MICROSPOHERES AS AN OCULAR DRUG DELIVERY SYSTEM-A REVIEW

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Received 17 Nov 2012; Review Completed 01 Jan 2013; Accepted 03 Jan 2013, Available online 15 Jan 2013

ABSTRACT

Ophthalmic drug delivery is most interesting and challenging delivery system facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. These barriers affect the bioavailability of drugs. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. These includes iontophoresis, liposome bioadhesive gels, ocular insert, contact lenses, liposomes & a special one is microspheres. Microsphere is a well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. This approach delivering a therapeutic substance to the target site in a sustained controlled release fashion & achieve a good bioavailability in ocular delivery system.

Key words: Ophthalmic, bioavailability, microspheres, sustained or controlled release, therapeutic efficacy

INTRODUCTION

In ocular drug delivery system, there is a main problem of rapid and extensive elimination of conventional eye drops from the eye. This problem results in extensive loss of drug. Only a few amount of drug penetrates the corneal layer and reached to internal tissue of eye. The main region of drug loss includes lachrymal drainage and drug dilution by tears. This superfluity reduces the ocular bioavailability and lead to unwanted toxicity and side effect. The following characteristics are required to optimize ocular drug delivery systems.

- A good corneal penetration.
- A prolonged contact time of drug with corneal tissue.
- Simplicity of installation and removal for the patient.
- A non-irritative and at ease form (the viscous solution should not irritate lachrymation and reflex flashing).
- Appropriate rheological properties and concentration of viscolyzer.

Over last two decades valuable attention is to be made on development of sustained and controlled release drug delivery system. The aim of such system based on localization on site of action so as to avoid the dose frequency and improvement in the drug effectiveness.

Advantages of controlled ocular drug delivery systems

- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.

- To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
- To circumvent the protective barriers like drainage, lacrimation and conjunctive absorption.
- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
- To provide better housing of delivery system.
- Easy convenience and needle free drug application without the need of trained personnel assistance for the application, self medication, thus improving patient compliances compared to parenteral routes.
- Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
- Rapid absorption and fast onset of action because of large absorption surface area and high vascularisation.
- Ocular administration of suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

Disadvantages

Various disadvantages of ocular drug delivery system are given below.

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the
Physiological barriers of ophthalmic drug delivery systems

- Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints responsible for poor ocular bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turnover and conjunctival absorption.
- Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage forms.
- The instilled dose leaves the precorneal area within 2 minutes of installation in humans. The ophthalmic dropper delivers 50–75 μl of the eye drops. If the patient does not blink, the eye can hold about 30 μl, without spilling on to the cheek.
- The natural tendency of the cul-de-sac is to reduce its volume to 7-10 μl. However, most of the drug is rapidly lost through nasolacrimal drainage immediately following dosing. The drainage allows the drug to be absorbed across the nasal mucosa into the systemic circulation. The conjunctiva also possesses a relatively large surface area, 5 times the surface of cornea making the loss significant. Both conjunctival and nasal mucosa has been indicated as the main potential sites for systemic absorption of topically applied drugs.

Mechanism of controlled sustained drug release into the eye

- The corneal absorption represents the major mechanism of absorption for the most conventional ocular therapeutic entities.
- Passive Diffusion is the major mechanism of absorption for nor-erodible ocular insert with dispersed drug.
- Controlled release can further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solution.

ANATOMY AND FUNCTION OF THE EYE

The eye is a spherical structure with a wall made up of three layers: the outer part sclera, the middle parts choroid layer, Ciliary body and iris and the inner section nervous tissue layer retina.

The structure of the cornea

The clear transparent bulge cornea situated at the front of the eye that conveys images to the back of the nervous system. The adult cornea has a radius of approximately 7-8mm that covers about one-sixth of the total surface area of the eye ball that is a vascular tissue to which provides nutrient and oxygen are supplied via lachrymal fluid and aqueous humor as well as from blood vessels of the junction between the cornea and sclera in fig.1.

Conjunctiva

The conjunctiva protects the eye and also involved in the formation and maintenance of the precorneal tear film. The conjunctiva is a thin transparent membrane lies in the inner surface of the eyelids and that is reflected onto the globe. The conjunctiva is made of an epithelium, a highly vascularised substantia propria, and a submucosa.

Nasolachrymal drainage system

Nasolachrymal drainage system consists of three parts; the secretory system, the distributive system and the excretory system. The secretory portion is composed of the lacrimal gland that secreted tears are spread over the ocular surface by the eyelids during blinking. The distributive system consists of the eyelids and the tear meniscus around the lid.
edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing. The excretory part of the Nasolachrymal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac, and the nasochoymal duct.

![Schematic diagram of nasolachrymation drainage system](image)

**Figure 2: Schematic diagram of nasolachrymation drainage system**

**Tear film**

A thin fluid layer is covered the exposed part of the eye called as precorneal tear film. The film thickness is about 3–10 Am depending on the measurement method with the resident volume approximately 10 μl. The osmolality of the tear fluid is approx. 310–350 mOsm/kg in normal eyes and is maintained by the monovalent and divalent inorganic ions present in fluid such as Na+, K+, Cl-, HCO3-, and proteins. The mean pH of normal tears is about 7.4. Diurnal patterns of pH changes the pH of tear, which a general shift from acid to alkaline during the day. The buffer capacity of the tears fluid is determined by bicarbonate ions, proteins, and mucins. Tears exhibit a non-Newtonian rheological behaviour with viscosity is about 3m Pas 12. The mean surface tension of tear film value is about 44 mN/m.

