

New concepts regarding micro/nanopharmaceutical polymer systems with applications in ophthalmology and neurosciences

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Abstract

Particulate systems like micro/nanoparticles have been used as a physical approach to modify the pharmacokinetic and pharmacodynamic properties of various types of drug molecules increasing this way the drug bioavailability and avoiding the toxic level. The major advantages of the particulate systems include the protection of the drug entity in the systemic circulation, restriction access of the drug to the chosen sites and delivery of the drug at a controlled and sustained rate to the site of action. Various materials have been used in the formulation of micro/nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Each class of materials (metals, lipids, polymers) presents advantages which make them suitable for different classes of applications. This paper focuses mainly on polymer particulate systems due to their large applicability area given by the diversity of the polymers properties. We review various aspects of micro/nanoparticle formulation including preparation, release mechanisms, effect of their characteristics and their applications in the field of ophthalmology and neurosciences. Some of the most

interesting applications of polymer micro/nanoparticulates in glaucoma, retinal disorders and optical nerve disorders, respectively in neurology and neurosurgery are presented.

Keywords: controlled drug delivery, micro/nanoparticles, neuroscience, ophthalmology

Introduction

The word “micro/nanopharmaceutical” tends to be as magic as the message “Open Sesame!” for the diagnostic and treatment of diseases offering the opportunity to find new ways to attack the illness causes, respective complications and to improve the quality of patient life. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body while achieving it rapidly and maintaining desired drug concentrations in the body circulation. Most drugs are delivered to patients using a systemic approach, the belief being that if you flood the body with enough active compounds, there will be a desired therapeutic effect on the body. The drug delivery systems are supposed to deliver the drug at a rate dictated by the needs of the body over a specified period of the treatment. The

idealized objective for the DDS points to two major aspects, namely spatial placement and temporal delivery of the drug. Spatial placement relates to targeting a drug to a specific organ or tissue. Temporal delivery refers to controlling the rate of delivery to the target tissues. The reduction or prevention of side effects can also be achieved by controlled release. Micro/nanoparticles provide a better penetration of the particles inside the body as their size allows delivery via intravenous injection or other routes. The micro/nanoscale size of these particulate systems also minimizes the irritant reactions at the injection site. [Thassu D. et al., 2009].

This paper focuses mainly on polymer particulate systems due to their large applicability area given by the diversity of the polymers properties. We review various aspects of micro/nanoparticle formulation including preparation, release mechanisms, effect of their characteristics and their applications in the field of ophthalmology and neurosciences. Some of the most interesting applications of polymer micro/nanoparticulates in glaucoma, retinal disorders and optical nerve disorders, respectively in neurology and neurosurgery are presented.

Polymer micro/nanoparticles as controlled drug delivery system

Micro/nanoparticulate drug-delivery systems are being explored for the purpose of solving the challenges of drug delivery. Coming in many shapes and sizes, micro and especially nanoparticles have the potential to eliminate or at least ameliorate many problems associated with drug distribution. As many drugs have a hydrophobic component, they often suffer from problems of precipitation in high

concentration, and there are many examples of toxicity issues with excipients designed to prevent drug aggregation. To combat these issues, many micro/nanoparticulates provide both hydrophobic and hydrophilic environments, which facilitate drug solubility. Alternatively, many drugs suffer from rapid breakdown and/or clearance in vivo. Encapsulating the drugs in a protective environment, micro/nanoparticles increase their bioavailability, thereby allowing the clinicians to prescribe lower doses.

The advantages of using nanoparticles as a drug delivery system include the following:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.

3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles, or use of magnetic guidance.

5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

In spite of these advantages, micro/nanoparticulate systems do have

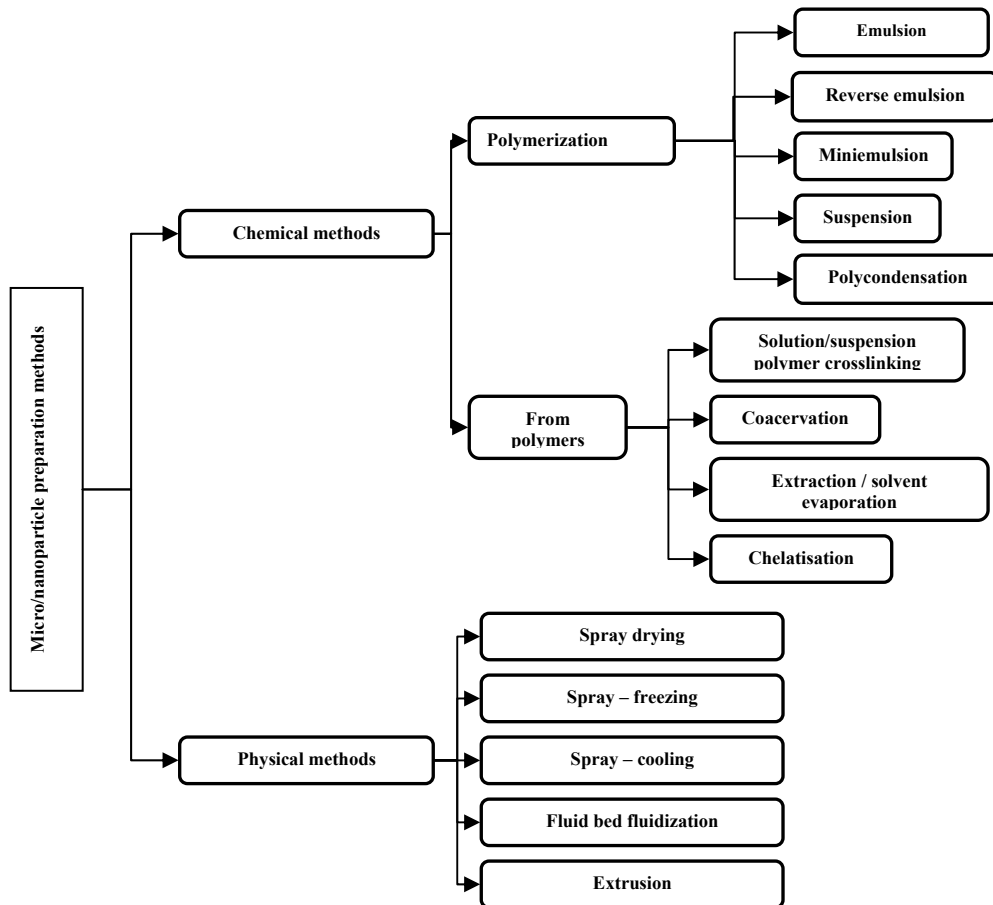
limitations, for example their small size and large surface area can lead to particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms; also, the small particles size and large surface area readily result in limited drug loading and burst release.

