

A review on present and probable drug delivery systems for Latanoprost a antiglaucoma drug .

Aakash Parikh

Department of Pharmaceutical Science and Technology , ICT
Email id : adparikh94@gmail.com
Contact number : 9819873829

Abstract:

Latanoprost a prostaglandin F₂-alpha isopropyl ester prodrug is an effective antiglaucoma drug which is currently administered via sterile ophthalmic solution but suffers from certain drawbacks like tedious regimen of dose and extensive wastage of drug . Due to above drawbacks novel delivery systems such as drug eluting contact lenses , coated ocular films , liposomes and in-situ intravitreal implants have been discussed briefly along with the benefits and drawbacks associated with each of delivery systems .

Keywords : ophthalmic , latanoprost , novel , prostaglandin etc

Introduction :

Glaucoma is one of the major causes of blindness and roughly is 13% of all causes of blindness . A large population currently suffers from glaucoma more than 60.5million and the number is expected to swell upto 79 million by 2020(Quigley and Broman 2006).The imbalance in production and drainage of aqueous humor causes an increment in the intra-ocular pressure due to which the vitreous body presses against the retina and the blood vessels which feed the retina is blocked which is termed as glaucoma . The imbalance is caused when the drainage canals become either clogged or blocked due to a disorder or an unknown cause .

Glaucoma is classified depending upon the 'angle' closure into two types : open angle and close angled of which former is the more common . In open angle the canals are not visibly blocked but the drainage is still insufficient . Thus even though the production rate of fluid is normal the pressure increases due to slow rate of drainage . In closed angle the drainage canals in the eye are covered due to the narrow angle between iris and cornea . The rise in pressure in the eye is directly proportional to the blockage (Gemenetzi, Yang et al. 2011).

Various prostaglandin analogues have been tested and Latanoprost is shown to have sufficient ocular hypotensive activity with minimal side effects. Latanoprost is a prostaglandin F₂-alpha isopropyl ester prodrug which is converted into its active form by hydrolysis by esterase into latanoprost acid . This form exerts activity at the prostaglandin receptor F . Latanoprost being a selective FP receptor agonist mediates its ocular hypotensive activity by enhancing uveoscleral outflow . This effect is mediated by substantial remodelling of extracellular matrix adjacent to the ciliary muscle cells . Exposure to PGF- α 2 has shown increase in matrix production of metalloproteinases which degrades ciliary muscle extracellular matrix which could lead to reduction in resistance to outflow of uveoscleral (Russo, Riva et al. 2008). The therapeutic efficiency of latanoprost was shown to be as effective as timolol which is the standard drug for glaucoma in its action of hypotensivity . The are also given in combination therapy since latanoprost does not affect humor production significantly . Latanoprost therapy is given only once daily as opposed to thrice daily administering of timolol .

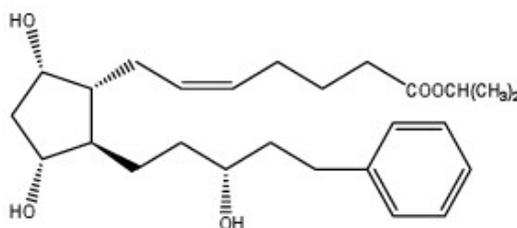


Fig 1 : structure of latanoprost

Problems associated with latanoprost delivery:

In the current delivery form Latanoprost is supplied as a 0.005% (50µg/mL) clear solution and the recommended dose is 1.5µg (one drop) in the affected eye daily and in case a dose is missed treatment should continue as normal. But the major disadvantage of latanoprost is its insolubility in water . Thus a solubilizing step has to be incorporated in the manufacturing process to improve the solubility or by increasing the concentration of the preservative used for example benzalkonium chloride but then it has adverse reactions due to use of higher concentration (Louati and Shaarawy 2012).

Moreover the API(active pharmaceutical ingredient) must remain stable in the formulation at room temperature for long periods of atleast 12-18 months . The current formulation Xalatan can be stored at room temperature only for 6 weeks after the seal has been broken before that it must be stored in the refrigerator between 2 – 8 °C . The formulation must also remain stable in contact with the packaging material such as polyethylene and prevent from getting absorbed onto the container (Mercier 2014). Additionally some of the current formulations do not allow for consistent lowering in intra-ocular pressure . This unsteady profile harms the eye by allowing the damage of the optic nerve .

Current available delivery systems for Latanoprost :

1. Sterile ophthalmic solutions with antimicrobial agent :

Xalatan[®] was the first formulation of latanoprost and was developed by Pfizer . It was supplied as sterile , isotonic , buffered aqueous solution with a pH of 6.7 and an osmolality of approximately 267mOsmol/kg . Each ml of xalatan contains 50µg of latanoprost . Benzalkonium chloride 0.02% is added as preservative . Sodium chloride , sodium dihydrogen phosphate monohydrate , disodium hydrogen phosphate and water for injection . The formulation must be kept away from light and unopened bottles are stored under refrigeration at approximately 5°C . Bottle may be kept at 40°C for less than 8 days during shipment . Once bottle if opened it may be stored at room temperature upto 6 weeks at 25°C . The use of benzalkonium chloride has been questioned due to its harmful effects(Louati and Shaarawy 2012) . After Xalatan's patent expiry a variety of generic products such as 9PM(Cipla) , Latoprost(Sun Pharma) are available in the market .