**SIGNIFICANCE OF MICROSPHERES IN OCULAR DRUG DELIVERY**

Even though the various drug delivery systems mentioned above offer numerous advantages over conventional drug therapy, nonetheless, they are not devoid of pitfalls, including:

- Poor patient compliance and difficulty of insertion for ocular inserts.
- Tissue irritation and damage caused by penetration enhancers and collagen shields.

Much of the published data suggests that in the case of ophthalmic drug delivery, an appropriate particle size and a narrow size range, ensuring low irritation, adequate bioavailability and compatibility with ocular tissues, should be sought for every suspended drug. Other formulation factors, that are the use of correct wetting, suspending and buffering agents, protective colloids, preservatives, and so on, should also be carefully considered. Thus, an optimum ocular drug delivery system should be one which can be delivered in the form of eye drops, causing no blurred vision or irritability and would need no more than one to two administrations per day. Various criteria that need to be considered, while deciding the formulation parameters for developing a suitable ophthalmic drug delivery system are shown in (Table 1). Though the delivery of drugs to the anterior segment of the eye is achieved mainly through topical delivery, very little of the topically applied drug reaches the posterior segment of the eye. This necessitates the administration of some drugs, such as antiglaucoma drugs, corticosteroids and certain antibiotics by the systemic route. However, a very small fraction of the dose reaches the ocular tissues, following systemic administration. The doses required to give a therapeutic effect via this route, however, can lead to considerable side effects. The use of nanotechnology-based drug delivery systems like nanosuspensions, solid lipid nanoparticles, liposomes & microspheres has led to the solution of various solubility-related problems of poorly soluble drugs, like dexamethasone, budenoside, ganciclovir and so on.

Drugs can also be targeted to mononuclear phagocyte systems to allow regional specific delivery and minimize side effects in other organs. Besides this, depending on their particle charge, surface properties and relative hydrophobicity, nanoparticles can be designed to be successfully used in overcoming retinal barriers. In addition to these points, encapsulation of drugs in nanospheres, liposomes, and so on, can also provide protection for the drug and hence prolong exposure of the drug by controlled release.

Nanotechnology-based drug delivery is also very efficient in crossing membrane barriers, such as the blood retinal barrier in the eye. The drug delivery systems based on nanotechnology may prove to be the best drug delivery tools for some chronic ocular diseases, in which frequent drug administration is necessary, for example in ophthalmic diseases like chronic cytomegalovirus retinitis (CMV). In this disease, the topical delivery of drugs like ganciclovir (GCV) is prevented and intravitreal delivery is preferred. Though the half-life of GCV, following intravitreal administration, is 13 h, frequent injections are necessary to maintain therapeutic levels, since this drug prevents the replication of the viral deoxy ribonucleic acid (DNA), but does not eliminate the virus from the tissue.

Therefore, long term therapy is necessary, which may result in cataract development, retinal detachment and endophthalmitis. GCV intravitreal implants can be used, which release drugs for six to eight months, but there can be issues, such as side effects like astigmatism and vitreous hemorrhage; moreover, the need for surgery to remove the implants seriously restricts their use. These difficulties can be overcome by using nanoparticles made up of various natural polymers like albumin, because of their smaller size and controlled release properties. When delivered to the eye, these nanoparticles did not induce inflammatory reactions in the retinal tissue or disturb the organization of the surrounding ocular tissues.

Nanotechnology-based drug delivery is also suitable in the case of the retina, as it has no lymph system, hence retinal neovascularization and CNV have similar environments to that of solid tumors, in which the EPR effect may be available for drug targeting by nanoparticles. The major problem of intravitreal injection is of inducing the
stimulation of pathogenic immune responses, resulting in photoreceptor degeneration. Various studies have also shown that intravitreal administration of nanoparticles did not generate organ-specific autoimmune phenomena.\textsuperscript{5}

### Table 1: Criteria for the selection of optimal formulation parameters when developing an ophthalmic drug delivery system\textsuperscript{5}

| Factor             | Preference                                                                 |
|--------------------|-----------------------------------------------------------------------------|
| Drug               | Preferentially lipophilic. Non-ionisable lipophilic compounds will concentrate into the corneal epithelium, while ionisable lipophilic ones will partition into the aqueous humor |
| Vector type        | Depends on encapsulated molecule. Should allow a high loading dose to reduce the instilled volume |
| Carrier size       | Lowest as possible to facilitate corneal uptake and passage |
| Osmotic pressure   | Isotonic with physiological fluids to avoid irritation and lacrimation |
| pH                 | Close to physiological pH to avoid irritation and lacrimation. If buffering is necessary, the lowest possible buffer concentration is to be used (<0.1 M) |

**Figure 3:** Different delivery systems which are currently used for ocular therapy\textsuperscript{4}

**MICROSFERES IN OCULAR DELIVERY\textsuperscript{6,14,17}**

One of the main problems in ophthalmic drug delivery, the rapid elimination of conventional liquid eye drops from the eye, still remains unsolved. A number of factors, namely rapid tear turnover and the resulting precorneal loss, induction of tear flow due to irritation caused by the drug preparation, as well as the relatively large volume of the administered eye drop (50 ~1 versus 7 ~1 of corneal tear film), lead to a high rate of lacrimal drainage. Due to the resulting elimination rate, the precorneal half life of drugs applied by these pharmaceutical formulations is considered to be between about 1-3 min. As a consequence, only the very small amount of about 1-3% of the dosage actually penetrates through the cornea and is able to reach intraocular tissues.

The poor productive absorption, on the other hand, results in a high amount of drug that is drained into the nose or into the gut. Especially the nose but also the gut are very efficient absorption organs of the body. This in turn leads to an extensive systemic absorption and may result in unwanted side effects and toxicity of the drug. Although these problems have been recognised for a long time, surprisingly little effort has been made by drug companies to improve the situation, and only very few alternative oculan drug delivery systems are on the market. One possibility for such systems is the employment of small particles. These colloidal particles have the advantage that they may be applied in liquid form just like eye drop solutions.

