Resumen

En la actualidad existen numerosos fármacos con excelentes propiedades biológicas, capaces de actuar eficientemente una vez que hayan alcanzado el sitio de acción de interés, dando un tratamiento adecuado a la correspondiente patología. Sin embargo, las propiedades fisicoquímicas de muchos de ellos dificultan la vehiculización, direccionamiento y en último término, la biodisponibilidad de la sustancia activa en el sitio de acción, comprometiendo la eficacia y seguridad del tratamiento.

La farmacotecnia moderna se enfrenta a una serie de dificultades generalmente relacionadas a la baja solubilidad, inestabilidad, biodisponibilidad errática, irritación o necesidad de altas dosis de fármaco; haciendo necesario el diseño de estrategias de formulación que superen estas propiedades adversas. Una alternativa interesante es el diseño de sistemas portadores de fármacos, que constituyan plataformas capaces de superar muchos de los problemas antes mencionados. La investigación y desarrollo en esta área de las Ciencias Farmacéuticas es un campo de marcado interés científico, tecnológico y económico.

En este sentido, las formas farmacéuticas de uso ocular tradicionales, (tales como soluciones, suspensiones y ungüentos) presentan serias limitaciones, las cuales llevan a una disminución de la capacidad terapéutica en un gran número de patologías oculares. Uno de los factores determinantes que interviene en este detrimento es la pérdida rápida y extensiva de la formulación en el área precorneal en virtud del drenaje, el parpadeo y el recambio lagrimal. Por otra parte, las formas farmacéuticas inyectables perioculares como las subconjuntivales y retrobulbares no proporcionan niveles adecuados de fármaco. Finalmente, técnicas de naturaleza más invasiva como las inyecciones intravítreas o intracamerales pueden producir serias complicaciones intraoculares, por lo tanto se reservan para situaciones especiales (retinitis por citomegalovirus, intolerancia al tratamiento endovenoso, retinopatía diabética, degeneración macular húmeda, etc.)

Teniendo en cuenta lo anteriormente expuesto, se propuso como alternativa a las terapias tradicionales de uso oftálmico una plataforma bioadhesiva de aplicación tópica ocular obtenida a partir de polímeros de origen natural modificados estructuralmente. Esto permitió encontrar opciones alternativas a las limitaciones que presentan las formas farmacéuticas convencionales para dar respuesta a diversas patologías oftalmológicas en virtud de las características anatomofisiológicas que presenta el ojo.

En el presente trabajo de tesis se ha explorado exitosamente la obtención y caracterización de nuevos materiales y sistemas bioadhesivos portadores de fármacos (films y comprimidos), con potencial utilidad como plataformas farmacoterapéuticas. En ese sentido se abarcó la modificación química del material base seleccionado (ácido hialurónico) mediante reacciones de entrecruzamiento con glutaraldehído y polietilenglicol diglicidil éter, para otorgarle propiedades mecánicas y bioadhesivas adecuadas. Posteriormente se caracterizaron los materiales obtenidos en cuanto a sus propiedades fisicomecánicas y biofarmacéuticas, incluyendo liberación de fármacos, estudios de toxicidad y eficacia en cultivos celulares y modelos animales.

Abstract

Today many drugs capable of acting efficiently once they have reached the site of interest to give adequate treatment to a specific pathology are available. However, the physicochemical properties of some of these drugs difficult their vehiculization affecting the efficiency and safety of the pharmaceutical treatments.

Modern pharmacology faces a number of difficulties generally related to the low solubility, instability, erratic bioavailability, irritation or the need of high doses of drugs, requiring the design of formulation strategies to overcome these adverse properties. An interesting alternative is the design drug of carrier platforms capable of overcoming many of the aforementioned problems. Research and development in this area of Pharmaceutical Sciences is a field of important scientific, technological and economic interest.

In this sense, traditional dosage forms of ocular use, such as solutions, suspensions and ointments have serious limitations, which lead to a reduction of their therapeutic capacity in a large number of eye disorders. One of the factors involved in this reduction is the rapid and extensive loss of the formulation in the precorneal area due to drainage, blinking and tear replacement. Moreover, periocular injectable dosage forms such as subconjunctival and retrobulbar applications do not release adequate levels of drug. Finally, more invasive techniques such as intravitreal or intracameral injections can cause serious intraocular complications. For this reason they are set aside for special situations (cytomegalovirus retinitis, intolerance to endovenous treatment, diabetic retinopathy, wet macular degeneration, etc.)

Considering the limitations of conventional dosage forms to face diverse eye diseases two alternative methods to ophthalmic traditional therapies are proposed in the present thesis. The preparation and characterization of new materials and drug carrier bioadhesive systems in the form of films and tablets with potential utility as pharmacotherapeutic platforms is explored. These platforms are synthesized by crosslinking hyaluronic acid with glutaraldehyde and polyethylene

glycol diglycidyl ether in the presence of itaconic acid. New materials with suitable mechanical and bioadhesive properties were obtained and characterized in terms of their physicomechanical and biopharmaceuticals properties including drug delivery capacity, toxicity and efficacy studies in cell culture and animal models.

1.4 Bibliografía

Belmonte, C., Simon, J., & Gallego, A. (1971). Effects of Intraocular Pressure Changes on the Afferent Activity of Ciliary Nerves. *Experimental Eye Research*, *12*(3), 342–355.

Bito, L. Z., & Salvador, E. V. (1972). Intraocular Fluid Dynamics . III . The Site and Mechism of Prostaglandin Transfer across the Blood Intraocular Fhdd Barriers *. *Experimental Eye Research*, *14*(3), 233–241.

