POLY-(D, L, LACTIDE-CO-GLYCOLIDE) (PLGA): A NOVEL BIODEGRADABLE POLYMER FOR OCULAR THERAPEUTICS

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ABSTRACT

Ocular disorders are mainly treated with topical application of eye drops; however, this method is impeded by poor ocular bioavailability due to the protective mechanism of the ocular biological barriers. These barriers include extensive precorneal drug loss by high tear fluid turnover, transient precorneal residence time, nonproductive absorption, nasolacrimal drainage, impermeability of the corneal epithelium, and metabolism of the drug by anterior segment enzymes, thus drug ocular barrier limits the utility of ophthalmic medication. These are the various challenges to overcome the ocular biological barriers and are extensively explored by various polymeric nano-carriers. The advancement of drug delivery technology through biodegradable polymer based nanocarrier significantly achieved effective drug targeting to the site of action without side effects. Poly-(D, L, lactide-co-glycolide) (PLGA) is a novel biodegradable polymer and is most popular in ocular therapy due to several advantages as self-degradation, non-toxic, non-immunogenic, non-irritant, biocompatible. The use of biodegradable nanocarrier in these strategies to overcome the barrier associated issues remains a major goal for ocular pharmacotherapy. In the recent years, several Poly-(D, L, lactide-co-glycolide) (PLGA) nano-carrier systems, such as nanoemulsions, microemulsions, nanoparticles, and dendrimers, have emerged as novel strategies. More recently, Solid Lipid Nanoparticles (SLNs) & Nanostructured Lipid Carriers (NLCs) have shown their potential biomedical application in ocular inflammation therapy. Present paper emphasizes on the potential utility of biodegradable polymeric nano-carriers for ocular drug delivery in the management of ocular inflammation and also summarizes the success of biodegradable polymeric nano-carriers for ophthalmic pharmacotherapy which is prominent for new hopes and fulfilling the expectation of researcher.

KEY WORDS: Biodegradable polymer, nano-carrier, ocular drug delivery, PLGA.

INTRODUCTION

Delivery of the drug to the ocular segments is the most challenging area for the pharmaceutical scientist (Gonjari et al., 2010). The major ocular illnesses like glaucoma, conjunctivitis, inflammation, dry eye disease, and bacterial infection require timely dosing of the drug to the eye but limitation associated with the conventional

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formulation is the low ocular bioavailability (< 1%) which is crucial, and it is due to the precorneal loss of the drug from the anterior segment of the eye. It comprising rapid tearing, non-productive absorption, less residence time of the drug in the cul-de-sac and low permeation profile of the drug to the corneal surface (Sah et al., 2016) (Figure 1).

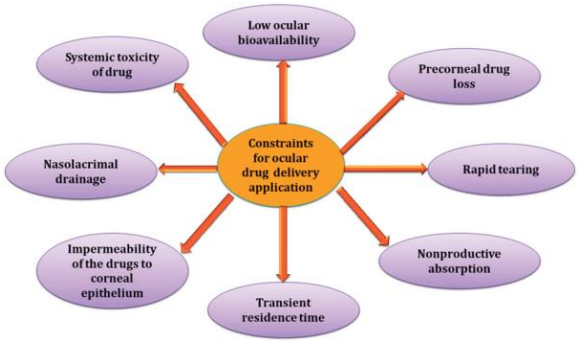

Figure 1: Major constraints for the ocular drug delivery.

Presently eye drops and ocular suspensions are the globally accepted formulations to treat the eye illness due to convenience and ease of the application. However these conventional formulations are still insufficient to combat the disease due to loss of the drug due to rapid tearing and drainage (Mysore et al., 1996). To overcome these limitations of the conventional formulations novel nano-carriers have been investigated and include polymeric nanoparticles, nanosuspensions, vesicular systems, dendrimers (Figure 2). Other novel systems like ocular implants, hydrogels, ocular inserts, and in situ gels have also been investigated. Additionally, nano-carriers offer several benefits over the conventional formulations like improving drug bioavailability, avoid drug systemic toxicity, improving drug therapeutic efficacy and better patient compliance (Wadhwa et al., 2010). For the ocular drug delivery application, biodegradable polymers play significant contribution for the development of polymeric nanoparticle for different eye disorders and it is mainly because of improving residence time on the precorneal area in the anterior segment of the eye (Kaur et al., 2012). In addition, Poly (D, L-lactide-co-glycolide) (PLGA) have been recently explored for their exclusive features.