Thus they avoid the discomfort that is combined with the application of viscous or sticky preparations such as ointments. The latter preparations lead to a total blurring of vision if they are properly utilised. Large inserts, on the other hand are difficult to administer or if they are designed as non-dissolving inserts they are even more difficult to remove, especially by elderly patients. Another alternative to small particle systems are liposomes. Liposomes, however, may have the disadvantage of lower stability. Suitable small particle systems include microspheres and microcapsules as well as nanoparticles.
and nanocapsules. Microparticles and microcapsules have a particle size above 1μm.

Microspheres are monolithic particles possessing a porous or solid polymer matrix, whereas microcapsules consist of a polymeric membrane surrounding a solid or liquid drug reservoir. Nanoparticles have a particle size in the nanometer size range below 1 μm. The definitions for these particles include nanospheres as well as nanocapsules. In micro- or in nanocapsules the drug can be present in a liquid form, it can be dissolved or suspended in a liquid or solid core or it may be present in the core itself. Monolithic micro- or nanoparticles contain the drug either dissolved in the polymer matrix in form of a solid solution or suspended in form of a solid dispersion. Alternatively the drug may be adsorbed to the particle surface. It is important to note that the particle size for ophthalmic applications should not exceed 10 μm because with larger sizes a scratching feeling might occur. Therefore, a reduction in particle size improves the patient comfort during administration.

MANUFACTURING METHODS OF OCULAR MICROSPHERES

A large number of production methods exist for microspheres, microcapsules and nanoparticles. The optimal method that may be used for the preparation depends mainly on the drug to be used. Since the description and the discussion of the various production methods would by far exceed the space allocated to the present review, the reader who is interested in further details is referred to various books and reviews that extensively describe these topics. A high incorporation ratio, in combination with a considerable amount of free drug in order to obtain an adequate initial drug level, as well as a sustained drug release during the residence time of the carrier systems in the precorneal area are required for ophthalmic use. So far, various synthetic and natural biocompatible polymers have been used in order to manufacture microspheres for ocular drug delivery (Table 2). Preparation techniques using natural biopolymers like albumin are summarised in Table 3.

| Drug             | Polymer                                           | Reference |
|------------------|---------------------------------------------------|-----------|
| Amikacin         | Poly(butyl)cyanoacrylate                          | 20        |
| Betaxolol        | Poly(epsilon)caprolacton                          | 21, 22    |
|                  | Poly(isobutyl)cyanoacrylate                       | 22, 23    |
|                  | Polylactic-co-glyeolic acid                       | 22        |
| Carteolol        | Poly(epsilon)caprolacton                          | 24        |
| Chloramphenicol  | Polylactic acid                                   | 25        |
| Hydro-cortisone  | Albumin                                           | 26        |
| Indomethacin     | Poly(epsilon)caprolacton                          | 27        |
| Pilocarpine      | Albumin                                           | 28, 29, 30, 31, 32 |
|                  | Cellulose-acetate-hydrogenphthalate               | 33, 34, 35, 36 |
|                  | Gelatine                                          | 28        |
|                  | Poly(butyl)cyanoacrylate                          | 37, 38, 39, 40, 41, 42, 43 |
|                  | Poly(hexyl)cyanoacrylate                          | 38, 40, 43 |
|                  | Polylactic acid                                   | 44        |
|                  | Poly(methyl)methacrylateacrylic-acid- copolymer   | 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 |
|                  | Poly(methyl)methacrylate                          | 38, 40    |
|                  | Polylamide                                        | 56        |
|                  | Polypthalamide                                    | 57        |
| Progesterone     | Poly(hexyl)cyanoacrylate                          | 58        |
|                  | Poly(butyl)cyanoacrylate                          | 59        |
| Timolol          | Poly(alkyl)cyanoacrylate                          | 60        |
Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydrogels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs.

In contrast, polymer based colloidal system were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine). The micro particulate drug carrier (micro spheres) seems a promising means of topical administration of acyclovir to the eye. The duration of efficacy of the ofloxacin was increased by using high MW (1930 kd) chitosan. Microspheres for ophthalmic drug delivery prepared from synthetic polymers (i.e. poly (alkyl) cyanoacrylates) have been mainly produced by emulsion polymerisation. In this process, a poorly soluble monomer is dissolved in the continuous phase. This continuous phase can be aqueous or organic. Additional monomer may be emulsified in emulsion droplets that are stabilized by emulsifiers.

The polymerisation is started by chemical initiation, pH shift, or by irradiation with gamma-rays, ultraviolet (UV) or visible light. The location of the polymerisation is in the continuous phase where dissolved monomer molecules react with each other and grow until particle formation by phase separation occurs. Additional monomer molecules diffuse to the resulting growing polymer particles and maintain the polymerisation. The emulsion droplets mainly act as monomer reservoirs. In later stages, the emulsifiers stabilise the resulting polymer particles. It has to be noted, that the nanoparticles are not formed by one single polymer molecule but consist of a large number of macromolecules. Nanocapsules with an oily core were prepared mainly by the addition of benzylbenzoate or mineral oils.