Daar, A. S., Thorsteinsdóttir, H., Martin, D. K., Smith, A. C., Nast, S., & Singer, P. A. (2002). Top ten biotechnologies for improving health in developing countries. *Nature Genetics*, *32*(2), 229 – 232.

Dey, S., Patel, J., Anand, B. S., Jain-Vakkalagadda, B., Kaliki, P., Pal, D., … Mitra, A. K. (2003). Molecular Evidence and Functional Expression of P-Glycoprotein (MDR1) in Human and Rabbit Cornea and Corneal Epithelial Cell Lines. *Investigative Ophthalmology & Visual Science*, *44*(7), 2909–2918. doi:10.1167/iovs.02-1142

Ding, S. (1998). Recent developments in ophthalmic drug delivery. *Pharmaceutical Science & Technology Today*, *1*(8), 328–335.

Engstrom, R. E., & Holland, G. N. (1995). Local therapy for cytomegalovirus retinopathy. *American Journal of Ophthalmology*, *120*(3), 376–385.

Farmacopea Nacional Argentina. (2003) (7th ed.).

Gallego, R., & Belmonte, C. (1974). Nervous Efferent Activity in the Ciliary Nerves Related to Intraocular Pressure Changes. *Experimental Eye Research*, *19*(4), 331–334.

John Park, D. J., & Karesh, J. (2006). Topographic Anatomy of the Eye: An Overview. In W. Tasman & E. A. Jaeger (Eds.), *Duane's Foundations of Clinical Ophthalmology*. Philadelphia: Lippincott Williams & Wilkins.

Kawazu, K., Yamada, K., Nakamura, M., & Ota, A. (1999). Characterization of Cyclosporin A Transport in Cultured Rabbit Corneal Epithelial Cells: P-Glycoprotein Transport Activity and Binding to Cyclophilin. *Investigative Ophthalmology & Visual Science*, *40*(8), 1738–1744.

Krakau, C. E. T., & Wilke, K. (1974). Effects of Loading of the Eye on the Intraocular Pressure and on the Episcleral Venous Pressure. *Acta Ophthalmologica*, *52*(1), 107-124.

Maurice, D. (1995). The Effect of the Low Blink Rate in Rabbits on Topical Drug Penetration. *Journal of Ocular Pharmacology and Therapeutics*, *11*(3), 297–304. doi:10.1089/jop.1995.11.297

Norn, M. S. (1965). Tear secretion in normal eyes. Estimated by a new method: The lacrimal streak dilution test. *Acta Ophthalmologica*, *43*(4), 567–573. doi:10.1111/j.1755-3768.1965.tb03693.x

Patton, T. F., & Robinson, J. R. (1976). Quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eyes. *Journal of Pharmaceutical Sciences*, *65*(9), 1295–1301. doi:10.1002/jps.2600650909

Qureshi, K., Kashani, S., & Kelly, S. P. (2009). Intracameral bevacizumab for rubeotic glaucoma secondary to retinal vein occlusion. *International Ophthalmology*, *29*(6), 537–539. doi:10.1007/s10792-008-9262-y

Records, R. E. (2005). The tear film. In W. Tasman & E. A. Jaeger (Eds.), *Duane's Foundations of Clinical Ophthalmology*. Philadelphia: Lippincott Williams & Wilkins.

Saha, P., Yang, J., & Lee, V. (1998). Existence of a p-glycoprotein drug efflux pump in cultured rabbit conjunctival epithelial cells. *Investigative Ophthalmology & Visual Science*, *39*(7), 1221–1226.

Smolek, M. K., & Klyce, S. D. (2006). Cornea. In William Tasman & E. A. Jaeger (Eds.), *Duane's Foundations of Clinical Ophthalmology*. Philadelphia: Lippincott Williams & Wilkins.

Snell, R. S., & Lemp, M. A. (1998). *Clinical Anatomy of the Eye* (2nd ed.). Oxford: Wiley. doi:10.1002/9781118690987

Tártara, L. I. (2013). *Efecto del sistema portador sobre la biodisponibilidad intraocular de farmacos*. Universidad Nacional del Córdoba.

Wilson, C. G., Semenova, E. M., Hughes, P. M., & Olejnik, O. (2007). Eye Structure and Physiological Functions. In E. Touitou & B. W. Barry (Eds.), *Enhancement in Drug Delivery* (pp. 473–487). CRC Press.

2.5 Bibliografía

Herper, M. (2013). The Cost Of Creating A New Drug Now $5 Billion, Pushing Big Pharma To Change. *Forbes*.

Palmer, E. (2012). FDA Approvals of 2012. *Fierce Biotech*. Retrieved from http://www.fiercebiotech.com/slideshows/fda-approvals-2012.

3.3 Bibliografía

Chickering III, D. E., & Mathiowitz, E. (2013). Definitions, mechanisms, and theories of bioadhesion. In E. Mathiowitz, D. E. Chickering III, & C.-M. Lehr (Eds.), *Bioadhesive drug delivery systems: Fundamentals, novel approaches, and development* (pp. 1–10). CRC Press.

Derjaguin, B. ., Toporov, Y. ., Muller, V. ., & Aleinikova, I. . (1977). On the relationship between the electrostatic and the molecular component of the adhesion of elastic particles to a solid surface. *Journal of Colloid and Interface Science*, *58*(3), 528–533.

Duchêne, D., & Ponchel, G. (1997). Bioadhesion of solid oral dosage forms, why and how? *European Journal of Pharmaceutics and Biopharmaceutics*, *44*(1), 15–23.