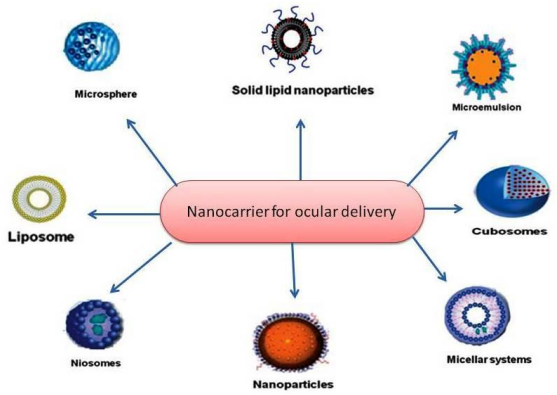

Figure 2: Nano-carrier for ocular delivery.

Poly (D, L-lactide-co-glycolide) (PLGA)

PLGA is the co-polymer of poly lactic acid (PLA) and poly glycolic acid (PGA). PLA consists of an asymmetric α carbon which is called as D or L form classically and sometimes as R and S. In case of the enantiomer PLA are poly D lactic acid (PDLA) and poly L lactic acid (PLLA). Additionally, PLGA is the short form of the poly D, L –lactic-co-glycolic acid where D and L lactic acids are in the equal proportion (Makadia and Siegel, 2011). It is a novel biodegradable polymer which is already approved by the FDA for the application in ocular therapeutics (Sah and Suresh, 2017a). It has special features like biodegradability along with biocompatibility and having excellent potential in the drug delivery. The fragments of this polymer are degraded into the non-toxic metabolite such as lactic acid and glycolic acid which are metabolize by

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hydrolytic degradation pathway (Kreuter, 1994) and easily eliminated from the body (Barcia et al., 2009). For the excretion aspects, PLGA has tendency for simple excretion form the systemic circulation, therefore this polymer is highly recommended for the development of nanoparticulate technology and recently it has been extensively investigated in the area of ocular therapeutics by the pharmaceutical researchers (Sah and Suresh, 2017b). Additionally Most of the literature showed that the PLGA does not involve in any enzymatic degradation and is purely through hydrolysis process. However, some researchers have suggested for an enzymatic activity in PLGA biodegradation based upon the difference in the in vitro and in vivo degradation rates (Makadia and Siegel, 2011). The chemical structure of PLGA is depicted in the Figure 3.

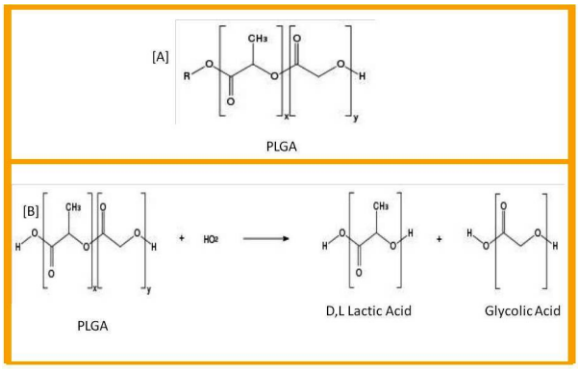

Figure 3: Showing [A] Chemical Structure of PLGA, [B] Degradation of PLGA in its metabolite.

Recent advancement of PLGA based nano-carrier for ocular delivery

Due to its excellent potential for drug delivery, various investigations have been carried out for the development of ocular nano-carrier that include polymeric nanoparticles, liposomal formulations, Solid Lipid Nanoparticles (SLNs), Nano Structured Lipid Carriers (NLCs), ocular implant, dendrimers, nanomicelles, etc and listed in the table 1.

Conclusions and Future Prospects

Biodegradable polymers especially PLGA open new avenues for the controlled release of the therapeutic agents, proteins, peptides due to its excellent property of biocompatibility and biodegradability. Commonly the degradation of the PLGA and the rate of drug release can be improved by improvement in hydrophilicilty, increase in chemical interaction within the hydrolytic moiety, low crystallinity along with the larger volume to surface ratio of the device. This polymer exhibits benefits over other traditional polymers and can be used for the delivery of newer therapeutic agents that include genes, antibodies and bioactive proteins (Dewangan et al., 2018). Furthermore, various investigations reveal that PLGA can easily be formulated into the drug carrying devices at all scales, i.e., as nanospheres, microspheres and even as millimeter sized implants and can be delivered over different periods of time with diverse routes of delivery. Recently one of the researchers developed the cyclosporine loaded sorbitan ester nanoparticles (SENS) coated with hyaluronic acid (SENS-OPT-HA NPs) for ocular delivery (Trabado et al., 2018). The particle size and zeta potential of developed formulation was found to be 177.6 nm and −20.6 mV. The formulation showed good stability profile over the storage at different temperature upto 3 months. Additionally toxicity study was also carried out in which no toxicity was found against cultured human corneal epithelial (HCE) cell when exposed NPs up to 0.4% (w/v). Higher cellular uptake of SENS-OPT-HA NPs was reported as

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compared to SENS-OPT NPs and higher corneal penetration which was 1.3 fold higher as compared to marketed formulation Sandimmun®. For the drug loaded SENS-OPT-HA NPs showed 2.1 fold higher than marketed formulation.