In this case, the polymerisation of the poly(alkyl)cyanoacrylates (i.e.poly(isobutyl) cyanoacrylate) is located at the interface between the oily and the aqueous phase resulting in a small capsule covered by a polymer membrane. As shown in Table 1, a number of studies deal with the preparation and application of ophthalmic drugs loaded to micro- and nanospheres. Pilocarpine is still among one of the most important drugs for ocular delivery and glaucoma therapy. Also, beta-blockers like timolol and more recently betaxolol were investigated as potent candidates for particular ophthalmic drug delivery systems. In most cases, the drug is present during the polymerisation- or particle manufacturing process leading to an incorporation of the drug in form of a solid solution or solid dispersion. Alternatively, a drug can be adsorbed onto the particle surface after the manufacturing process. In the case of hydrocortisone it was shown that a very high loading capacity can be reached. Similar results were observed for other steroids like progesterone.

**DRUG LOADING AND DRUG RELEASE KINETICS**

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc.

Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micro-morphology of the carrier and the properties of the polymer itself. The drugs could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second by pore diffusion mechanism, and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuse into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by three factors the macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres.

The pore diffusion method is named so because as penetrating water front continue to diffuse towards the core. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the

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**Table 3: Manufacturing techniques used for preparing micro- and nanospheres**

| Manufacturing process |
|-----------------------|
| 1. Denaturation or cross-linking of macromolecules in emulsion form |
| 2. Interfacial polymerisation |
| 3. Formation in an aerosol phase |
| 4. Desolvation |
| 5. Aggregation by pH adjustment and heat treatment |
| 6. Formation of nanoparticles via microemulsions |
matrix. Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, i.e. whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients.

Table 4: Literature Related to Micro-and Nanoparticles Used in Ocular Drug Delivery

| Drug                          | Prodrug | Evaluation | Remarks                                                                 | Ref. |
|-------------------------------|---------|------------|--------------------------------------------------------------------------|------|
| Vancomycin                    | PLGA    | In vitro & in vivo studies | In vitro studies revealed high encapsulation efficiency (84.2-99.5%) & increased AUC values(2 fold) of drug | 61   |
| Calcein                       | Starch acetate | In vivo studies | Studies showed 82% viability of RPE culture cells when incubated with microparticles for 24 hrs | 62   |
| Colecoxib                     | PLGA-PEG | In vitro studies | In vivo studies showed high loading efficiency(68.5%) of colecoxib in PLGA microparticles which inhibits diabetes induced retinal oxidative damage | 63   |
| Ketorolac                     | NIPAAM, VP, AA | In vitro studies | Ocular bioavailability in cornea was enhanced upto 2 fold and studies showed high anti-inflammatory activity of ketorolac NP with no corneal damage | 64   |
| Cyclosporin A                 | Chitosan | In vitro & In vivo studies | In vitro studies showed the fast release of CyA NP (293 nm) during the first hr.then followed by a gradual released during a 24 hr period. In vivo studies showed high therapeutic concentration in ocular tissue | 65   |
| Acyclovir                     | PEG-PECA | Tolerance & Bioavailability studies | Acyclovir loaded PEG coated (PECA) enhanced the drug level upto 25 fold in aqueous humour with better tolerance capacity | 66   |
| Rhodamine /Nile red           | Polylactide | Ocular kinetics | Studies shows steady and continuous delivery of drugs is achieved in the RPE | 67   |
| Ganciclovir                   | Albumin | Tolerance studies | Well tolerated with no signs of inflammation in the retinal tissues (photoreceptor layer) | 68   |
| Fluorescein                   | Chitosan | In vitro & In vivo studies | In vitro studies showed stability of nanoparticles upon incubation with lysozyme & in vivo studies shows high amount of (Cs-fl) NP in corneal tissues as compared to Cs-fl solutions | 69   |
| Betamethasone phosphate       | Poly (lactic acid) | In vivo studies | Studies shows that NP controls the intraocular inflammation when administered systemically in EAU | 70   |
| LHRH agonist deslorein and transferrin | Polystyrene | Surface modification | Surface modification of NP by conjugating LHRH agonist provides a rapid & efficient delivery of NP into cornea and conjunctiva | 71   |
| Gatifloxacin                  | Chitosan-Sodium Alginate | In vitro studies | In vitro studies shows the fast release of gatifloxacin nanoparticles during the first hr.followed by a more gradual release during a 24 hr.period | 72   |
| Dexamethasone Acetate         | PLGA    | In vitro & In vivo studies | In vitro studies showed that drug was released in a controlled manner to treat CNV by inhibiting inflammatory responses | 73   |
| Indomethacin                  | Chitosan | Bioavailability Studies | Studies showed a high level of drug in vivo as compared to solutions; so enhance the delivery to both external & internal ocular tissues | 74   |
| Dorzolamide & Pramipexole     | Chitosan | In vitro studies | In vitro studies shows sustained release of dorzolamide in PBS (pH 7.4) & pramipexole in SIF | 75   |
| Gene delivery (GFP,RFP)       | Chitosan, PCEP | Transfection & toxicity studies | PCEP & MNP nanoparticles are nontoxic and shows high transfection efficiency while MNP yields good transfection as compared to PCEP | 76   |
| Cyclosporin A                 | Hyaluronic acid (PECA) | In vitro studies | In vitro studies shows HA coated PCL/BKC increased the level of CyA about 10-15 fold in cornea as compared to NP preparation in castor oil solution & PCL/BKC | 77   |
| Pilocarpine                   | Albumin | In vivo or in vitro studies | -- | 7 |

**RECENT STUDIES ON OPHTHALMIC DRUG DELIVERY SYSTEM USING MICROSPHERES:**

Rathod *et al.* prepared egg albumin microspheres of pilocarpine nitrate by using the heat stabilization method. Factors that affect the size and encapsulation efficiency were optimized to obtain microspheres in the size range 1 to 12 µm to make them undetectable by eyes and sufficient to entrap drug efficiently. Encapsulation efficiency of egg
albumin microspheres was found to be that was to be 63.4%. By using spherical matrix in vitro release of drug was evaluated. In the preparation of microsphere gel Carbopol–940 polymer was used. Comparative evaluations were made by preparing simple gels of same drug concentration. Bioavailability parameters of all the formulations were evaluated and comparisons were made.\(^{78}\)