The micro/nanoparticles can be classified in the following main types,

Particles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on many factors including: (a) size of nanoparticles required; (b) the drug properties in terms of aqueous solubility and stability; (c) surface characteristics such

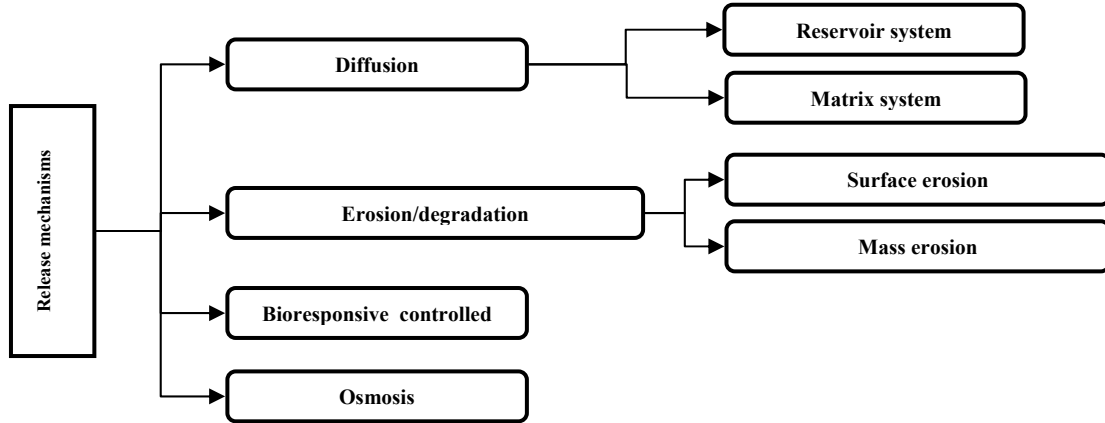
as charge and permeability; (d) biodegradability, biocompatibility and toxicity; (e) The desired drug release profile; and (f) Antigenicity of the final product [Kreuter J., 1994].

Depending on the desired properties, the micro/nanoparticles can be prepared by using either a chemical or a physical method, as presented in the Scheme 1. A variety of methods have been reported for producing micro/nanoparticles, chemical methods generally include: a) Preparation of the particles by polymerisation starting with a monomer and b) preparation of the particles directly from polymers, and physical methods assume only the use of polymers.



Scheme 1 Micro/nanoparticles preparation methods

There are many mechanisms for drug release from micro/nanoparticulate systems, as described in the Scheme 2:



Scheme 2 Schematic representation of the most important mechanisms of controlled drug release

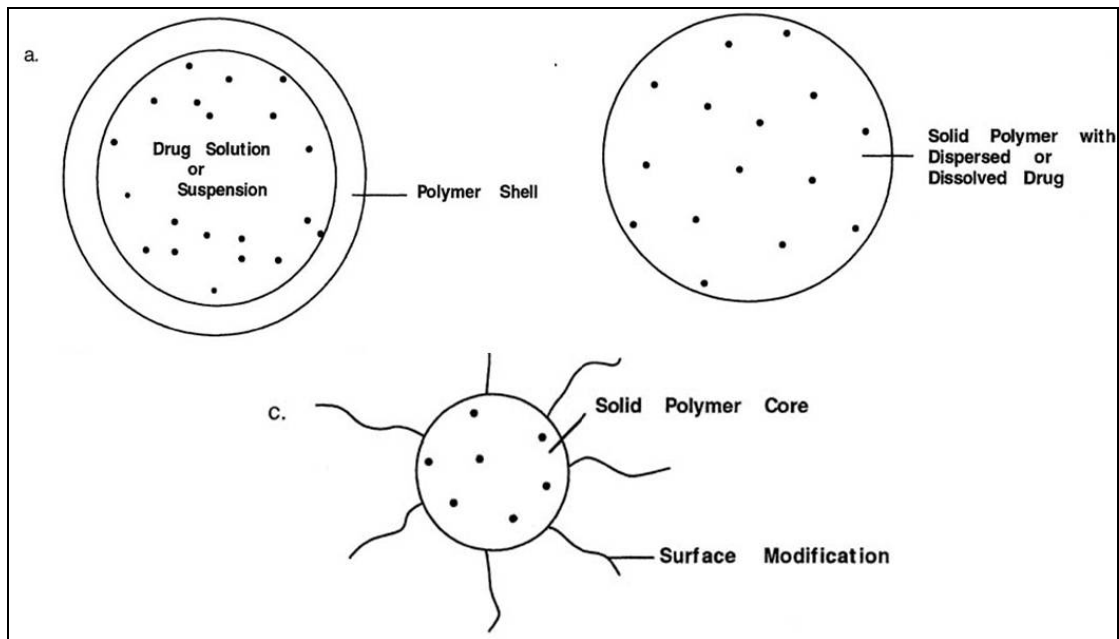


Figure 1 Different types of polymeric particles used as drug delivery systems [Saltzman W. M., Drug Delivery Engineering Principles For Drug Therapy, 2001, Chapter 9.5. Particulate delivery systems, Oxford University Press]

Several different classes of particulates with different release mechanisms are generally examined for use as drug delivery vehicles including microcapsules, microspheres, and nanospheres/nanocapsules (Figure 1) [Saltzman W. M., 2001]. Microcapsules

consist of a polymer shell enclosing a drug-loaded core. Microspheres are homogeneous particles in which the drug of interest is dispersed or dissolved within the solid polymer phase. Nanospheres are much smaller than microcapsules or microspheres. Nanospheres are usually

homogeneous particles, similar to microspheres, but they are frequently modified at the surface to increase their stability in the body or to provide targeting capability.