Esposito, P., Colombo, I., & Lovrecich, M. (1994). Investigation of surface properties of some polymers by a thermodynamic and mechanical approach: possibility of predicting mucoadhesion and biocompatibility. *Biomaterials*, *15*(3), 177–182.

Gu, J. M., Robinson, J. R., & Leung, S. H. (1988). Binding of acrylic polymers to mucin/epithelial surfaces: structure-property relationships. *Critical Reviews in Therapeutic Drug Carrier Systems*, *5*(1), 21–67.

Lehr, C.-M., Boddé, H. E., Bouwstra, J. A., & Junginger, H. E. (1993). A surface energy analysis of mucoadhesion II. Prediction of mucoadhesive performance by spreading coefficients. *European Journal of Pharmaceutical Sciences*, *1*(1), 19–30. doi:10.1016/0928-0987(93)90014-2

Lehr, C.-M., & Haas, J. (2002). Developments in the area of bioadhesive drug delivery systems. *Expert Opinion on Biological Therapy*, *2*(3), 287–298. doi:10.1517/14712598.2.3.287

Llabot, J. M. (2007). *Sistemas Bioadhesivos de Administración de Fármacos*. Universidad Nacional de Córdoba.

Rodríguez, I. C., Cerezo, A., & Salem, I. I. (2000). Bioadhesive delivery systems. *Ars Pharmaceutica*, *1*(41), 115–128.

Salamat-Miller, N., Chittchang, M., & Johnston, T. P. (2005). The use of mucoadhesive polymers in buccal drug delivery. *Advanced Drug Delivery Reviews*, *57*(11), 1666–1691.

Shojaei, A. H., & Li, X. (1997). Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monomethylether monomethacrylate. *Journal of Controlled Release*, *47*(2), 151–161.

Smart, J. D. (2005). The basics and underlying mechanisms of mucoadhesion. *Advanced Drug Delivery Reviews*, *57*(11), 1556–1568.

Vasir, J. K., Tambwekar, K., & Garg, S. (2003). Bioadhesive microspheres as a controlled drug delivery system. *International Journal of Pharmaceutics*, *255*(1-2), 13–32.

4.3 Bibliografía

Akasaka, H., Komasaki, H., & Arai, T. (1989). Fermentation method for producing hyaluronic acid. U.S. Patent 4801539.

Ali, M., & Byrne, M. E. (2009). Controlled Release of High Molecular Weight Hyaluronic Acid from Molecularly Imprinted Hydrogel Contact Lenses. *Pharmaceutical Research*, *26*(3), 714–726. doi:10.1007/s11095-008-9818-6

Ambrosio, L., Borzacchiello, A., Netti, P. A., & Nicolais, L. (1999). Rheological study on hyaluronic acid and its derivative solutions. *Journal of Macromolecular Science - Pure and Applied Chemistry*, *36*(7-8), 991–1000.

Anders, R., & Merkle, H. P. (1989). Evaluation of laminated muco-adhesive patches for buccal drug delivery. *International Journal of Pharmaceutics*, *49*(3), 231–240.

Avila, L. Z., Gianolio, D. A., Konowicz, P. A., Philbrook, M., Santos, M. R., & Miller, R. J. (2008). Drug delivery and medical applications of chemically modified hyaluronan. In H. G. Garg, M. K. Cowman, & C. A. Hales (Eds.), *Carbohydrate Chemistry, Biology and Medical Applications* (pp. 333–357). Elsevier Science.

Avitabile, T., Marano, F., Castiglione, F., Bucolo, C., Cro, M., Ambrosio, L., Ferrauto C., Reibaldi, A. (2001). Biocompatibility and biodegradation of intravitreal hyaluronan implants in rabbits. *Biomaterials*, *22*(3), 195–200.

Balazs, E. A., & Denlinger, J. L. (1993). Viscosupplementation: a new concept in the treatment of osteoarthritis. *The Journal of Rheumatology. Supplement*, *39*, 3–9.

Balazs, E. A., & Gibbs, D. A. (1970). The rheological properties and biological function of hyaluronic acid. In *Chemistry and Molecular Biology of the Intercellular Matrix* (pp. 1241–1253). New York: Academic Press.

Berry, M., Pastis, W., Ellingham, R., Frost, L., Corfield, A., & Easty, D. (1998). Hyaluronan in dry eye and contact lens wearers. *Advances in Experimental Medicine and Biology*, *438*, 785–790.

Bogdansky, S. (1990). Natural Polymers as Drug Delivery Systems. In M. Chasin & R. Langer (Eds.), *Biodegradable Polymers as Drug Delivery Systems* (pp. 231–259). New York: Marcel Dekker, Inc.

Borzacchiello, A., Mayol, L., Gärskog, O., Dahlqvist, A., & Ambrosio, L. (2005). Evaluation of injection augmentation treatment of hyaluronic acid based materials on rabbit vocal folds viscoelasticity. *Journal of Materials Science: Materials in Medicine*, *16*(6), 553–557. doi:10.1007/s10856-005-0531-2

Brown, M. B., & Jones, S. A. (2005). Hyaluronic acid : a unique topical vehicle for the localized delivery of drugs to the skin. *Journal of the European Academy of Dermatology and Venereology*, *19*(3), 308–318.

Calles, J. A., Ressia, J. A., Llabot, J. M., Chetoni, P., Palma, S. D., & Vallés, E. M. (2011). Improved Properties of Cross-Linked Sodium Hyaluronate Films. In *Proceedings of the European Polymer Congress* (p. 1318). Granada.

