair assay	- Wound healing test - Histological examination	- The drug eluting membranes continuously released metformin for three weeks. The wound closure in group metformin-eluting PLGA membrane was visibly faster than those in groups - There were keratinocytes migrated and proliferated fastest without significant inflammatory response surrounding skin. Additionally, the groups treated with nanofibers exhibited more stratum corneum in the wound.
Lee et al. 2015 China	Glucophage	Sprague–Dawley rats	40 mg	<i>In vivo</i> and <i>In vitro</i> by HPLC	Wound healing assay	- Wound healing test - Histological examination	- <i>In vitro</i> release the glucophage-loaded membranes continuously released drug for three weeks. On all days of evaluation wound closure in collagen/PLGA with glucophage-loaded group had proceeded visibly faster. - The nanofibrous scaffolds demonstrated highly integration into the surrounding skin without any significant inflammatory response and the use of collagen in the nanofibers increased the collagen content compared the others and demonstrated complete epithelialization with the thinning of epidermis at the wound region
Merrell et al. 2009 USA, China	Curcumin	Male C57/B6 mice	3 and 17%wt/wt	<i>In vitro</i> by cell culture media using fluorometer	Wound healing assay	- <i>In vitro</i> anti-inflammatory property - <i>In vivo</i> diabetic mouse wound closure	- The fibers with a higher content of curcumin released an amount of significantly higher after 12 h, and so three days later - Curcumin loaded PCL nanofibers showed reduction pro-inflammatory response in mouse peritoneal macrophages <i>in vitro</i> and enhanced the rate of wound closure <i>in vivo</i>
Choi; Leong and Yoo 2008 Republic of Korea and USA	rhEGF	Female C57BL/6 mice	0.0045 nmol/mg of rhEGF to the amine groups	---	Wound healing assay	- Degree wound animal healing models - Immunohistochemical staining	- The rhEGF nanofiber accelerated wound healing rates at the initial stage of the healing process. This accelerated wound healing rates at the initial stage of the healing process because of the degradation and inactivation of EGF on the nanofiber and EGF was required only at the initial state of the wound healing process - <i>In vitro</i> release the bFGF/PELA fibrous mats

Table 2. Contd.

Yang et al. 2011 China	bFGF	Male rats	SD	12.5 mg	<i>In vitro</i> by immersion in solution using the method of ELISA assay	Skin regeneration assay	<ul style="list-style-type: none"> - Macroscopic evaluation of wound healing - Histological and immunohistochemical evaluation 	<p>occurred for 25 days. The burst release was detected during initial 12 h, followed with a constant fast release for 15 days, and then a slow release for another 10 days.</p> <ul style="list-style-type: none"> - The regenerated skin of bFGF/PELA group was similar with normal skin, enhances the collagen expression, had no inflammatory cell remaining and showed similar structure with normal skin with hair growth and the shriveling of the epithelium - The release profile occurred in two phases: an initial burst release followed by a sustained phase for 4 weeks. - The wounds were almost closed after 3 week treatment with polyplex-infiltrated in fibers content PEG with molecular weights of 2 kDa and at week 4 the epidermic cells were fully differentiated, basal cells were closely arranged, and the horny layer and large amounts of hair, sebum could be clearly observed and the histological sections showed similar structure with normal skin 4 weeks after operation
Yang et al. 2012 China	pbFGF and PEI	Male rats	SD	-	<i>In vitro</i> by immersion in solution using the detection with Hoechst 33258 dye	Wound healing assay	<ul style="list-style-type: none"> - Evaluation of Wound Healing Process 	<ul style="list-style-type: none"> - The <i>in vitro</i> kinetic study showed that pioglitazone saw a sustained release from DES for up to 4 days. - The stimulation of scaffolds with pioglitazone increase the secretion of insulin and thus yielded an accelerated elimination of hyperglycemia compared to non-stimulated subjects and the glucose level in the scaffold pioglitazone group returned to physiological level by 60 min whereas the glucose level in the control group remained abnormally high - The <i>in vitro</i> release of insulin on the nanofibers showed the sustained and controlled release profile. The drug was released as primarily diffusion based for the initial period of 2 to 3 h beyond which it is based on the erosion of the polymer until the 10th hour when the maximum amount of drug is released
He et al., 2014 China and USA	Pioglitazone	C57BL/6 mice		12 mg/ml of pioglitazone by polymer solution	<i>In vitro</i> kinetics of drug release was measured by a HPLC	Drug-eluting scaffold	<ul style="list-style-type: none"> - The insulin production by transplanted islets - Blood glucose concentrations; 	<p>The insulin production by transplanted islets</p> <ul style="list-style-type: none"> - Blood glucose concentrations;