The most common drug release mechanism for polymeric micro/nanoparticulate systems is represented by diffusion. There are two main types of polymer-drug systems where the release is mainly based on diffusion: reservoir system and monolith (matrix) system. The reservoir system is characterised by the fact that the bioactive principle forming a core surrounded by a polymeric inert shell. In this case, the rate of diffusion of drug molecules through the membrane follows Fick's Law and is thus dependent on the partition and diffusion coefficient of the drug in the membrane, the available surface area, the membrane thickness and the drug concentration gradient. If the drug concentration gradient remains constant, for example where solid drug particles are present and constant dissolution maintains the concentration of the drug in solution, the rate of drug release does not vary with time and zero order controlled release is attained. For the monolith system the bioactive principle is uniformly dispersed within a polymeric matrix which will control the release rate; this system implies the physical interaction between the drug and the polymer resulted from their co-processing. Regardless of a drug's physical state in the polymeric matrix, such devices do not provide a zero-order drug release kinetic. This is because as the drug molecules at the surface of the device are released, those in the centre of the device have to migrate longer distances to be released, which takes a longer time. This increased diffusion time results in a

decrease in the release rate from the device with time. Generally the rate of release is found to decrease in proportion to the square root of time ("M t^{1/2}" kinetics) [Hillery A. M., 2001].

In erosion-controlled drug release systems, drug release is controlled by adjusting the dissolution / erosion rate of the polymer. The erosion of polymeric materials is the most important factor of this mechanism; that's why the polymers used must be water soluble and/or degradable in water. The choice of a specific polymer for a particular controlled release dosage form depends on various factors such as the dissolution mechanism, delivery period, delivery route, the drug etc.

In the case of the systems controlled by osmosis it is important to mention that the Osmosis is defined as the movement of water through a semi-permeable membrane into a solution. This movement of water will determine an increase in pressure in the solution and the excess pressure is known as the osmotic pressure which can be used to pump out the drug at a constant rate from the delivery system so that drug release is zero order.

Bio-responsive controlled drug delivery systems should adjust the drug release in respect to certain changes in the external environment like pH or ionic strength, temperature.

Nanoparticles are solid particles ranging in size from 10 nm to 1000 nm (1 μ m). They consist of macromolecular materials in which the active principle (drug or biologically active material) is dissolved, entrapped, or encapsulated, and/or to which the active material is adsorbed or attached. Microparticles are similar particles in the size range of 1 μ m to 1000 μ m (1 mm) [Kreuter J., 1996].

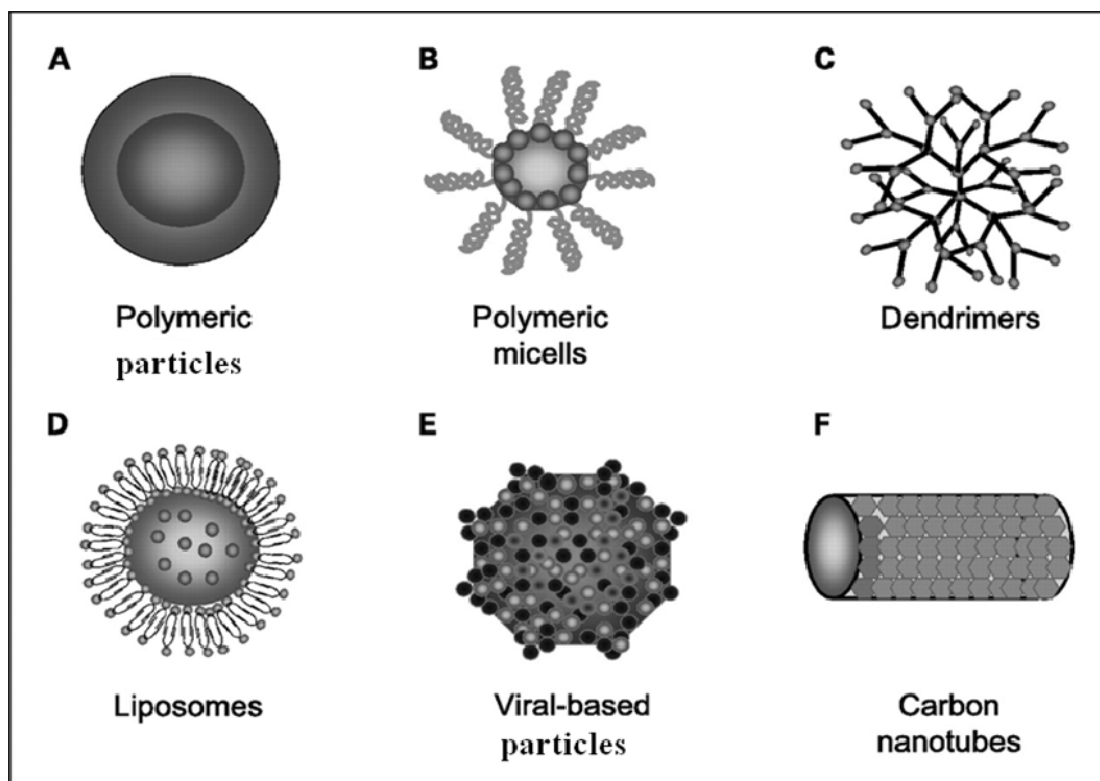


Figure 2 Types of carriers for particulate drug delivery: **A** polymeric nanoparticles: polymeric nanoparticles in which drugs are conjugated to or encapsulated in polymers. **B** polymeric micelles: amphiphilic block copolymers that form core/shell structures in aqueous solution. **C** dendrimers: synthetic polymeric macromolecule of nanometer dimensions, which is composed of multiple highly branched monomers that emerge radially from the central core. **D** liposomes: self-assembling structures composed of lipid bilayers in which an aqueous volume is entirely enclosed by a membranous lipid bilayer. **E** viral-based nanoparticles: in general structure are the protein cages, which are multivalent, self-assembles structures. **F** carbon nanotubes: carbon cylinders composed of benzene rings. [Kwangjae C., Wang X., Nie S., Chen Z., Dong M. Shin, Therapeutic Nanoparticles for Drug Delivery in Cancer, 2008, Clin Cancer Res., 14: 1310]

As it can be observed in the figure 2 there are different types of polymer particles especially designed in order to cover all needs in terms of application and administration path.[Kwangjae C. et al, 2008].

I. Application of micro/nanopharmaceutics in ophthalmology

Despite numerous scientific efforts, efficient ocular drug delivery remains a great challenge for scientists, currently most of the ocular diseases are treated by topical drug application in the form of solutions,

suspensions and ointment. These conventional dosage forms suffer from the problems of poor ocular bioavailability, because of various anatomical and pathophysiological barriers prevailing in the eye.

