

REVIEW ARTICLE

MICROSPHERES 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 include 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.¹

Advantages of controlled ocular drug delivery systems^{2,78}

- ❖ 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 system².
- ❖ 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 delivery⁷⁸.

Disadvantages^{78,79}

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

therapeutic effect resulting in a frequent dosing regimen^{78,79}

the main potential sites for systemic absorption of topically applied drugs.

Physiological barriers of ophthalmic drug delivery systems²

- ❖ 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

Mechanism of controlled sustained drug release into the eye²

- ❖ 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 non-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.²

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^{3,13}

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.

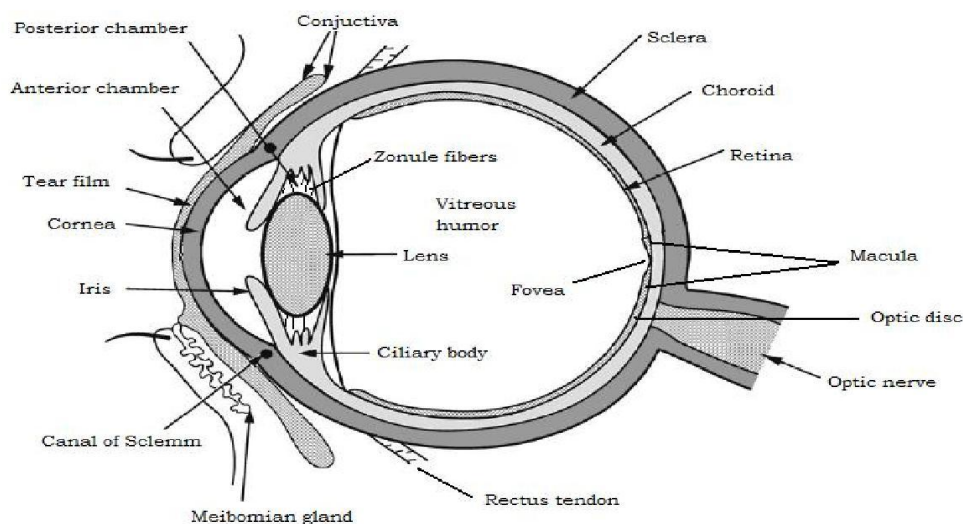


Figure 1: The structure of the eye³

Conjunctiva^{3,10}

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 system³

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 nasolachrymal duct.

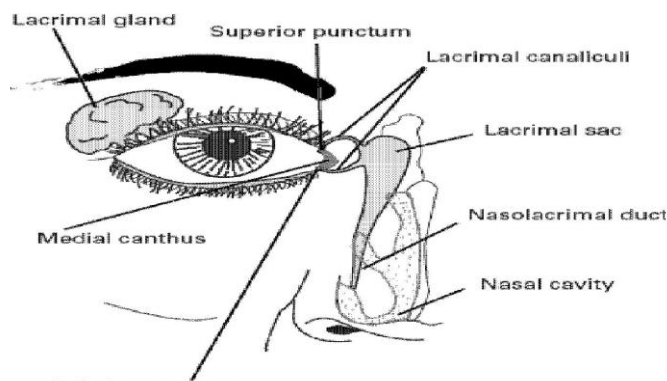


Figure 2: Schematic diagram of nasolachrymation drainage system³

Tear film³

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 DELIVERY⁵

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, budesonide, 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.⁵

Table 1: Criteria for the selection of optimal formulation parameters when developing an ophthalmic drug delivery system⁵

Factor	Preference
Drug	Preferentially lipophilic. Non-ionisable lipophilic compounds will concentrate into the corneal epithelium, while ionisable lipophilic ones will partitionate 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)