Cantor, J. O., & Nadkarni, P. P. (2006). Hyaluronan: The Jekyll and Hyde Molecule. *Inflammation & Allergy-Drug Targets*, *5*(4), 257–260.

Chen, W. Y. J., & Abatangelo, Gi. (1999). Functions of hyaluronan in wound repair. *Wound Repair and Regeneration*, *7*(2), 79–89.

Collins, M. N., & Birkinshaw, C. (2007). Comparison of the Effectiveness of Four Different Crosslinking Agents with Hyaluronic Acid Hydrogel Films for Tissue-Culture Applications. *Journal ofApplied Polymer Science*, *104*(5), 3183–3191. doi:10.1002/app.25993

Crescenzi, V., Francescangeli, A., Capitani, D., Mannina, L., Renier, D., & Bellini, D. (2003). Hyaluronan networking via Ugi's condensation using lysine as cross-linker diamine. *Carbohydrate Polymers*, *53*(3), 311–316. doi:10.1016/S0144-8617(03)00079-1

Davies, A., Gormally, J., & Wyn-Jones, E. (1982). A study of hydration of sodium hyaluronate from compressibility and high precision densitometric measurements. *International Journal of Biological Macromolecules*, *4*(7), 436–438.

De Laco, P. A., Stefanetti, M., Pressato, D., Piana, S., Donà, M., Pavesio, A., & Bovicelli, L. (1998). A novel hyaluronan-based gel in laparoscopic adhesion prevention: preclinical evaluation in an animal model. *Fertility and Sterility*, *69*(2), 318–23.

Florey, K. (1987). *Analytical Profiles of Drug Substances Volume 16*. *Analytical Profiles of Drug Substances* (Vol. 16). Orlando: Academic Press, Inc.

Fonn, D. (2007). Targeting Contact Lens Induced Dryness and Discomfort : What Properties Will Make Lenses. *Optometry and Vision Science*, *84*(4), 279–285.

Frescura, M., Berry, M., Corfield, A., Carrington, S., & Easty, D. (1994). Evidence of hyaluronan in human tears and secretions of conjunctival cultures. *Biochemical Society Transactions*, *22*(2), 228S.

Fukuda, M., Miyamoto, Y., Miyara, Y., Mishima, H., & Otori, T. (1996). Hyaluronic acid concentration in human tear fluids. *Investigative Ophthalmology and Visual Science*, *37*(5), S848.

Girish, K. S., & Kemparaju, K. (2007). The magic glue hyaluronan and its eraser hyaluronidase : A biological overview. *Life Sciences*, *80*(21), 1921 – 1943.

Gomes, J. A. P., Amankwah, R., Powell-Richards, A., & Dua, H. S. (2004). Sodium hyaluronate (hyaluronic acid) promotes migration of human corneal epithelial cells in vitro. *British Journal of Ophthalmology*, *88*(6), 821–825.

Gurtler, F., & Gurny, R. (1995). Patent Literature Review of Ophthalmic Inserts. *Drug Development and Industrial Pharmacy*, *21*(1), 1–18.

Hamano, T., Horimoto, K., Lee, M., & Komemushi, S. (1996). Sodium hyaluronate eyedrops enhance tear film stability. *Japanese Journal of Ophthalmology*, *40*(1), 62–65.

Hargittai, I., & Hargittai, M. (2008). Molecular structure of hyaluronan : an introduction. *Structural Chemistry*, *19*(5), 697–717. doi:10.1007/s11224-008-9370-3

He, M., Zhao, Z., Yin, L., Tang, C., & Yin, C. (2009). Hyaluronic acid coated poly(butyl cyanoacrylate) nanoparticles as anticancer drug carriers. *International Journal of Pharmaceutics*, *373*(1-2), 165–173.

Inoue, M., & Katakami, C. (1993). The effect of hyaluronic acid on corneal epithelial cell proliferation. *Investigative Ophthalmology & Visual Science*, *34*(7), 2313–2315.

Itoi, M., Kim, O., Kimura, T., Kanai, A., Momose, T., Kanki, K., … Komemushi, S. (1995). Effect of sodium hyaluronate ophthalmic solution on peripheral staining of rigid contact lens wearers. *CLAO Journal*, *21*(4), 261–264.

Jeong, B., Bae, Y. H., Lee, D. S., & Kim, S. W. (1997). Biodegradable block copolymers as injectable drug-delivery systems. *Nature*, *388*(6645), 860–862.

Jinghua, C., Jingtao, C., Zheng, X., & Qisheng, G. (2008). Characteristic of hyaluronic acid derivative films cross-linked by polyethylene glycol of low water content. *Journal of Medical Colleges of PLA*, *23*(1), 15–19.

Johnson, M. E., & Murphy, P. J. (2006). Effectiveness of sodium hyaluronate eyedrops in the treatment of dry eye. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *244*(1), 109–112. doi:10.1007/s00417-005-0028-1

Jones, D. S., & Medlicott, N. J. (1995). Casting solvent controlled release of chlorhexidine from ethylcellulose films prepared by solvent evaporation. *International Journal of Pharmaceutics*, *114*(2), 257–261.

Jones, L., Mann, A., Evans, K., Franklin, V., & Tighe, B. (2000). An in vivo comparison of the kinetics of protein and lipid deposition on group II and group IV frequent-replacement contact lenses. *Optometry & Vision Science*, *77*(10), 503–510.