One of the most important problem of the eye as a target organ, from therapeutic point of view is the presence of several barriers that impede direct and systemic drug access to the specific site of action.

Superficial barriers include the ocular surface epithelium and the tear film, and

internal barriers include the blood-aqueous and blood-retina barriers. Topical application of the drugs is the preferred route at ocular level, even when the target tissues are at the back part of the eye where intraocular injections are currently the most common route of administration. The advantages of using micro/nanoparticles include improved topical passage of large, poorly water-soluble molecules such as glucocorticoid drugs or cyclosporine for immune-related, vision-threatening diseases [Diebold Y., 2010].

Interesting examples concerning the applications of polymer micro/nanotechnology are presented in correlation with the following ocular disorders:

- A. Glaucoma
- B. Retinal disorders
- C. Optical nerve disorders

A. Applications of the micro/nanoparticles in glaucoma

Glaucoma is defined as an optic neuropathy, which is diagnosed clinically from its characteristic disk appearance and typical changes in the visual field and which can be caused by various risk factors including raised intraocular pressure. The goal of glaucoma treatment is avoidance of further progression of the disease by lowering the intraocular pressure. Various types of drugs are currently in use in different formulations. One of the major disadvantages of all locally applied antiglaucoma drops is intolerance reactions and local cytotoxic effects. The main classes of drugs used in therapy of glaucoma are: sympathomimetics, sympatholytics, carbonic anhydrase inhibitors, parasympathomimetics (cholinergics), prostaglandin derivatives, osmotic agents.

Casalengua et colab. have developed a microparticulate system based on poly(lactic-co-glycolic acid) (PLGA) in which they have encapsulated GDNF (glial cell line-derived 31 neurotrophic factor) used as protector in glaucoma treatment, in combination with vitamin E and intravitreal administered in rats which were artificially glaucoma induced [Checa-Casalengua P. Et al., 2011]. The neurotrophic factor (GDNF) in combination with vitamin E released from the microspheres was demonstrated to be effective for at least eleven weeks after a single intravitreal injection; the efficacy of the treatment was measured in terms of retinal glial cells loss (figure 3). This approach should be considered as a future treatment of retinal degenerative diseases, as intravitreal PLGA administration is safe and effective, with no obvious side effects on the retinal integrity.

Another interesting study is provided by Dos Santos et al. and is related to the wound healing of conjunctiva after glaucoma filtration surgery [Gomes dos Santos A. L. Et al., 2006]. For this, they have prepared PLGA microspheres in which transforming growth factor- β (TGF- β) or 2'-O-methoxyethyl modified phosphorothioate antisense oligonucleotide (AsPS-ODN) – as bioactive principle were entrapped and subconjunctival injected. The authors designed PLGA microspheres (PLGA-MS) containing PS-ODN either naked (MS-PS-ODN) or complexed (MS-PS-ODN-PEI) and the most appropriate formulation was then tested in an experimental model of filtering surgery in rabbits being the first time that a system combining sustained release and enhanced intracellular penetration of antisense ODN was successfully assessed in an in vivo model (figure 4).

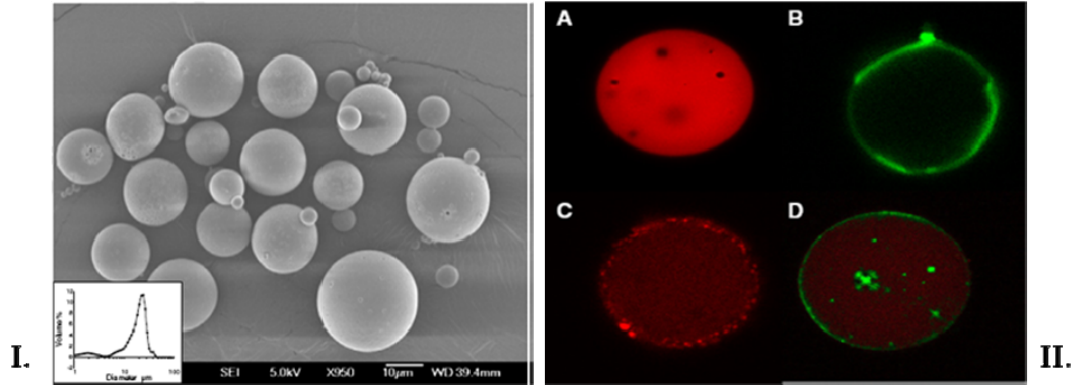


Figure 3 I - SEM images of GDNF-loaded microspheres; **II** - Confocal microscopy images of Nile red labeled PLGA microspheres. (A) MS elaborated with PLGA and Nile red. The absence of dye might be related with an inner porous structure. (B) MS elaborated with PLGA, Vit E and BSA-FITC. Protein was mainly located near to MS surfaces. (C) MS elaborated with PLGA, Vit E and TRITC-DHPE as lipid dye. The oily lipids (Vit E and dye) were distributed in all the MS, but was mainly located close to the MS surface. (D) MS elaborated with PLGA, Vit E, TRITC-DHPE, and BSA-FITC. A heterogeneous distribution was observed with higher quantities of protein and oily additive close to the MS surface [Checa-Casalengua P., Jiang C., Bravo-Osuna I., Budd A. Tucker, Irene T. Molina-Martínez, Michael J. Young, Rocío Herrero-Vanrell “Retinal ganglion cells survival in a glaucoma model by GDNF/Vit E PLGA microspheres prepared according to a novel microencapsulation procedure”, 2011, *Control. Release*, doi:10.1016/j.jconrel.2011.06.023].