2. Sterile ophthalmic solution without antimicrobial agent

Monopost by spectrumThea laboratories was the first latanoprost formulation to be marketed without preservatives . Clear sterile ophthalmic drops of 0.05ml / day contains 50µg of latanoprost per mL of eye drops solution which is 0.005% . They are provided in polyethylene containers of 0.2ml to avoid contamination .

NEED FOR NOVEL DELIVERY:

One of the major drawbacks pertaining eye drops is that only small amount of drug penetrates the cornea and reaches the tissue , where some is lost due to blinking reflex and drainage of nasolacrimal . Additionally the drug not absorbed by cornea is absorbed into the blood via nasolacrimal duct and thereby causes undesirable side-effects(Gulsen and Chauhan 2004) . The latanoprost acid the active form formed by hydrolysis is more hydrophilic due to which it also penetrates endothelium and epithelium of the cornea and hence bioavailability decreases (Natarajan, Ang et al. 2012) . The most essential characteristic required is the delivery of the dose in a sustained manner with sufficient bioavailability along with improved patient compliance . Thus need for novel delivery systems are a must because of :

1. Tedious dose regimen
2. Extensive wastage of drug
3. Low permeability of drug across tissue

DELIVERY SYSTEMS :

1. Biodegradable nanoparticles(Giarmoukakis, Labiris et al. 2013) :

Nanotechnology should have been an ideal solution to the problems related to ocular delivery especially due to high bioavailability brought about by nanoparticles . Thus latanoprost entrapped in nanoparticles made up of polylactic – polyethylene glycol (PLA – PEG) copolymers which is biodegradable and biocompatible . The development of the nanoparticles of latanoprost is feasible and has shown decrease in the intraocular pressure . However these nanoparticles have to be injected via subconjunctival injection and thus is not patient compliant .

There is a lot of wastage of drug due to low entrapment efficiency (approximately 20%) . Such low levels of efficiency will not be economically feasible at an industrial scale . There is 20% drug release in 24 hours known as burst release and hence a much higher dose should be administered almost three times the current amount in order to sustain the therapeutic level for two week period .Though this method is interesting and feasible for ocular delivery the system needs optimization to attain ideal characteristics .

2. Drug eluting contact lenses (Ciolino, Stefanescu et al. 2014) :

Rate of drug release from a contact lens is difficult and the duration of the release tends to be only for a few hours even though they can absorb and deliver drugs . However drug eluting contact lenses could be a promising prospect for glaucoma treatment . Major advantage is that the lens can release latanoprost for atleast 4 weeks

and could replace the daily dose. This is a very big plus point because in majority of the cases patients miss the dose and thus take a long time to cure the disease .

There are a certain drawbacks attributed to the maximum concentration limit of the drug which can be present in the body . Since the volume of aqueous humor is 0.25ml only 0.25 μ g of drug can be present since the limit is 100ng/ml .This value (0.25 μ g is way lesser than required amount of dose which is 1.5 μ per day . Moreover the patient will remove the lens since they cause slight blurring of vision. Although lens is a possibility but its drawbacks have to be ironed out for improving its patient compliance and concentration profile .

3. Liposomes (Natarajan, Ang et al. 2012) (Thakur, Fallows et al. 2014) :

Encapsulation of drug enables to prolong the duration of drug release in systemic circulation and reduce toxicity and also aids in increasing the selectivity . Liposomes which are bilayered lipid vesicles constituting cholesterol and phospholipids have shown potential in being nanocarriers for drugs in ocular use .Liposomes have shown to successfully cross the ocular barriers and act like a depot system in subconjunctival space .

The initial high drug release may cause severe adverse effects in the humans but it is essential in maintaining a high initial concentration which will cause sustained release of the drug . Furthermore liposomal injections may cause injury to delicate ocular tissues or may also cause infections . It may also cause a irregular bulge (bleb) in the subconjunctival space which evens out eventually but still causes discomfort to the patients .

Since patient experiences pain for invasive procedures such as intravitreal or periocular injections due to initial piercing and penetration of scleral tissue and also due to rise of intraocular pressure administering of liposomes via microneedles has come into light . Microneedles are 25-2000 μ m in height . They may be solid or hollow needles and the later is used for localized delivery in supra-achorodial space , sclera tissue , subconjunctival region or ocular regions . Sustained drug delivery can be achieved by varying the depth of the needle penetration and composition of drug solution without the pain and risk of injury associated with regular hypodermic needles . Moreover liposomal formulation has higher loading efficiency than consistent release than nanoparticulate formulation as well as lower frequency of administration approximately once a month . Thus delivery of liposomes via microneedles is minimally invasive and overcomes the drug wastage .