Jong, C., Stolwijk, T., Kuppens, E., Keizer, R., & Van Best, J. (1994). Topical timolol with and without benzalkonium chloride: epithelial permeability and autofluorescence of the cornea in glaucoma. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *232*(4), 221–224. doi:10.1007/BF00184009

Kim, M. R., & Park, T. G. (2002). Temperature-responsive and degradable hyaluronic acid/Pluronic composite hydrogels for controlled release of human growth hormone. *Journal of Controlled Release*, *80*(1-3), 69–77.

Laurent, T. C., Hellsing, K., & Gelotte, B. (1964). Cross-linked Gels of Hyaluronic Acid. *Acta Chemica Scandinavica*, *18*(1), 274–275.

Laurent, U. B. G., & Reed, R. K. (1991). Turnover of hyaluronan in the tissues. *Advanced Drug Delivery Reviews*, *7*(2), 237–256. doi:10.1016/0169-409X(91)90004-V

Le Bourlais, C., Acar, L., Zia, H., Sado, P. A., Needham, T., & Leverge, R. (1998). Ophthalmic drug delivery systems—Recent advances. *Progress in Retinal and Eye Research*, *17*(1), 33–58.

Leach, J. B., & Schmidt, C. E. (2005). Characterization of protein release from photocrosslinkable hyaluronic acid-polyethylene glycol hydrogel tissue engineering scaffolds. *Biomaterials*, *26*(2), 125–135.

Lee, H., Mok, H., Lee, S., Oh, Y.-K., & Park, T. G. (2007). Target-specific intracellular delivery of siRNA using degradable hyaluronic acid nanogels. *Journal of Controlled Release*, *119*(2), 245–252.

Lee, J. Y., & Spicer, A. P. (2000). Hyaluronan: a multifunctional, megaDalton, stealth molecule. *Current Opinion in Cell Biology*, *12*(5), 581–586.

Lehr, C.-M., & Haas, J. (2002). Developments in the area of bioadhesive drug delivery systems. *Expert Opinion on Biological Therapy*, *2*(3), 287–298. doi:10.1517/14712598.2.3.287

Lerner, L. E., Schwartz, D. M., Hwang, D. G., Howes, E. L., & Stern, R. (1998). Hyaluronan and CD44 in the Human Cornea and Limbal Conjunctiva. *Experimental Eye Research*, *67*(4), 481–484.

Li, H., Liu, Y., Shu, X. Z., Gray, S. D., & Prestwich, G. D. (2004). Synthesis and biological evaluation of a cross-linked hyaluronan-mitomycin C hydrogel. *Biomacromolecules*, *5*(3), 895–902. doi:10.1021/bm034463j

Luo, Y., Kirker, K. R., & Prestwich, G. D. (2000). Cross-linked hyaluronic acid hydrogel films: new biomaterials for drug delivery. *Journal of Controlled Release*, *69*(1), 169–84.

Luten, J., Nostrum, C. F. van, Smedt, S. C. De, & Hennink, W. E. (2008). Biodegradable polymers as non-viral carriers for plasmid DNA delivery. *Journal of Controlled Release*, *126*(2), 97–110.

Maltese, A., Borzacchiello, A., Mayol, L., Bucolo, C., Maugeri, F., Nicolais, L., & Ambrosio, L. (2006). Novel polysaccharides-based viscoelastic formulations for ophthalmic surgery : Rheological characterization. *Biomaterials*, *27*(29), 5134–5142. doi:10.1016/j.biomaterials.2006.05.036

Matarasso, S. L. (2004). Understanding and using hyaluronic acid. *Aesthetic Surgery Journal*, *24*(4), 361–364.

Milas, M., & Rinaudo, M. (2004). Characterization and Properties of Hyaluronic Acid (Hyaluronan). In Severian Dumitriu (Ed.), *Polysaccharides Structural Diversity and Functional Versatility* (Second Edi., pp. 535–549). New York: CRC Press. doi:10.1201/9781420030822.ch22

Miyauchi, S., Sugiyama, T., & Machida, A. (1993). A 26-week ophthalmic instillation test of sodium hyaluronate in rabbits. *Pharmacometrics*, *46*(5), 317–328.

Moriyama, K., Ooya, T., & Yui, N. (1999). Hyaluronic acid grafted with poly(ethylene glycol) as a novel peptide formulation. *Journal of Controlled Release*, *59*(1), 77–86.

Murray, C., Zloty, D., & Warshawski, L. (2005). The evolution of soft tissue fillers in clinical practice. *Dermatologic Clinics*, *23*(2), 343–363.

Nagelhout, T. J., Gamache, D. A., Roberts, L., Brady, M. T., & Yanni, J. M. (2005). Preservation of tear film integrity and inhibition of corneal injury by dexamethasone in a rabbit model of lacrimal gland inflammation-induced dry eye. *Journal of Ocular Pharmacology and Therapeutics*, *21*(2), 139–148.

Nakamura, M., Hikida, M., Nakano, T., Ito, S., Hamano, T., & Kinoshita, S. (1993). Characterization of water retentive properties of hyaluronan. *Cornea*, *12*(5), 433–436.

Nakamura, M., Sato, N., Chikama, T.-I., Hasegawa, Y., & Nishida, T. (1997). Hyaluronan Facilitates Corneal Epithelial Wound Healing in Diabetic Rats. *Experimental Eye Research*, *64*(6), 1043–1050.

Nishida, T., Nakamura, M., Mishima, H., & Otori, T. (1991). Hyaluronan stimulates corneal epithelial migration. *Experimental Eye Research*, *53*(6), 753–758.

Noecker, R. (2001). Effects of common ophthalmic preservatives on ocular health. *Advances in Therapy*, *18*(5), 205–215. doi:10.1007/BF02853166

O'Regan, M., Martini, I., Crescenzi, F., De Luca, C., & Lansing, M. (1994). Molecular mechanisms and genetics of hyaluronan biosynthesis. *International Journal of Biological Macromolecules*, *16*(6), 283–286.