Parmar et al. reported that mucoadhesive microspheres can be prepared by different methods and was evaluated for their mucoadhesive properties. The microsphere prepared by glutaraldehyde (as a crosslinking agent) and thermal cross linking showed good stability in HCl as compared with microsphere prepared by triplyphosphate and emulsification ionotropic gelation method. In controlled and targeted drug delivery system, microspheres can be used because it overcomes the problems associated with conventional drug delivery like poor absorption, loss contact time and poor bioavailability.\(^{78}\)

Giunchedi et al. studied that the poly (lactide-co-glycolide) (PLGA) microspheres serve as carriers for the topical ocular delivery of a peptide drug vancomycin. In this experiment microspheres were prepared by an emulsification/spray-drying technique that can be proposed as an alternative to the double emulsion method for preparation of peptide-loaded microparticles. The drug encapsulation efficiencies were evaluated that was close to the theoretical values (84.2–99.5%); the average particle size was about 11 mm. The microspheres were able to modulate the in vitro drug release of vancomycin with behaviour dependent on their composition: the highest drug content corresponded to the highest release rate. In vivo studies were carried out by determining the pharmacokinetic profile of VA in the aqueous humor of rabbits after topical administration of aqueous suspensions of microspheres. High and prolonged VA concentrations and increased AUC values (2-fold) with respect to an aqueous solution of the drug were observed. Increasing the viscosity of the microsphere suspension by addition of a suspending-viscosizing agent (hydroxy propyl cellulose) did not produce an increase of the ocular bioavailability. PLGA microspheres can be proposed as a system for ocular delivery of peptide drugs.\(^{78}\)

Giunchedi et al. evaluated the Pectin microspheres as ophthalmic carriers for piroxicam. In this they were prepared the microspheres by a spray-drying technique; their morphological characteristics were investigated by scanning electron microscopy (SEM) and their in vitro release behaviour was determined at pH 7.0 USP buffer using a flow-through apparatus. Px loaded in the pectin microspheres showed a faster in vitro dissolution rate with respect to solid micronized drug. The precorneal retention of fluorescein-loaded microspheres was evaluated in vivo in albino rabbits: an aqueous dispersion of fluorescent microspheres showed a significantly increased residence time in the eye (2.5 vs. 0.5 h) then fluorescein solution. Hence, concluded that increased bioavailability. In vivo tests in rabbits of dispersions of Px-loaded microspheres also indicated a significant improvement of Px bioavailability in the aqueous humour (2.5-fold) when compared with commercial Px eye drops.\(^{78}\)

Kreuter et al. reported that nanoparticles and microspheres provide the promising drug carriers for ophthalmic applications. The binding of drugs depends on the physicochemical properties of the drugs and polymer used, as well as of the nano and microparticle material and also on the manufacturing process for these particles. After optimal drug binding to these particles, the ocular bioavailability of a number of drugs is significantly enhanced in comparison to normal aqueous eye drop solutions as increased solubility. Generally, smaller particles are better tolerated by the patients than larger particles (no irritation). For this reason especially nanoparticles may be preferred for long-acting ocular drug delivery systems, although larger microparticles showed slower elimination kinetics from the precorneal compartment.\(^{78}\)

CONCLUSION

Microspheres show promising drug carriers for ophthalmic applications. The ocular bioavailability of a number of drugs is significantly enhanced in comparison to normal aqueous eye drop solutions. Generally, smaller particles are better tolerated by the patients than larger particles. For this reason especially microspheres may be preferred for long-acting ocular drug delivery systems, although larger microparticles showed slower elimination kinetics from the precorneal compartment. In future It has been found that ocular delivery based formulations have great applications for local treatment of eye disease with relatively lesser side effects as compared to other route of drug delivery.

REFERENCE

1. Sikandar MK, Sharma PK and Visht Sikandar S, ocular drug delivery system: an overview IJPSR, 2011, Vol. 2(5), 1168-1175.
2. Arul kumaran KSG, Karthika K AND Padmapreetha J, Comparative review on conventional and advanced ocular drug delivery formulations, International Journal of Pharmacy and Pharmaceutical Sciences, 2010, Vol 2, Issue 4.
3. Jitendra, Sharma P.K. Banik A. and Dixit S. A new trend: ocular drug delivery system Pharma science monitor, An international journal of pharmaceutical sciences, 2011, Vol-2, Issue-3.
4. Wadhwa S, Paliwal R, Paliwal SR and Vyas SP, Nanocarriers in Ocular Drug Delivery: An Update Review, Current Pharmaceutical Design, 2009, vol.15, 2724-2750.
5. Sahoo SK, Dilnawaz F and kumar SK, Nanotechnology in ocular drug delivery, drug discovery today, 2008, volume 13, numbers 3/A.

6. Zimmer A, J & G Kreuter, Microspheres and nanoparticles used in ocular delivery Systems Advanced Drug Delivery Reviews,1995, vol. 16, 61-73.
7. Rathod S. & Deshpande S.G., Albumin microspheres as an ocular delivery system for Pilocarpine Nitrate, IJPS, 2011.
8. Palani S, Joseph NM, Goda CC, Zachariah A and Ayenew Z, Ocular drug delivery: A Review, IJPSR, 2010, Vol. 1, Issue 3.
9. Professor (Dr.) Rakesh Kumar Jat, Vice principal, Rajasthan pharmacy college, Jaipur.
10. Kreuter, J, J.S. and J.C. Boylan (Eds.), Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York, 1994, pp. 165-190.
11. Kreuter, J., Evaluation of nanoparticles as drug delivery systems, Preparation methods, Pharm. Acta Helv. 58, 1983, 196-209.
Tichawala SP, Kompella UB. Subconjunctively administered celecoxib-PLGA microparticles sustain retinal drug levels and alleviate diabetes-induced oxidative stress in a rat model. Eur J Pharm 2005; 511: 191-8.