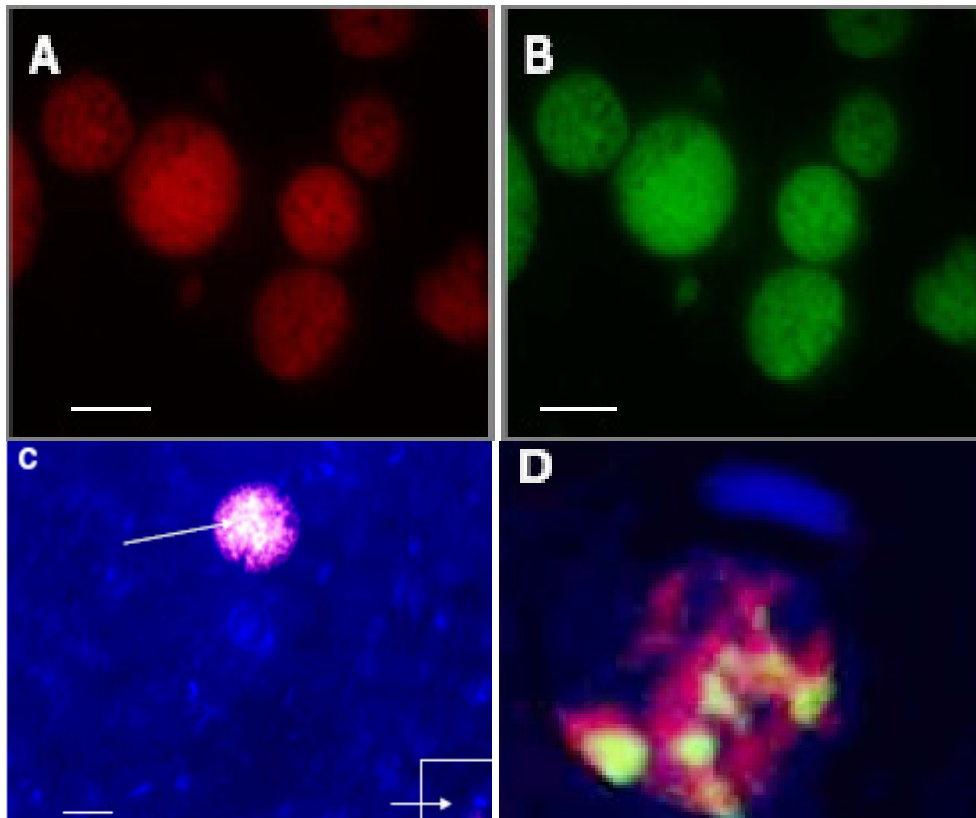


Figure 4 Fluorescent photographs of cryosections of the rabbit conjunctiva 1 day after subconjunctival injection. **A** Microspheres made of PLGA labelled with Nile red are seen in red and **B** complexes made with FITC ODNs and PEI are seen in green. **C** Combination with DAPI nuclei staining (blue) shows the microspheres in the tissue (arrows). **D** Higher magnification shows one microsphere with pores and complexes containing FITC labelled ODN next to a nucleus. Scale bar=20 μ m [Gomes dos Santos A. L., Bochot A., Doyle A., Tsapis N., Siepmann J., Siepmann F., Schmalzer J., Besnard M., Behar-Cohen F., Fattal E., “Sustained release of nanosized complexes of polyethylenimine and anti-TGF- β 2 oligonucleotide improves the outcome of glaucoma surgery”, 2006, *Journal of Controlled Release*, 112-3-369-381].

Nanosized complexes used were shown first to enhance the intracellular penetration of antiTGF β 2 and also to down regulate TGF β 2 in Rat Retinal Müller Glial cells as shown by RTPCR and Elisa. Nanosized complexes having an adequate encapsulation efficiency and release profiles allowed to improve the outcome of glaucoma filtration surgery.

B. Applications of the micro/nanoparticles in retinal disorders

Retinal drug delivery is one of the most challenging area in the field of ophthalmic drug delivery. An ideal drug delivery system for the retina and vitreous humor has not yet been found, despite extensive research. Drug delivery to retinal tissue and vitreous via systemic administration is constrained due to the presence of a blood-retinal barrier (BRB) which restrains the permeation of substances from blood to the retina. Although intravitreal administration overcomes this barrier, it is associated with several other problems. In recent years, transporter targeted drug delivery has become a clinically significant drug delivery approach for enhancing the bioavailabilities of drug molecules with poor membrane permeability characteristics. Various nutrient transporters, which include peptide, amino acid, folate, monocarboxylic acid transporters and so on, have been reported to be expressed on the retina and BRB. Prodrug derivatisation of drug molecules which target these transporters

could result in enhanced ocular bioavailability [Duvvuri S. et al, 2003].

Kim’s research group have studied the biodistribution of intravitreal human serum albumin nanoparticle (HSA-NP) and the mechanism for transretinal penetration of intravitreal nanoparticles into the subretinal space; the reason for using this kind of nanoparticles is that they showed excellent intraocular tolerance [Kim H. et al., 2009]. Nanoparticles having under 100 nm were prepared using desolvation-crosslinking technique and part of them were then cationized with ethylenediamine by covalent coupling at carboxyl groups.

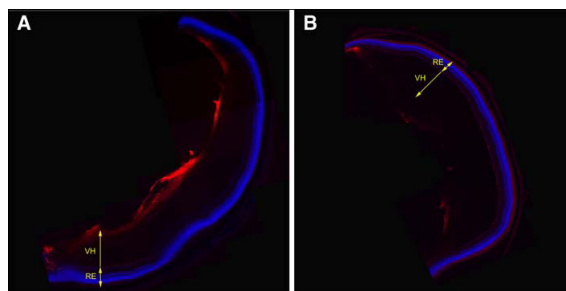


Figure 5 The vitreal distribution of Alexa 555 (fluorescent dye) conjugated **A** cationic and **B** anionic HSA-NP 5 h post intravitreal administration [Kim H., Robinson S. B., Csaky K. G., “Investigating the Movement of Intravitreal Human Serum Albumin Nanoparticles in the Vitreous and Retina”, 2009, *Pharmaceutical Research* 26 (2): 329-337]

Figure 5 shows the vitreal distribution of cationic HSA-NP (A) and anionic HSA-NP (B) 5 h post intravitreal administration. The cationic HSA-NPs were filtered and could not penetrate the vitreous, but most

of intravitreal anionic HSA-NPs penetrated the vitreous and were located within the retina at 5 h. Anionic HSA-NPs penetrated the vitreal barrier more easily than cationic HSA-NPs, the author's explanation being the electrostatic attraction between cationic HSA-NPs and the negatively charged vitreal glycosaminoglycan. Also, the authors have shown the transretinal penetration of HSA-NP into the RPE in normal retina and laser coagulated retina 5 h post intravitreal injection. Another interesting observation is that trans-retinal penetration of HSA-NP occurs through a specific route. The anionic HSA-NP were proved to be a promising drug delivery carrier for the treatment of age-related macular degeneration as HSA-NPs were observed to reach the choroid through the disruption site of the RPE and Bruch's membrane.