Oh, E. J., Park, K., Kim, K. S., Kim, J., Yang, J.-A., Kong, J.-H., … Hahn, S. K. (2010). Target specific and long-acting delivery of protein, peptide, and nucleotide therapeutics using hyaluronic acid derivatives. *Journal of Controlled Release*, *141*(1), 2–12.

Okamoto, H., Taguchi, H., Iida, K., & Danjo, K. (2001). Development of polymer film dosage forms of lidocaine for buccal administration: I. Penetration rate and release rate. *Journal of Controlled Release*, *77*(3), 253–260.

Pfister, R. R., & Burstein, N. (1976). The effects of ophthalmic drugs, vehicles, and preservatives on corneal epithelium: a scanning electron microscope study. *Investigative Ophthalmology & Visual Science*, *15*(4), 246–259.

Polack, F. M. (1986). Healon(R) (Na Hyaluronate): A Review of the Literature. *Cornea*, *5*(2), 81–94.

Prabhasawat, P., Tesavibul, N., & Kasetsuwan, N. (2007). Performance profile of sodium hyaluronate in patients with lipid tear deficiency: randomised, double-blind, controlled, exploratory study. *British Journal of Ophthalmology*, *91*(1), 47–50. doi:10.1136/bjo.2006.097691

Presti, D., & Scott, J. (1994). Hyaluronan-mediated protective effect against cell damage caused by enzymatically produced hydroxyl (OH.) radicals is dependent on hyaluronan molecular mass. *Cell Biochemistry and Function*, *12*(4), 281–288.

Prestwich, G. D. (2001). Biomaterials from Chemically-Modified Hyaluronan. *Hyaluronan Today*.

Pustorino, R., Nicosia, R., Sessa, R., Santino, I., Dastoli, F., Bonci, E., … Izzo, G. (1996). Effect of bovine serum, hyaluronic acid and netilmicine on the in vitro adhesion of bacteria isolated from human-worn disposable soft contact lenses. *Annali Di Igiene: Medicina Preventiva E Di Comunita*, *8*(4), 469–475.

Robert, L., Robert, A.-M., & Renard, G. (2010). Biological effects of hyaluronan in connective tissues, eye, skin, venous wall. Role in aging. *Pathologie Biologie*, *58*(3), 187–198.

Salk, R. S., Chang, T. J., D'Costa, W. F., Soomekh, D. J., & Grogan, K. A. (2006). Sodium Hyaluronate in the Treatment of Osteoarthritis of the Ankle: A Controlled, Randomized, Double-Blind Pilot Study. *The Journal of Bone & Joint Surgery*, *88*(2), 295–302. doi:10.2106/JBJS.E.00193

Sand, B. B., Marner, K., & Norn, M. S. (1989). Sodium hyaluronate in the treatment of keratoconjunctivitis sicca. *Acta Ophthalmologica*, *67*(2), 181–183.

Scott, J. E. (1995). Extracellular matrix, supramolecular organisation and shape. *Journal of Anatomy*, *187*(Pt 2), 259–269.

Scott, J. E., Cummings, C., Brasst, A., & Chen, Y. (1991). Secondary and tertiary structures of hyaluronan in aqueous solution , investigated by rotary shadowing-electron microscopy and computer simulation. *Biochemical Journal*, *274*(Pt 3), 699–705.

Segura, T., Chung, P. H., & Shea, L. D. (2005). DNA delivery from hyaluronic acid-collagen hydrogels via a substrate-mediated approach. *Biomaterials*, *26*(13), 1575–1584.

Shu, X. Z., & Prestwich, G. D. (2004). Therapeutic Biomaterials from Chemically Modified Hyaluronan. In H. G. Garg & C. A. Hales (Eds.), *Chemistry and Biology of Hyaluronan* (pp. 475–504). Elsevier Ltd.

Stern, R., Kogan, G., Jedrzejas, M. J., & Soltés, L. (2007). The many ways to cleave hyaluronan. *Biotechnology Advances*, *25*(6), 537–57.

Strand, V., Conaghan, P. G., Lohmander, L. S., Koutsoukos, A. D., Hurley, F. L., Bird, H., … Band, P. A. (2006). An integrated analysis of five double-blind, randomized controlled trials evaluating the safety and efficacy of a hyaluronan product for intra-articular injection in osteoarthritis of the knee. *Osteoarthritis and Cartilage*, *14*(9), 859–866. doi:10.1016/j.joca.2006.02.012

Stuart, J. C., & Linn, J. G. (1985). Dilute sodium hyaluronate (Healon) in the treatment of ocular surface disorders. *Annals of Ophthalmology*, *17*(3), 190–192.

Tomihata, K., & Ikada, Y. (1997a). Crosslinking of Hyaluronic Acid with Glutaraldehyde. *Journal of Polymer Science: Part A: Polymer Chemistry*, *35*(16), 3553–3559.

Tomihata, K., & Ikada, Y. (1997b). Preparation of cross-linked hyaluronic acid films of low water content. *Biomaterials*, *18*(3), 189–195.

Van Beek, M., Jones, L., & Sheardown, H. (2008). Hyaluronic acid containing hydrogels for the reduction of protein adsorption. *Biomaterials*, *29*(7), 780–789. doi:10.1016/j.biomaterials.2007.10.039

Van Beek, M., Weeks, A., Jones, L., & Sheardown, H. (2008). Immobilized hyaluronic acid containing model silicone hydrogels reduce protein adsorption. *Journal of Biomaterials Science, Polymer Edition*, *19*(11), 1425–1436.