15. Gupta AK, Madan S, Majumdar DK, Maitra AK. Ketrolarol entrapped in polymeric micelles; preparation, characterization and ocular anti-inflammatory studies. Int J Pharm 2000; 2005; 209: 1-14.

16. Xu J, Wang Y, Li Y, Yang X, Zhang P, Hou H. Inhibitory efficacy of intravitreal dexamethasone acetate-loaded PLGA nanoparticles on choroidal neovascularization in a laser-induced rat model. J Ocul Pharmacol Ther, 2007; 23: 527-39.

17. Papadimitriou S, Bikiaris D, Avgoustakis K, Karavas E, Georgarakis M. Chitosan nanoparticles loaded with dorzolamide. Int. J. Pharm. 2008; 367-373.

18. Piao TW, Bhutto I, Kim SY, Grebe R, Merges C, McLeod DS, et al. Ocular nanoparticle toxicity and transfection of the retina and retinal pigment epithelium. Nanomed, Nanotech, Biol Med, 2008, 4: 340-9.

19. Alagusundaram M, Madhu sudana chetty, C, Umashankari, A, Attuluri venkata badarainath, lavana, C and ramkanth, S. Microspheres as a novel drug delivery system - a review, international journal of chemtech research, 2009, vol. 1, no. 3, 526-534.

20. Alonso, MJ, Losu C, Seijo B, Torres D and Vila- Jato JL. New ophthalmic drug release systems: formulation and ocular disposition of amikacin-loaded nanoparticles, 5th Int. Conf. Pharm. Tech. I, 1989, 77-83.

21. Marchal-Heusler S, Sirbat D, Hoffman M and Mainpent C. Nanoparticles de P-bloquants, un nouveau vecteur de mCkicaments en ophthalmologie, J. Fr. Ophthalmol. 14, 1991, 371-375.

22. Marchal-Heusler S, FessIh, Devissaguet JP, Hoffman M and Mainpent C. Colloidal drug delivery systems for the eye: A comparison of the efficacy of three different polymers: Polysobutylyanoacrylate, poly(lactic-co-glycolic acid, polypepsilon-caprolacton, STP Pharma Sci. 2, 1992, 98-104.

23. Marchal-Heusler L, Mainpent C, Hoffman M, Spitterl J and Couvreur P. Antiglaucomatous activity of betaxolol chlorhydrate sorbed onto different isobutylynoacrylate nanoparticle preparations, Int. J. Pharm. 58, 1990, 115-122.

24. Mainpent C, Marchal-Heusler L, Sirbat D, Thouvenot V, Hoffman M, and Vallet J.A. Polycaprolacton colloidal carriers for controlled ophthalmic delivery, Proc. Int. Symp. Control. Rel. Biode. Mater. 1, 1992, 423.

25. Shell JW, Ophthalmological bioerodible drug dispensing formulation, U.S. Patent 4,001, 1977,388.

26. Zinner A.K., Mainpent C, Thouvenot P and Kreuter J. Hydrocoristine delivery to healthy and inflamed eyes using a micellar polysorbate 80 solution or albumin nanoparticles, Int. J. Pharm. 110, 1994, 211-222.

27. Billardon P, Fassi H, Devissaguet JP, and Puisieux F. Tolerance studies and pharmacokinetic evaluation of isothematin-loaded nanoparcules in rabbit eyes, Proc. Int. Symp. Control. Rel. Biode. Mater. 19, 1992.

28. Leucuta SE. The kinetics of in vitro release and the pharmacokinetics of miotic response in rabbits of gelatin and albumin microspheres, Int. J. Pharm. 54, 1989, 71-78.

29. Diepold RW, Entwicklung und Untersuchung von kolloidalen Depot-Antihypertgensystemen zur Koronarbehandlung, Dissertation, Fachbereich Biochemie, Pharmazie und Lebensmittelwissenschaft, JWG-Universist, Frankfurt a.M., Germany,,1988.

30. Zinner AK, Kreuter J, Saetteme MF and Zerbe H. Size dependency of albumin carrier systems on the in vivo effects of pilocarpine in the rabbit eye, Proc. Symp. Control. Rel. Mater. 18, 1991, 493.

31. Zinner AK, Zerbe H and Kreuter J. Evaluation of pilocarpine-loaded albumin particles as drug delivery systems for controlled delivery in the eye, In vitro and in vivo characterisation. J. Contrroll. Release 32, 1994, 57-70.

32. Zinner AK, Saetteme MF, Zerbe H, and Kreuter J. Evaluation of pilocarpine-loaded albumin particles as drug delivery systems for controlled delivery in the eye II. Coating of pilocarpine-loaded albumin nanoparticles with biodegradable and viscous polyesters J. Control. Release 53, 1995, 31-46.

33. Boye T, Gurny R and Buri P, Développement et Evaluation d’un nouveau type de forme orphaleigique g IBrCitation prolongée, 2ème Congrès Européen de Biopharm. et Pharmacocinétique, Salamanca, Spain, 1984.

34. Gurny R, Preliminary study of prolonged acting drug delivery systems for the treatment of glaucoma, Pharm. Acta Helv. 56, 1981, 130-142.

35. Gurny R, Boye T and Ibrahim H, Ocular therapy with nanoparticulate systems for controlled drug delivery, J. Control. Release 2, 1985, 353-361.