Table 1: Polymeric drug delivery systems used in ophthalmic research

Polymer	**Drug Used**	**Nanocarrier**	**Experimental model**	**Major outcomes**	**Reference**
PLGA	Brinzolamide	NPs	*In-vivo*	Prolonged drug release for the treatment of IOP	Salama et al., 2017
PLGA	Triamcinolone acetonide	NPs	*In-vivo*	Improved therapeutic profile of TA loaded PLGA-NPs by prolonging the drug release in the treatment of EIU	Sabzevari et al., 2013
PLGA	Cyclosporine A	NPs	*In-vivo*	CsA loaded NPs exhibited highest degree of cellular uptake, improved tear film concentration and pharmacokinetic profile of the drug	Aksungur et al., 2011
PLGA	Dexamethasone, hydrocortisone acetate, Prednisolone acetate	NPs	*In vitro, ex vivo*	Drug loaded nanoparticle suspended in thermo sensitive gels offer sustained drug release patten over the retinal/choroidal tissue followed by episcleral administration	Boddu et al., 2010
PLGA	Sparfloxacin	NPs	*In-vivo*	Enhanced precorneal drug residence time and improved drug penetration profile	Gupta et al., 2010
PLGA	Antivascular endothelial growth factor	NPs	*In-vivo*	NPs allow targeted delivery to the neovascular eye. Surface-functionalized nanoparticles allow targeted gene delivery to the neovascular eye on intravenous administration and inhibit the progression of laser-induced CNV in a rodent model	Singh et al., 2009
PLGA	Diclofenac	NPs	*In-vivo*	Extended the drug release profile for the treatment of ocular inflammation, and no any irritant effect on cornea	Agnihotri et al., 2009
PLGA	Triamcinolone acetonide	Controlled release intra ocular lens	*In-vivo*	TA loaded PLGA NPs with different molecular weight significantly reduced postoperative Ocular inflammation	Eperon et al., 2008
PLGA	Flurbiprofen	NPs	*In-vivo*	Significantly increased the bioavailability of the anti-inflammatory drug by NPs along with improved drug corneal permeation	Valls et al., 2008
PLGA	Flurbiprofen	NPs	*In-vivo*	Drug loaded nanosphere improved corneal permeation profile with drug penetration by two fold as compared with conventional eye drop formulation containing PVA and by four fold in pH 7.4 PBS	Vega et al., 2008
PLA	Betamethasone	NPs	*In-vivo*	Controlled intraocular inflammation by BP-PLA-NPs	Sakai et al., 2006
PLGA	Ciprofloxacin	NPs	*In-vivo*	Prolonged drug release along with significant antimicrobial activity against P. aeruginosa and S. aureus	Dillen et al., 2006
PLGA	Vancomycine	Microsphere	*In-vivo*	Increased prolong release of the therapeutic agent along with	Gavini et al., 2004

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Polymer	Drug Used	Nanocarrier	Experimental model	Major outcomes	Reference
				improved pharmacokinetic profile by 2-fold as compared with drug solution	
PLGA	Dexamethasone	Implant	*In-vivo*	Drug loaded implant significantly reduced the intra ocular inflammation in EIU and EAU animal	Kodama et al., 2003
PLA	Ganciclovir	Implant	*In-vivo*	Suggested drug loaded implant controlled the intraocular cytomegalovirus retinitis by controlled release of the drug over several months to one year	Kunou et al., 2000
PLGA	5-fluorouracil	Implant	*In-vivo*	Drug loaded PLGA implant significantly prevent the retinal detachment in an animal model of proliferative vitreoretinopathy	Rubsamen et al., 1994

NPs: Nanoparticle, IOP: Intraocular pressure, PLGA: - Poly-(D, L, lactide-co-glycolide), PLA: Poly lactic acid, TA: Triamcilone Acetonide, EIU: Endotoxin induced uveitis, CsA: Cyclosporine A, CNV: Choroidal neovascularization, PVA: Poly vinyl alcohol, PBS: Phosphate buffer saline, BP: Betamethasone phosphate, EIU: Endotoxin induced uveitis, EAU: experimental autoimmune uveoretinitis.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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