Vercruysse, K. P., & Prestwich, G. D. (1998). Hyaluronate derivatives in drug delivery. *Critical Reviews in Therapeutic Drug Carrier Systems*, *15*(5), 513–555.

Widner, B., Behr, R., Von Dollen, S., Tang, M., Heu, T., Sloma, A., … Brown, S. (2005). Hyaluronic Acid Production in Bacillus subtilis. *Applied and Environmental Microbiology*, *71*(7), 3747–3752.

Witteveen, A. G. H., Sierevelt, I. N., Blankevoort, L., Kerkhoffs, G. M. M. J., & van Dijk, C. N. (2010). Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: Effects, safety and dose dependency. *Foot and Ankle Surgery*, *16*(4), 159–163.

Yoo, J.-W., Dharmala, K., & Lee, C. H. (309AD). The physicodynamic properties of mucoadhesive polymeric films developed as female controlled drug delivery system (*2006)*, *1-2*,139–145.

Yoshida, K., Nitatori, Y., & Uchiyama, Y. (1996). Localization of glycosaminoglycans and CD44 in the human lacrimal gland. *Archives of Histology and Cytology*, *59*(5), 505–513.

5.5 Bibliografía

Altman, F. P. (1976). Tetrazolium Salts and Formazans. *Progress in Histochemistry and Cytochemistry*, *9*(3), III–VI, 1–51.

Anoopkumar-Dukie, S., Carey, J. B., Conere, T., O'sullivan, E., van Pelt, F. N., & Allshire, A. (2005). Resazurin assay of radiation response in cultured cells. *The British Journal of Radiology*, *78*(934), 945–947. doi:10.1259/bjr/54004230

Araki-Sasaki, K., Ohashi, Y., Sasabe, T., Hayashi, K., Watanabe, H., Tano, Y., & Handa, H. (1995). An SV40-immortalized human corneal epithelial cell line and its characterization. *Investigative Ophthalmology & Visual Science*, *36*(3), 614–621.

Avdeef, A. (2007). Solubility of sparingly-soluble ionizable drugs. *Advanced Drug Delivery Reviews*, *59*(7), 568–590.

Azarmi, S., Roa, W., & Löbenberg, R. (2007). Current perspectives in dissolution testing of conventional and novel dosage forms. *International Journal of Pharmaceutics*, *328*(1), 12–21.

Baxter, J. L., Kukura, J., & Muzzio, F. J. (2005). Hydrodynamics-induced variability in the USP apparatus II dissolution test. *International Journal of Pharmaceutics*, *292*(1-2), 17–28.

Berridge, M. V., Herst, P. M., & Tan, A. S. (2005). Tetrazolium dyes as tools in cell biology: New insights into their cellular reduction. *Biotechnology Annual Review*, *11*, 127–152.

Billmeyer, F. W. J. (1975). *Ciencia de los polímeros*. Barcelona: Editorial Reverté S. A.

Brunner, E. (1904). Reaktionsgeschwindigkeit in heterogenen Systemen. *Zeitschrift Für Physikalische Chemie International Journal of Research in Physical Chemistry and Chemical Physics*, *43*, 56–102.

Bueno, C., Villegas, M. L., Bertolotti, S. G., Previtali, C. M., Neumann, M. G., & Encinas, M. V. (2002). The Excited-State Interaction of Resazurin and Resorufin with Aminesin Aqueous Solutions. Photophysics and Photochemical Reaction. *Photochemistry and Photobiology*, *76*(4), 385–390.

Calles, J. A., Palma, S. D., & Vallés, E. M. (2013). Dispositivo para evaluar la disolución o liberación de fármacos. Argentina: INPI.

Cid Cárcamo, E. (1992). *Control de Calidad Biofarmacéutico de Medicamentos*. Santiago de Chile.

Dokoumetzidis, A., & Macheras, P. (2006). A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System. *International Journal of Pharmaceutics*, *321*(1-2), 1–11.

Draize, J. H., Woodard, G., & Calvery, H. O. (1944). Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *The Journal of Pharmacology And Experimental Therapeutics*, *82*(3), 377–390.

Enríquez-de-Salamanca, A., Calder, V., Gao, J., Galatowicz, G., García-vázquez, C., Fernández, I., … Calonge, M. (2008). Cytokine responses by conjunctival epithelial cells : An in vitro model of ocular inflammation. *Cytokine*, *44*(1), 160–167.

González Vidal, N. L. (2008). *Estudios de similitud y caducidad farmacéutica de comprimidos y suspensiones extemporáneas del mercado argentino y países del MERCOSUR*. Universidad de Buenos Aires.

Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. (1997). Washington, DC.

Guidance for Industry: Dissolution testing of immediate release solid oral dosage forms. (1997). Washington, DC.

Hixson, A. W., & Crowell, J. H. (1931). Dependence of Reaction Velocity upon surface and Agitation. *Industrial & Engineering Chemistry*, *23*(8), 923–931.

Klein, S. (2006). The Mini Paddle Apparatus–a Useful Tool in the Early Developmental Stage? Experiences with Immediate-Release Dosage Forms. *Dissolution Technologies*, *13*, 6–11.

Kukura, J., Arratia, P. E., Szalai, E. S., & Muzzio, F. J. (2003). Engineering Tools for Understanding the Hydrodynamics of Dissolution Tests. *Drug Development and Industrial Pharmacy*, *29*(2), 231–239.