4. Ocular Films (Aburahma and Mahmoud 2011) (Mealy, Fedorchak et al. 2014) :

One of the most promising ways of administering ocular drug is the insertion of solid or semi-solid films made of polymeric material into the conjunctival sac . The advantages the film offers are :

- a. Increased in ocular residence time
- b. Accurate dosage
- c. Reduced side effects
- d. More patient compliant
- e. Sustained drug release

A film of three distinct layers in which the middle layer will be a polymer layer for example PLGA loaded with drug ,the uppermost layer will be drug-permeable , mucoadhesive polymer and bottom layer can be coated with an inert polymer which prevents drug release . These thin films are thin and releases the drug for a period of one week . Ocusert a coated film by Alza was implemented for delivering anti-glaucoma drug pilocarpine but was later discontinued because of the discomfort due to thickness issues .

5. Intravitreal in-situ forming implants (Manickavasagam and Oyewumi 2013) :

Intravitreal injections are good ocular delivery system because of the high bioavailability and low drug administration frequency .Implants may be of two types biodegradable and non-biodegradable . The former type have the advantage of not requiring removal post drug release . One of the example of biodegradable category is ozurdex (allergan) which was FDA approved intravitreal ocular implantation .Non-biodegradable example is that of Retisert which is composed of PVA , is approved by FDA and is designed for sustained release of fluocinolone acetonide a corticosteroid . But major disadvantage with non-biodegradable implants is the need for surgical procedure for its removal and prolonged stay of the implants may trigger immune response . Though a steady plasma profile would result in consistent lowering of intraocular pressure there are a few drawbacks associated with the implants such as quick drug elimination from posterior chamber , vitreous hemorrhage due to repeated intravitreal injection and also other complexities accompanying an invasive treatment .

Conclusion:

The currently available systems such as sterile ophthalmic solutions has its set of drawbacks associated with it and hence novel systems such as liposomes , biodegradable nano-particles , drug eluting contact lenses , Coated ocular films and in-situ intravitreal implants were discussed briefly . Out of the above suggestions coated ocular films which are intended to be placed in the cul-de-sac of eye have shown to overcome primary problems such as bioavailability and low patient compliance . Also further work should be carried out in ascertaining a suitable candidate for the biodegradable polymer for sustained release as well as a mucoadhesive polymer. Thus differentially coated thin polymeric films are a feasible prospect for administering latanoprost .

References :

- [1] Aburahma, M. H. and A. A. Mahmoud (2011). "Biodegradable ocular inserts for sustained delivery of brimonidine tartarate: preparation and in vitro/in vivo evaluation." *Aaps Pharmscitech* 12(4): 1335-1347.
- [2] Ciolino, J. B., et al. (2014). "In vivo performance of a drug-eluting contact lens to treat glaucoma for a month." *Biomaterials* 35(1): 432-439.
- [3] Gemenetzi, M., et al. (2011). "Current concepts on primary open-angle glaucoma genetics: a contribution to disease pathophysiology and future treatment." *Eye* 26(3): 355-369.
- [4] Giarmoukakis, A., et al. (2013). "Biodegradable nanoparticles for controlled subconjunctival delivery of latanoprost acid: In vitro and in vivo evaluation. Preliminary results." *Experimental eye research* 112: 29-36.
- [5] Gulsen, D. and A. Chauhan (2004). "Ophthalmic drug delivery through contact lenses." *Investigative ophthalmology & visual science* 45(7): 2342-2347.
- [6] Louati, Y. and T. Shaarawy (2012). "Controversy: Is Benzalkonium Chloride Necessary in Antiglaucoma Drops?" *Journal of Current Glaucoma Practice* 6(3): 104-107.
- [7] Manickavasagam, D. and M. O. Oyewumi (2013). "Critical Assessment of Implantable Drug Delivery Devices in Glaucoma Management." *Journal of drug delivery* 2013.
- [8] Mealy, J., et al. (2014). "In vitro characterization of a controlled-release ocular insert for delivery of brimonidine tartrate." *Acta biomaterialia* 10(1): 87-93.
- [9] Mercier, F. (2014). Polymeric delivery system for a nonviscous prostaglandin-based solution without preservatives, Google Patents.
- [10] Natarajan, J. V., et al. (2012). "Nanomedicine for glaucoma: liposomes provide sustained release of latanoprost in the eye." *International journal of nanomedicine* 7: 123.
- [11] Quigley, H. A. and A. T. Broman (2006). "The number of people with glaucoma worldwide in 2010 and 2020." *British Journal of Ophthalmology* 90(3): 262-267.
- [12] Russo, A., et al. (2008). "Latanoprost ophthalmic solution in the treatment of open angle glaucoma or raised intraocular pressure: a review." *Clinical ophthalmology (Auckland, NZ)* 2(4): 897.
- [13] Thakur, R. R. S., et al. (2014). "Microneedle-mediated intrascleral delivery of in situ forming thermoresponsive implants for sustained ocular drug delivery." *Journal of Pharmacy and Pharmacology* 66(4): 584-595.