Rafat et al. have evaluated polyethylene glycol-poly(lactic acid) (PEG-PLA) microparticles for encapsulation and delivery of a Transactivator of transcription-enhanced green fluorescent protein fusion (Tat-EGFP) to retinal cells; microparticles were also analysed in vivo by sub-retinal injection into rat eyes. The microparticles were proved to be appropriate for targeted delivery to cells at the back of the retina (i.e. photoreceptor cells), which could prove effective in the treatment of blinding diseases caused by photoreceptor cell loss. They also can effectively deliver proteins to the outer segment of the retina, without any apparent cytotoxic effects. PEG-PLA microparticles show great potential for sustained ocular drug delivery because of their high stability in vitro and in vivo, and their release profile (figure 6) [Rafat M. et al., 2010].

Another example was raised from the following need: the dysfunction of RPE

cells can cause disruption in the neural retinal homeostasis, the RPE being this way an important target tissue for ocular therapy due to the fact that continuous phagocytosis of the photoreceptor outer segments is an important function of retinal pigment epithelium (RPE) in maintaining the health of the neural retina. Due to the poor accessibility of drugs to the RPE by conventional drug delivery systems, Tuovinen and her research group have studied starch acetate microparticles for delivery of drugs to the retina [L. Tuovinen et al, 2004]. For this, the cellular uptake of starch acetate microparticles and degradation of starch acetate by cultured human RPE-cell line (D407) was examined.

The results after the incubation of cultured RPE cells with blank or calcein-containing starch acetate microparticles reveal that they did not markedly affect the viability of the cells: after 3-or 24-h incubation, the viability was at least 93%, this is probably due to the fact that starch-based polymers have been shown to be biocompatible and acetyl starch is actually used as a human plasma volume expander (figure 7).

C. Applications of the micro/nanoparticles in optic nerve disorders

Very recent work made by Rong et al. explored a sustained neuroprotective erythropoietin (EPO) loaded composite microspheres system on injured retinal ganglion cells (RGC) [Rong X. et al., 2011].

EPO, naturally occurred in the body, is well known for its neuroprotective and/or but also for the ability to cross the blood-brain barrier and blood-retina barrier when systemically applied. It was developed a new method for encapsulation of EPO: the EPO was first loaded into dextran

microparticles (figure 8) to keep its bioactivity and the final microspheres were formed by encapsulating the primary

dextran microparticles into poly (DL-lactide-co-glycolide)/Poly (DL-lactide) (PLGA/PLA).

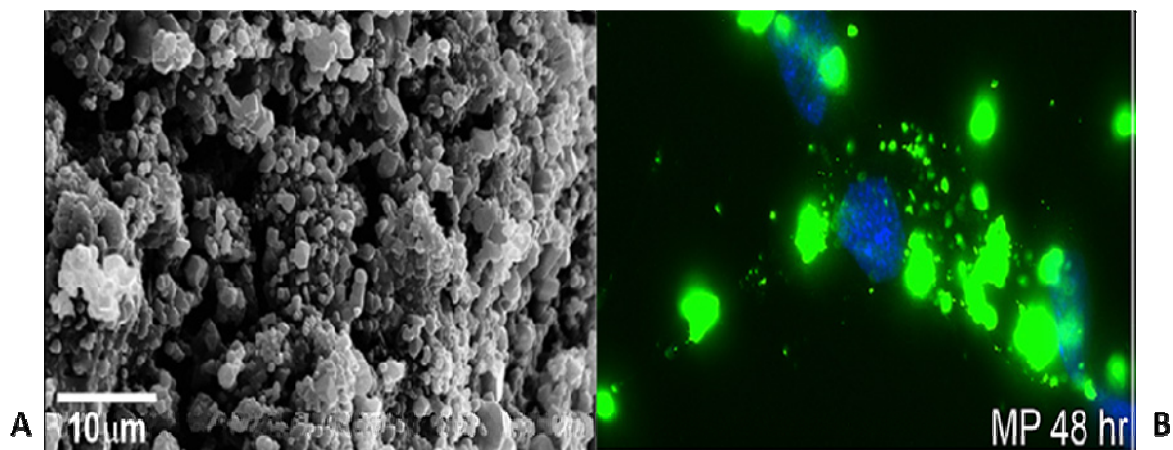


Figure 6 A - Scanning electron microscopy (SEM) images of PEG-PLA microparticle formulations; **B** - Fluorescence microscopy - cellular uptake of Tat-EGFP released from PEG-PLA microparticles in mouse photoreceptor-derived 661 W cells after 48 hours [Rafat M., Cleroux C. A., Fong W. G., Baker A. N., Leonard B. C., M. D. O'Connor, C. Tsilfidis, "PEG-PLA microparticles for encapsulation and delivery of Tat-EGFP to retinal cells", 2010, *Biomaterials* 31: 3414–3421]

