The pathologies involving the posterior segment of the eye are characterized by being devastating and compromising for the eyesight in a large number of subjects. Therefore, it is essential to achieve an early establishment of treatments as well as maintaining efficient concentrations in the area of action for as long as possible. However, the therapeutic efficiency of pharmacological treatments in this area is limited mainly due to the difficulty of the active substance in accessing the target tissues.

At present, different formulations of local and systemic effects are utilized with the aim of achieving efficient concentrations inside the eye. If the topical method is selected, the resistance offered by the cornea, the lens and the hematoaqueous and hematoretinal barriers mean that, in a high number of cases, the level of medication is inefficient in the vitreous, the retina and the choroid. On the other hand, if the oral pathway is selected, access by the drug to the posterior segment from the general bloodflow is very low. These difficulties mean that a direct deposit of the active substance must be made at the site of action or in surrounding areas in order to establish the effect in a quick and efficient manner. Peri- and intra-ocular injections are more effective although they are not free of adverse effects. When intra-vitreous injections are utilized, the treatment generally requires successive administrations in a frequency depending on the intra-vitreous life of the drug. Regardless of the advantages offered by this administration, it is not exempt of risk because the frequency of the injections involves important secondary effects such as cataract, retina detachment, vitreous hemorrhages and endophthalmitis.

The ideal treatment for the pathologies involving the posterior segment would involve a formulation which, in a single application, should initially release an amount of the drug equal to the shock dosage, followed by a slow and gradual release of the active substance for a given period of time. To this end, prolonged action systems are utilized at present such as the «depot» preparations in which the active substance is slower to dissolve and is responsible for the duration of the effect. A typical example of this type of formulation is the triamcinolone injection.

If we resort to controlled release systems, their main advantage is the capacity of releasing the active substance for prolonged periods of time. Within the group of controlled release intra-ocular substances developed to date we have intra-ocular implants, scleral devices, liposomes and micro- and nanoparticles. These systems may be biodegradable depending on the polymer involved. In any case, the bio-material utilized in the preparation thereof must be biocompatible and tolerable.

Within the intra-vitreous devices approved by the FDA for human use we find two non-biodegradable implants, Vitrasert and Retisert™. The former is made of ganciclovir and has been utilized for treating retinitis caused by cytomegalovirus, and the latter is fluocinolone acetonid for treating posterior segment uveitis. Both implants are not biodegradable and therefore it is necessary to withdraw them at the end of the treatment (1).

In the group of controlled release systems in the vitreous (utilizing the sclera), to date we have developments of scleral implants, scleral pins, in situ gellification systems (Pluronic F-127) and bio-
adhesive systems. Scleral implants were designed to be less invasive than intra-ocular injections and are comprised of non-biodegradable polymers [ethyl-vinyl acetate (EVA)] as well as biodegradable polymers [poli-DL-lactic (PLA)]. Therapeutic levels have been achieved with both types of implants with the active substance in the vitreous, retina and choroids, and have therefore been proposed as possibly efficient systems for delivering drugs. If the systems are bio-degradable, they add the advantage of disappearing from the area after producing the desired effect. This is extremely advantageous because it avoids an intervention for extraction.

The «particular» systems are made up by liposomes and micro- and nano-particles. Their main advantages lie in administration with injections and their gradual disappearance because they are prepared on the basis of bio-degradable polymers (2-5).

The intra-ocular administration of liposomes has been the focus of several studies. For instance, cytomegalovirus-induced retinitis has been inhibited in rabbits by means of intra-vitreous injections of liposomes containing a ganciclovir lipidic drug. Similarly, liposomes have been utilized for intra-vitreous administration of oligo-nucleotids in the treatment of eye viral infections such as Herpes simple or cytomegalovirus, finding that these lipidic vesicles were capable of protecting the oligo-nucleotids from degradation by nucleases. However, the intra-vitreous administration of liposomes involves drawbacks such as the appearance of vitreous bodies which gather in the lower part of the eye, with an ensuing VA reduction. These bodies tend to disappear between 14 and 21 days after administration. Even though liposomes are highly advantageous, they exhibit other disadvantages which restrict their therapeutic utilization, such as reduced shelf life and low stability of biological fluids, which may produce premature releases of the active principle.

At present, colloidal suspensions of polymeric micro- and nanoparticle are the systems having the highest degree of innovation and versatility. The differences between these particles lies in the size, with micro-particles having sizes above 1 µm while nanoparticles have sizes below that value. The most widely used polymers for manufacturing micro- and nanoparticles for intra-ocular administration are derived from lactic-glycolic acid. These polymers are accepted by the Food and Drug Administration (FDA) for use in humans, and have been utilized for a number of years as suture materials. Microparticles, more specifically microspheres, have been developed in ophthalmologic therapeutics for treating a range of pathologies. For instance, Adriamycin, 5-fluoracile (5-FU) and retinoic acid microspheres have been developed for treating proliferative vitreoretinopathy; dexametasone microspheres for preventing uveitis after surgical procedures, acyclovir microspheres for treating retinal necrosis, and ganciclovir microspheres for cytomegalovirus-induced retinitis. The intra-ocular administration of microspheres is carried out with the injection of a suspension thereof with a needle having a diameter selected according to the particle size. The most widely utilized diameters are between 25-30G for particle sizes between 1 and 50 micrometers, and 18G for particles up to 500 micrometers.

Sterility is a critical factor for intra-ocular administration systems, with a final product sterilization process being preferred to manufacture in sterile conditions. However, some polymers (such as those derived from lactic and glycolic acid) are vulnerable to most of the usual sterilization methods (involving heat and ethylene oxide). A few years ago the first works were published on the use of a method based on ionizing radiation with gamma rays for sterilizing microspheres for parenteral use. Gamma rays have a high penetration capacity, and the necessary dosage for achieving sterilization is comprised between 25 and 20 kGy. A broad range of materials are compatible with gamma radiation sterilization, which has facilitated the acceptance of this method for sterilizing polymeric materials including polyethylene, polyessters, polystyrenes, polysulfoxides and polycarbonates. This sterilization method is generally used for heat-sensitive health products and the most adequate for this type of formulations, mainly due to its high penetration capacity, low chemical reactivity, low residue levels, small temperature changes in the sample and low amount of variables to be controlled during the process. However, the dosage which ensures the sterility of a drug (25 kGy, over-sterilization dosage described in the Spanish and American Pharmacopeia) generates a significant reduction in the polymer’s molecular weight and therefore has a considerable effect on the properties of the end product. This problem seems to have been resolved by the utilization of low temperatures during microparticle exposure to gamma radiation. To this drawback we must add the possibility that the physical and che-
mical properties of the active substance could also be altered by said exposure.

Although a great deal of progress has been made in this field, none of the above described systems is fully satisfactory, and the intra-ocular administration of drugs is demanding the development of formulations and new materials having more advanced properties than their predecessors. An essential requirement is that the material utilized as release modulator and its degradation products must be highly biocompatible and free of toxicity. In addition, it must have characteristics allowing for the inclusion of active substance of different types, with the added ability of releasing these in a controlled manner in the posterior segment of the eye.

REFERENCES