36. Gurny R, Ibrahim H, Aebi A, Buri P, Wilson CG, Washington N, Edman P and Camber O, Design and evaluation of controlled release systems for the eye, J. Control. Release 6, 1987, 367-373.

37. Harmia T, Speiser P and Kreuter J. A solid colloidal drug delivery system for the eye. Encapsulation of pilocarpine in nanoparticles, J. Microencapsulation 3, 1986, 3-12.

38. Harmia T, Speiser P and Kreuter J. Optimization of pilocarpine loading onto nanoparticles by sorption procedures, Int. J. Pharm. 33, 1986, 45-54.

39. Harmia T, Speiser P, Kreuter J, Boye T, Gurny R and Kubis A, Enhancement of the miotic response of rabbits with pilocarpine-loaded polybutylcyanoacrylate nanoparticles, Int. J. Pharm. 33, 1986, 187-193.

40. Harmia T, Speiser P and Kreuter J. Nanoparticles as drug carriers in ophthalmology, Pharm. Acta Helv. 62, 1986, 322-331.

41. Diepold R, Kreuter J, Himber J, Gurny R, Lee VHL., Robinson JR, Saetteme MF and Schnaudigel OC, Comparison of different models for the testing of pilocarpine eyedrops using conventional eyedrops and novel depot formulation (nanoparticles), Graefes Arch. Clin. Exp. Ophthalmol. 227, 1989, 118-193.

42. Kreuter J. Nanoparticles and liposomes in ophthalmic drug delivery, Ophthalmic drug delivery, biopharmaceutical, technological and clinical aspects, In: Saetteme, Bucci, Speiser (Eds.), Ophthalmic Drug Delivery, Fidia Res. Series, Vol. 11, Liviana Press, Padua, 1987, 101-106.

43. Zinner A, Mutschler E, Lambricht G, Mayer D and Kreuter J. Pharmacokinetic and pharmacodynamic aspects of an ophthalmic pilocarpine nanoparticle-delivery system, Pharm. Res. 11, 1994, 1435-1452.

44. Vidmar V, Pelpenijak S and Jalseniak J, The in vivo evaluation of polylactic acid microcapsules of pilocarpine hydrochloride, Microencapsulation 2, 1985, 289 – 292.

45. Andermann C, de Burlet R and Cockett. C, Etude comparative de l’activité antiglaucomateuse de glauplex 2 et du nitré de pilocarpine sur le glaucome experimental a l’alphachymotrypsine, J. Fr. Ophthalmol. 5, 1982, 499-504.

46. Andermann C, Mialhe D, Amé, JL, Vende D and Bet P, Effet tensionnel apres instillation dune goutte de pilocarpine retard. Resultats cliniques de son action a moyen terme, J. Fr. Ophthalmol. 6, 1983, 367-374.

47. Blumenthal M, Ticho U, Zonis S, Gal A and Mazor Z, Further clinical trial with piloplex: A new long acting pilocarpine salt, Glaucoma, 1, 1979, 145-148.

48. Duzman E, Quinn CA, Warman A and Warman RA, one-month crossover trial comparing the safety and intraocular pressure control in patients treated with piloplex 3.4 applied twice daily with those treated with pilocarpine 2% applied 4 times daily. Int. Symp. on Glaucouma, Jerusalem, 1983.

49. Klein HZ, Lugo M, Shields MB, Leon J and Duzman E, A dose-response study of piloplex for duration of action in humans, Am. J. Ophthalmol. 99, 1985, 23-26.

50. Mazor Z, Ticho U, Rehany U and Rose L, Piloplex, a new longacting pilocarpine polymer salt B: Comp. study of the visual effects of pilocarpine and piloplex eye drops, Br. J. Ophthalmol. 63, 1979, 48-51.

51. Mazor Z, Kasan R., Kain N, Ladkani D, Ross M and Weiner B, Glauhib (Piloplex 3.4) A long acting anti-glaucoma medication, Recent Adv. Glaucouma,1984, 225-229.
52. Robinson JR and Li. VHK, Ocular disposition and bioavailability of pilocarpine from pilocarpine and other sustained release drug delivery systems, in: Ticho U. and David R. (Eds.), Recent Advances in Glaucoma 1984.

53. Stodmeister R, Brenner J, and Bauer MP, Pilocarpin Augentropfen mit einem neuartigen Pilocarpin - Polymersalz. Klin. Monatsbl. Augenheilk. 174, 1979, 276 - 280.

54. Ticho U, Blumenthal M, Zonis S, Gal. A and Mazor Z. A new long-acting pilocarpine compound, Ann. Ophthalmol. 11, 1978, 555561.

55. Ticho U, Blumenhal M., Zonis S, Gal A, and Mazor Z. Pilocarpine, a new long-acting pilocarpine polymer salt: A: Long-term study, Br. J. Ophthalmol. 63, 1979, 45-47.

56. Evans ME, Richardson NE and Norton DA. The preparation and properties of polyamide microcapsules containing pilocarpine in solutions, J. Pharm. Pharmacol. 19P, 1981.

57. Beal M, Richardson NE, Meakin BJ and Davies DJG, The use of polyhexamethylene microcapsules for obtaining extended periods of therapy in the eye. In: Davis, Illun, McVie, Tomlinson (Eds.) Microspheres and Drug Therapy. Pharmaceutical Immunological and Medical Aspects, 1984, 347-348.

58. Kreuter J, Li VHK, Wood R, Robinson JR, Harmia T, and Speiser P, Ocular disposition of polyhexylcyanoacrylate nanoparticles and of nanoparticle-bound progestrone, Proc. Int. Symp. Control. Rel. Bioact. Mater. 12, 1985, 304.