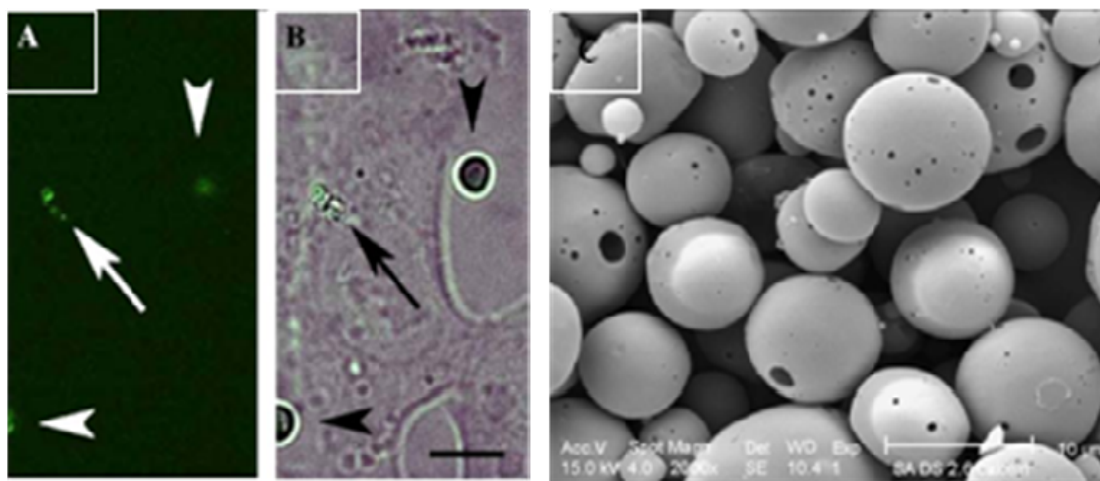


Figure 7. Confocal microscopy, (A) fluorescence and (B) light microscopic images of living RPE-cell culture after 24-h incubation with starch acetate microparticles. Microparticles in the cell are shown by an arrow and outside of cell by arrowheads. Bar indicates 6 μm; C - Scanning electron microphotograph (2000x) of starch acetate microparticles [Tuovinen L., E. Ruhanen, T. Kinnarinen, S. Ronkko, J. Pelkonen, A. Urtti, S. Peltonen, K. Jarvinen, "Starch acetate microparticles for drug delivery into retinal pigment epithelium—in vitro study", 2004, *Journal of Controlled Release* 98: 407– 413]

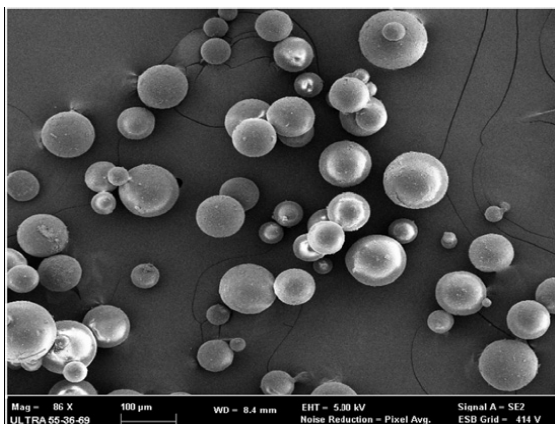


Figure 8 Scanning electron microscopic images of EPO-loaded PLGA/PLA microspheres [Rong X., Moa X., Ren T., Yang S., Yuan W., Dong J., Wang Y., Wang X. „Neuroprotective effect of erythropoietin-loaded composite microspheres on retinal ganglion cells in rats”, 2011, *European Journal of Pharmaceutical Sciences*, 43: 334–342].

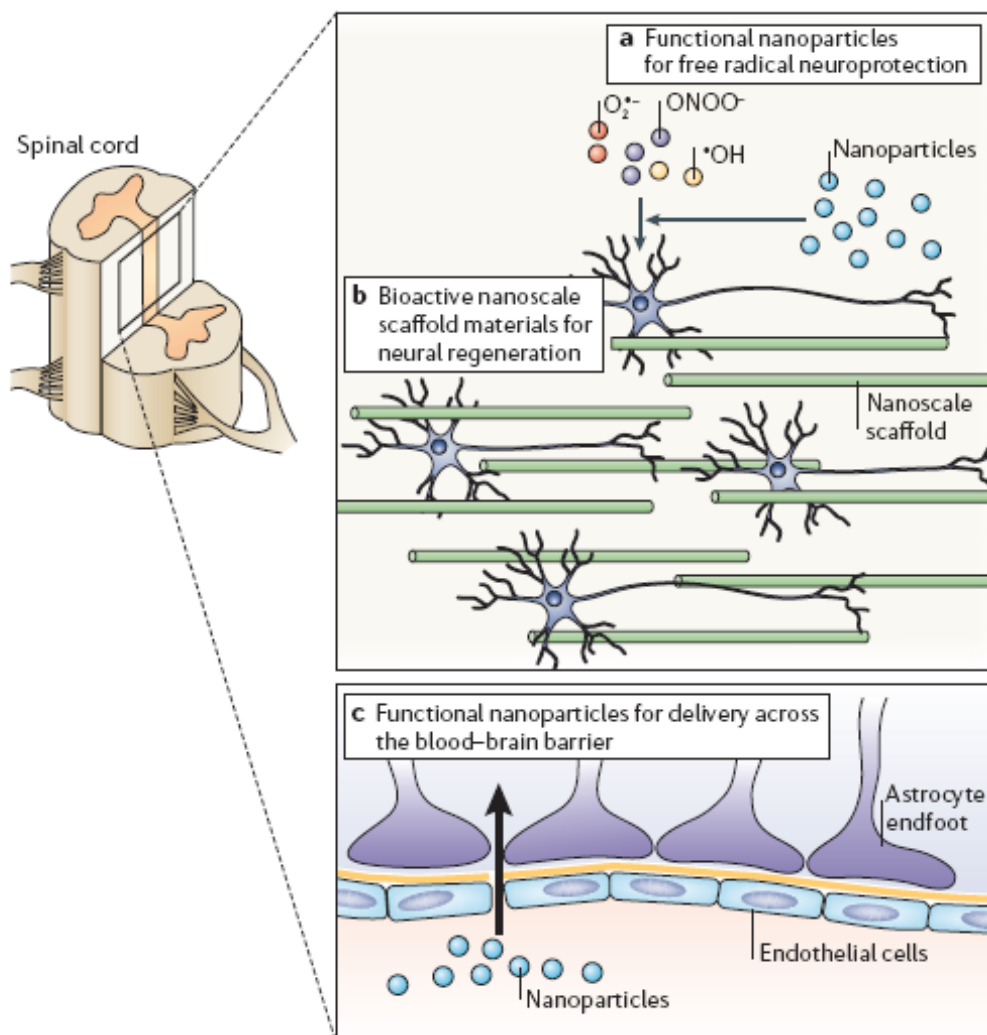
The authors have investigated their therapeutic efficacy on RGC in an optic nerve crush model through single intraperitone injection and compared it with the multiple injections of EPO solution. EPO-loaded PLGA/PLA microspheres showed a stable sustained release profile and significantly promoted RGC survival in optic nerve crush rats for a prolonged period when delivered through an intraperitone injection, showing that this delivery system can be used as an effective drug delivery system for EPO to prevent cell death from neurodegenerative CNS

diseases such as glaucoma in ocular, stroke, and Alzheimer's.