Table 2. Contd.

Sharma et al. 2013 India	Insulin	Male Wistar rats	-	<i>In vitro</i> by immersion in solution using the spectrophotometer	Delivery anti-diabetic drug assay	- <i>In vitro</i> release - <i>In vivo</i> evaluation of the drug loaded	- The insulin loaded in a PVA–NaAlg nanofiber had a significant decrease in the blood glucose level and the effect lasted for an average period of 10 h
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HPLC, High-performance liquid chromatography; bFGF, basic fibroblast growth factor; rhEGF, recombinant human epidermal growth factor; pbFGF, polyplexes of basic fibroblast growth factor-encoding plasmid; PEI, poly(ethylene imine).

2015, 2014). Furthermore, the use of collagen associated with metformin in membranes fibrous increases the content of collagen I, suggesting that nanofibrous containing metformin and collagen can be effective tissue-engineering scaffold for regenerating skin around diabetic wounds (Lee et al., 2015).

Curcumin possesses modulating effects on wound healing (AKBIK et al., 2014). The effect of its incorporation in the nanofibers returned wound closure in order of 80% along 10 days demonstrating the potential of curcumin-loaded nanofibers in the elevation of wound closure rate applied in a diabetic mouse (Merrell et al., 2009). Studies performed with curcumin in its raw state returned no significant response of material (Kant et al., 2015, 2014).

These studies show that the curcumin can be a new agent for accelerating diabetic wound healing in humans and animals since they show potential in the treatment of cutaneous wounds with corresponding improvement in cutaneous wound healing in acute phase diabetic rats (Kant et al., 2015) and still the topical application in the acceleration of cutaneous wound healing, with corresponding decrease in the persistence of the inflammatory state in acute diabetic rats (Kant et al., 2014).

Recent study reported that encapsulation of

curcumin circumvents conventional difficulties related with curcumin administration, enabling delivery of this therapeutic substance and allowing its use as a novel topical agent for burn wound infection and cutaneous injuries (Krausz et al., 2015). Thus, studies with the encapsulation of curcumin in fibers have a promising future for the reason that electrospun fibers can improve the delivery of the therapeutic substance.

The inflammatory response, formation of granulation tissue, reepithelialization, matrix formation and wound closure are provided and regulated by an equally complex signaling network involving numerous growth factors, cytokines and chemokines (Barrientos et al., 2008). Growth factors are important substances that have the ability to modulate cell behavior and guide tissue repair and renewal (Mitchell et al., 2016). Currently, the release of growth factors has great potential for development of new therapies which favors the healing and skin regeneration (Gainza et al., 2015). Articles suggest that electrospinning process can produce materials containing growth factors that allows the creation of multifunctionalized bioactive nanomaterials to chronic non-healing wounds and that can serve as skin tissue engineering scaffolds for wound healing (Schneider et al., 2009; Bertoncelj et al., 2014; Wang et al., 2016).