59. Li VHK, Wood RW, Kreuter J, Harmia T, and Robinson JR, Ocular drug delivery of progesterone using nanoparticles, J. Microencapsulation 3, 1986, 213-218.

60. Harmia-Pulkkinen T, Ihantola A, Tuomi A and Kristofferson E, Nanoencapsulation of timolol by suspension and micelle polymerization, Acta Phamac. Fennica, 95, 1986, 89-96.

61. Gavini E, Cheton P, Cosso M, Alvarez MG, Saetone MF, Giunchedi P, PLGA microspheres for the ocular delivery of a peptide drug, vancomycin using emulsification-spray-drying as the preparation method, in vitro/vivo studies. Eur J Pharm Biopharm 2003; 57: 207-12.

62. Tuovinen L, Ruhanen E, Kinnarinen T, Ronkko S, Pelkonen J, Urtti A, et al. Starch acetate microparticles for drug delivery into retinal pigment epithelium — in vitro study. J Control Release 2004; 98: 407-13.

63. Ayalaosmanyajala SP, Kompella UB, Subconjuничvally administered celecoxib-PLGA microparticles sustain retinal drug levels and alleviate diabetes-induced oxidative stress in a rat model. Eur J Pharm 2005; 511: 191-8.

64. Gupta AK, Madan S, Majumdar DK, Maitra AK. Ketorolac entrapped in polymeric micelles: preparation, characterization and ocular anti-inflammatory studies. Int J Pharm 2000; 209: 1-14.

65. De Campos AM, Sánchez A, Alonso MJ. Chitosan nanoparticles: a new vehicle for the improvement of the delivery of drugs to the ocular surface. Application to cyclosporin A. Int J Pharm 2001; 224: 159-68.

66. Fresta M, Fontana G, Bucolo C, Cavallaro G, Giannmona G, Puglisi G. Ocular tolerability and in vivo bioavailability of poly(ethylene glycol) (PEG)-coated polyethyl-2-cyanoacrylate nanosphereencapsulated acyclovir. J Pharm Sci 2001; 90: 288-97.

67. Bourges JL, Gautier SE, Delie F, Beijani RA, Jeanny JC, Gurny R, et al. Ocular drug delivery targeting the retina and retinal pigment epithelium using polylactide nanoparticles. Invest Ophthalmol Vis Sci 2002; 43: 213-20.

68. Merodio M, Espuelas MS, Mórich M, Arnedo A, Iraje JM. Efficacy of ganciclovir-loaded nanoparticles in human cytomegalovirus (HCMV)-infected cells. J Drug Target 2002; 10: 83-100.

69. De Campos AM, Diebold Y, Carvalho EL, Sánchez A, Alonso MJ. Chitosan nanoparticle as new ocular drug delivery systems: in vivo stability, in vivo fate and cellular toxicity. Pharm Res 2004; 21: 803-10.

70. Sakai T, Kohno H, Ishihara T, Higaki M, Saito S, Matsushima M, et al. Effect of betamethasone phosphate loaded polylactide nanoparticles on experimental autoimmune uveoretinitis. Exp Eye Res 2006; 82: 657-63.

71. Kompella UB, Raghavan SS, Escobar ERS. LHRH agonist and transferring functionalization enhance nanoparticle delivery in a novel bovine ex vivo eye model. Mol Vis 2006; 12: 1185-98.

72. Mishra DN, Gilhotra RM. Design and characterization of bioadhesive in-situ gelling ocular insert of gatifloxacin sesquhydrate. DARU 2008; 16: 1-8.

73. Xu J, Wang Y, Li Y, Yang X, Zhang P, Hou H, et al. Inhibitory efficacy of intravitreal dexamethasone acetate-loaded PLGA nanoparticles on choroidal neovascularization in a laser-induced rat model. J Ocul Pharmacol Ther 2007; 23: 527-39.

74. Badawi AA, El-Laithy HM, El Qidra RK, El Mofty H, El dally M. Chitosan based nanocarriers for indomethacin ocular delivery. Arch Pharm Res 2008; 8: 1040-9.

75. Papadimitriou S, Bikiaris D, Avgoustakis K, Karavas E, Georgarakis M. Chitosan nanoparticles loaded with dorzolamide and pramipexole. Carbohydr Polym 2008; 73: 44-54.

76. Prow TW, Bhatto I, Kim SY, Grebe R, Merges C, McLeod DS, et al. Ocular nanoparticle toxicity and transfection of the retina and retinal pigment epithelium. Nanomed: Nanotech, Biol Med 2008; 4: 340-9.

77. Yenice I, Mocan MC, Palaska E, Bochot A, Bilensoy E, Vural I, et al. Hyaluronic acid coated poly-episolon-caprolactone nanospheres deliver high concentrations of cyclosporine A into the cornea. Exp Eye Res 2008; 87: 162-7.

78. Ankit Kumar, Malviya R and Sharma P.K., Recent Trends in Ocular Drug Delivery: A Short Review, European Journal of Applied Sciences 3 (3): 86-92, 2011, ISSN 2079-2077.

79. Boarse Manoj B, Kale Sachin S, Bavisker Dheeraj T, Jain Dinesh K, Comparative review on conventional advanced ocular drug delivery system, IJRFPS 2012, 3(2), 215-223.

80. Kataria S, Middha A, Sandhu P, Bilandi A and Kapoor B, International journal of research in pharmacy and chemistry, ijrpc 2011, 1(4), issn: 2231:2781.

81. Khan S, Tiwari T, Rao N, Joshi A, Dubey B K, Microspheres: a review, World journal of pharmacy and pharmaceutical sciences, 2012, Volume 1, Issue 1, 125-145.