II. Application of micro/nanopharmaceutics in neurology and neurosurgery

The application of nanotechnology in cell biology and physiology enables targeted interactions at a fundamental molecular level. In neuroscience, this entails specific interactions with neurons and glial cells. Examples of current research include technologies that are designed to better interact with neural cells, advanced molecular imaging technologies, materials and hybrid molecules used in neural regeneration, neuroprotection, and targeted delivery of drugs and small molecules across the blood–brain barrier.

Applications of nanotechnology in basic and clinical neuroscience are only in the early stages of development, partly because of the complexities associated with interacting with neural cells and the mammalian nervous system. Despite this, an impressive body of research is emerging that hints at the potential contributions these technologies could make to neuroscience research. Gabriel A. Silva in the following schema has organized the main classes of nano/microtechnology applications in the field of clinical neuroscience [Silva G. A., 2006].



Scheme 3 Applications of nanotechnology in clinical neuroscience a. neuroprotection - limiting the effects of free radicals produced following trauma (for example, those produced by CNS secondary injury mechanisms); b. nanoengineered scaffold materials that mimic the extracellular matrix and provide a physical and/or bioactive environment for neural regeneration. c. Nanoparticles as drug delivery systems for the transport of drugs and small molecules across the blood-brain barrier [Silva G. A. "Neuroscience nanotechnology: progress, opportunities and challenges", 2006, Nature Reviews , Neuroscience, 7]

In the following paragraphs examples representing new frontiers of micro/nanotechnology in clinical neuroscience will be presented.

Kim and his research group have developed a nanoparticle system based on poly(lactic-co-glycolic acid) (PLGA) for methylprednisolone (MP) local delivery at spinal cord injury level;

methylprednisolone is generally used to reduce neurological deficits after acute spinal cord injury [Kim Y. Et al., 2009]. The conclusions of the study presented offer the potential advantages of MP-NP local delivery over conventional systemic delivery are as follows

1) Better therapeutic effect: The sustained and local delivery of MP

demonstrates significantly improved therapeutic effects on the injured spinal cord as compared to systemic MP delivery

2) More efficient, targeted delivery to the injury site (they have used a significantly lower dose of nanoparticle-encapsulated MP avoiding the side effects associated with high doses)

3) The possibility of adjusting the dose and the delivery rate

Wang et al. have performed GDNF (Glial cell line derived neurotrophic factor), which induces neuronal survival and tissue repair after spinal cord injury, encapsulated in PLGA (PLGA-GDNF) nanoparticles and administered by intraspinal injection proximal to the lesion of the injured spinal cord center [Y.C. Wang et al., 2008]. The therapeutic effect of PLGA-GDNF on the injured spinal cord was evaluated by examining the preservation of neurofilament (NF)-stained neuronal fibers and functional recovery using the Basso Beattie Bresnahan (BBB) locomotor rating scale. They have also investigated whether local administration of PLGA-GDNF affected glial activity in the injured spinal cord by immunofluorescence against glial fibrillary acidic protein (GFAP) for reactivated astrocytes, and ionized calcium binding adapter molecule (Iba1), a marker for activated microglia. The main conclusion of this study was that GDNF loaded in PLGA could be continually released and remains bioactive in the injured spinal cord, which in turn induces an increase in neuronal survival and improves better hindlimb locomotion function in spinal cord injured rats.

Another interesting example is given by Etame et al. in their study concerning the influence of the polyethylene glycol (PEG) chain used for covering the Au

nanoparticles on the permeability of brain microvasculature, being already well known that Au nanoparticles may have potential relevance for brain tumor passive targeting [Etame A. B. et al., 2011]. The authors have designed an in-vitro model to mimic the transport-permissive brain microvasculature, demonstrating size-dependent permeation properties with respect to core particle size and PEG chain length. In general short PEG chain length (molecular weight 1000–2000) in combination with smallest core size led to optimum permeation in our model system.

The invasive superficial and ventricular application of chemical or the application of drugs to brain parenchyma represent the main task for delivery at the brain level; the classical administration of drugs generally affect the patient compliance, involves more laborious and requiring specialized skill in order to not produce permanent damage to the brain. In view of these considerations, novel drug delivery systems such as the nanoparticles are being explored for their suitability for targeted brain delivery.

Abattastini et al. developed indomethacin-loaded nanocapsules using indomethacin, poly(ϵ -caprolactone), capric/caprylic triglyceride and sorbitan monostearate [Battastini A.M.O. et col, 2009]. Although indomethacin is not an agent used in the treatment of brain tumors, the study in rats with implanted C6 glioma demonstrated the effectiveness of sub-therapeutic (1 mg/(kg day)) dose of indomethacin-loaded nanocapsules to avert mortality and toxicity, while improving the body weight of treated animals, compared to the control group.

Alzheimer's is a progressive and fatal brain disease and the most common form of dementia. In the last years, it was found

that nanoparticles could serve as efficient carriers of imaging agents for Alzheimer's disease. A recent study have evaluate the release of radiolabeled clioquinol from butyl cyanoacrylate nanoparticles and their efficiency in imaging plaques during tests on animal models with Alzheimer's disease [Kulkarni P., 2007]. Autoradiography images showed localized uptake in brains of experimental animals, and was more pronounced in animals injected with clioquinol- nanoparticles compared to clioquinol itself.

The most malignant type of astrocytoma, glioblastoma, is the most common tumor of the central nervous system. One of the most promising therapeutic solutions for the treatment of human glioblastoma is the polymer nanoparticles–doxorubicin formulation. There are a lot of studies [Jătariu A. N. et al., 2010]. concerning this type of formulation, using different polymers and preparations methods and offering new opportunities for noninvasive chemotherapy of brain tumors.

Conclusions

Micro and nanoparticles represent promising drug carriers for ophthalmic and neurologic applications. The drug release properties depends on the physicochemical properties of the drugs as well as of the nano- and microparticle material and also on the manufacturing process for the particles. Generally, after optimal drug loading within the particles, the ocular bioavailability of many drugs is significantly enhanced in comparison to classical formulations. Also, in the case of neuroscience many drug delivery systems, especially in particulate form were found to be suitable for application in healing after complicated surgery or passing the blood –

brain barrier. The increasing ability to deliver the biologic active principles in a safe and effective way offer new opportunities to treat many of the ophthalmologic and neurologic diseases. The technologies required to deliver agents specifically and effectively to the target organs are rapidly evolving, the next years promise a real progress in therapy for many poorly treated or untreatable diseases.

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