The growth factors, such as basic fibroblast growth factor and recombinant human epidermal growth factor, immobilized or incorporated have healing activity in diabetic animals (Choi et al., 2008; Yang et al., 2011, 2012, Sun et al., 2014). Recombinant human epidermal growth factor (rhEGF) immobilized on the electrospun nanofibers for treating diabetic ulcers in female mice demonstrated enhanced keratinocytic expression of human primary keratinocytes in comparison to rhEGF in solution, accelerating wound healing rates at the initial stage of the healing process (Choi et al., 2008). Basic fibroblast growth factor (bFGF) incorporated into electrospun ultrafine fibers indicated that bFGF-loaded fibrous mats (*in vitro* investigations) enhances cell adhesion, proliferation, and secretion of extracellular matrix and enhanced collagen deposition and ECM remodeling. The arrangement and components of collagen fibers were similar to normal tissues (Yang et al. 2011). Polyplexes of basic fibroblast growth factor-encoding plasmid (pbFGF) with poly(ethylene imine) incorporates into electrospun fibers showed a sustained release of 4 weeks and demonstrated significant higher wound recovery rate with collagen deposition and maturation, complete reepithelialization and skin appendage regeneration (Yang et al. 2012).

Hyperglycemia control

The hyperglycemic is other problem related with the diabetes and all of its complications. The use of electrospun nanofibers allows a sustained and controlled release profile of drugs that can reduce blood glucose. Insulin is a hormone synthesized in the pancreas which plays a critical role in intermediary metabolism. It is the key hormone for regulation of blood glucose and, generally, normoglycaemia is maintained by the balanced interplay between insulin action and insulin secretion (Stumvoll et al., 2005). Recent trials have demonstrated progress in technologies for insulin delivery *in vivo* and/or *in vitro* (Zhang et al., 2011; Nishimura et al., 2012; Ling and Chen, 2013; Balducci et al., 2014). The poor oral bioavailability and invasive drug delivery methods represent important barriers to be overcome in this topic. To our knowledge, there are no studies about the encapsulation of insulin using electrospun fibers. A unique study reports that it is possible to encapsulate insulin on nanofibers. The sublingual route based on composite nanofiber diffusion along transmucosal patch can deliver the insulin in a sustained and controlled manner by controlling the morphology of the composite nanofiber patch (Sharma et al., 2013). This study also shows that the insulin cannot be easily released from the composite nanofiber patch due to the crosslinking between the drug molecule and polymeric chains unless polymeric nanofibers are degraded.

He et al. (2014) reported that scaffold with pioglitazone was able to locally deliver the drug to transplanted islets; hence, there was increased insulin secretion and a lower blood glucose level in diabetic mice. Furthermore, the decrease of hyperglycemic also aided in the recovery of renal functions compromised by the diabetes.

Thus, the encapsulation by electrospun fibers allows for better bioavailability of drugs, facilitates its sustained action and act as an adjuvant for recovery of complications caused by diabetes. In this direction, it is clear that studies are required in order to apply this technology and ensure its applicability *in vivo*.

The development of long-acting drug formulations has been explored in many applications in order to overcome challenges with adherence and emerging drug resistance (Chou et al., 2015) with the use of electrospun fibers, which has been considered a promising source for the treatment of diabetes and its complications, such as diabetic wounds.

CONCLUSIONS AND FUTURE PERSPECTIVES

The recent studies summarized in this article have showed advances in the treatment of diabetes and opens a discussion to expand the understanding of the use of electrospun fibers for treatment of chronic diseases associated with high cost to public health and quality of life of patients. We have highlighted in this review the

future trends for treatment of hyperglycemic and diabetic wound healing diabetics relates with use of electrospun fibers. The electrospinning is a promising technique with increasing interest in health area. The electrospun nanofiber has ability to load or immobilized drugs/substances, promotes a controlled and sustained release of the drug or substance. Besides that, the nanofibers can be explored for less vulnerable drugs to the attack by enzymes, providing improved stability. In diabetes, electrospinning technique has shown excellent results in relation to wound healing in *in vitro* and *in vivo* experiments, due to fast decrease in the area of the wound associated with better healing. In spite of few trials about the action of electrospun fibers in glycemic control, there are strong indications that *in vitro* and *in vivo* release has been improved and sustained. Further studies are needed to prove the effectiveness and efficiency of drug encapsulated and the associated risks and side effects of this encapsulation.

Conflict of Interests

The authors have not declared any conflict of interests.

ACKNOWLEDGMENT

This work was supported by Brazilian Funding Agency FACEPE.

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