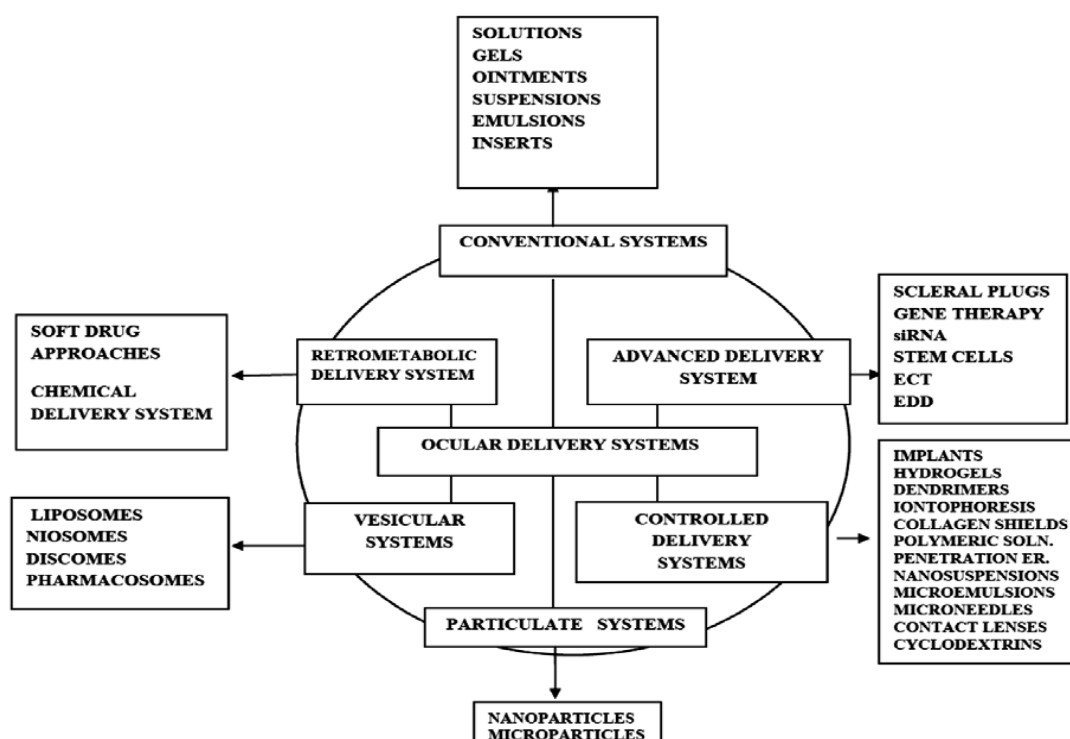


Figure 3: Different delivery systems which are currently used for ocular therapy⁴

MICROSPHERES IN OCULAR DELIVERY^{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 ocular 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 1 μm .

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 administration⁶.

MANUFACTURING METHODS OF OCULAR MICROSPHERES⁶

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.

Table 2: Nano- and microparticulate carriers in ophthalmology

Drug	Polymer	Reference
Amikacin	Poly(butyl)cyanoacrylate	20
Betaxolol	Poly(epsilon)caprolacton	21,22
	Poly(isobutyl)cyanoacrylate	22,23
	Poly(lactic-co-glycolic acid)	22
Carteolol	Poly(epsilon)caprolacton	24
Chloramphenicol	Poly(lactic 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
	Poly(lactic acid)	44
	Poly(methyl)methacrylateacrylic-acid- copolymer	45,46,47,48,49,50,51,52,53,54,55
	Poly(methyl)methacrylate	38,40
	Polyamide	56
	Polyphthalamide	57
Progesterone	Poly(hexyl)cyanoacrylate	58
	Poly(butyl)cyanoacrylate	59
Timolol	Poly(alkyl)cyanoacrylate	60

Table 3: Manufacturing techniques used for preparing micro- and nanospheres⁶

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

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^{80,81}. 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 drugcarrier (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) chitosan⁸⁰. 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 particulate 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 KINETICS¹⁹

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

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	<i>In vitro</i> & <i>in vivo</i> studies	<i>In vitro</i> studies revealed high encapsulation efficiency (84.2-99.5%) & increased AUC values(2 fold)of drug	61
Calcein	Starch acetate	<i>In vivo</i> studies	Studies showed 82% viability of RPE culture cells when incubated with microparticles for 24 hrs	62
Colecoxib	PLGA-PEG	<i>In vitro</i> studies	<i>In vivo</i> studies showed high loading efficiency(68.5%)of colecoxib in PLGA microparticles which inhibits diabetes induced retinal oxidative damage	63
Ketorolac	NIPAAm, VP, AA	<i>In vitro</i> 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	<i>In vitro</i> & <i>In vivo</i> studies	<i>In vitro</i> 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. <i>In vivo</i> 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	Poly lactide	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	<i>In vitro</i> & <i>In vivo</i> studies	<i>In vitro</i> studies showed stability of nanoparticles upon incubation with lysozyme & <i>in vivo</i> studies shows high amount of (Cs-fl) NP in corneal tissues as compared to Cs-fl solutions	69
Betamethasone phosphate	Poly (lactic acid)	<i>In vivo</i> studies	Studies shows that NP controls the intraocular inflammation when administered systemically in EAU	70
LHRH agonist deslorelin 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	<i>In vitro</i> studies	<i>In vitro</i> 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	<i>In vitro</i> & <i>In vivo</i> studies	<i>In vitro</i> 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 <i>in vivo</i> as compared to solutions; so enhance the delivery to both external & internal ocular tissues	74
Dorzolamide & Pramipexole	Chitosan	<i>In vitro</i> studies	<i>In vitro</i> 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)	<i>In vitro</i> studies	<i>In vitro</i> 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	<i>In vivo</i> or <i>in vitro</i> 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 μ m 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 made⁷⁸.

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 tripolyphosphate 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, less contact time and poor bioavailability⁷⁸.

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 nm. 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 drugs⁷⁸.

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 drops⁷⁸.

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 compartment⁷⁸.

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.

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