Llabot, J. M. (2007). *Sistemas Bioadhesivos de Administración de Fármacos*. Universidad Nacional de Córdoba.

Machida, Y., & Nagai, T. (1999). Bioadhesive preparations as topical dosage forms. In E. Mathiowitz, D. E. Chickering III, & C.-M. Lehr (Eds.), *Bioadhesive drug delivery systems: Fundamentals, novel approaches, and development* (pp. 641–658). New York: Marcel Dekker, Inc.

Masaro, L., & Zhu, X. . (1999). Physical models of diffusion for polymer solutions, gels and solids. *Progress in Polymer Science*, *24*(5), 731–775. doi:10.1016/S0079-6700(99)00016-7

McCarthy, L. G., Bradley, G., Sexton, J. C., Corrigan, O. I., & Healy, A. M. (2004). Computational fluid dynamics modeling of the paddle dissolution apparatus: agitation rate, mixing patterns, and fluid velocities. *AAPS PharmSciTech*, *5*(2), 50–59.

Michailova, V., Titeva, S., Kotsilkova, R., Krusteva, E., & Minkov, E. (2001). Influence of hydrogel structure on the processes of water penetration and drug release from mixed hydroxypropylmethyl cellulose/thermally pregelatinized waxy maize starch hydrophilic matrices. *International Journal of Pharmaceutics*, *222*(1), 7–17.

Mirza, T., Joshi, Y., Liu, Q. (Julie), & Vivilecchia, R. (2005). Evaluation of Dissolution Hydrodynamics in the USP, PeakTM and Flat-Bottom Vessels Using Different Solubility Drugs. *Dissolution Technologies*, *12*(1), 11–16.

Nernst, W. (1904). Theorie der Reaktionsgeschwindigkeit in heterogenen Systemen. *Zeitschrift Für Physikalische Chemie, Stoechiometrie Und Verwandtschaftslehre*, *47*, 52–55.

Nguyen-Xuan, T., Towart, R., Terras, A., Jacques, Y., Buri, P., & Gurny, R. (1996). Mucoadhesive semi-solid formulations for intraoral use containing sucralfate. *European Journal of Pharmaceutics and Biopharmaceutics*, *42*(2), 133–137.

North-Root, H., Yackovich, F., Demetrulias, J., Gacula, M., & Heinze, J. E. (1982). Evaluation of an in vitro cell toxicity test using rabbit corneal cells to predict the eye irritation potential of surfactants. *Toxicology Letters*, *14*(3-4), 207–212.

Noyes, A. A., & Whitney, W. R. (1897). The rate of solution of solid substances in their own solutions. *Journal of the American Chemical Society*, *19*(12), 930–934. doi:10.1021/ja02086a003

Parikh, R. K., Parikh, D. C., Delvadia, R. R., & Patel, S. M. (2006). A Novel Multicompartment Dissolution Apparatus for Evaluation of Floating Dosage Form Containing Poorly Soluble Weakly Basic Drug. *Dissolution Technologies*, *13*(1), 14–19.

Parnigotto, P. P., Bassani, V., Montesi, F., & Conconi, M. T. (1998). Bovine corneal stroma and epithelium reconstructed in vitro: characterisation and response to surfactants. *Eye*, *12*(2), 304–310. doi:10.1038/eye.1998.70

Pesch, K. L., & Simmert, U. (1929). Combined assays for lactose and galactose by enzymatic reactions. *Milchw. Forsch.*, *8*, 551.

Qureshi, S. A. (2004). A New Crescent-shaped Spindle for Drug Dissolution Testing — But Why a New Spindle ? *Dissolution Technologies*, *11*(4), 13–18.

Qureshi, S. A., & McGilveray, I. J. (1995). A Critical Assessment of the Usp Dissolution Apparatus Suitability Test Criteria. *Drug Development and Industrial Pharmacy*, *21*(8), 905–924. doi:10.3109/03639049509026656

Qureshi, S. A., & McGilveray, I. J. (1998). Assessment of Pharmaceutical Quality of Furosemide Tablets from Multinational Markets. *Drug Development and Industrial Pharmacy*, *24*(11), 995–1005.

Qureshi, S. A., & McGilveray, I. J. (1999). Typical variability in drug dissolution testing: study with USP and FDA calibrator tablets and a marketed drug (glibenclamide) product. *European Journal of Pharmaceutical Sciences*, *7*(3), 249–258.

Saona Santos, C. L. (2006). *Contactología Clínica* (2nd ed., p. 550). Barcelona: Elsevier-Masson.

Scudiero, D. A., Shoemaker, R. H., Paull, K. D., Scudiere, D. A., Paul, K. D., Monks, A., … Boyd, M. R. (1988). Evaluation of a Soluble Tetrazolium / Formazan Assay for Cell Growth and Drug Sensitivity in Culture Using Human and Other Tumor Cell Lines Evaluation of a Soluble Tetrazolium / Formazan Assay for Cell Growth and Drug Sensitivity in Culture Using Human an, 4827–4833.

Smart, J. D. (2005). The basics and underlying mechanisms of mucoadhesion. *Advanced Drug Delivery Reviews*, *57*(11), 1556–1568.

The dissolution procedure: Development and validation. (2005). *Pharmacopeial Forum*, *30*(1), 351–363.

The Dissolution Procedure: Development and Validation. (2007). In *United States Pharmacopeial*. Rockville: The United States Pharmacopeial Convention, Inc.

United States Pharmacopeia. (2005). Rockville: The United States Pharmacopeial Convention, Inc.

Wyttenbach, N., Alker, A., Grassmann, O., & Sceubel, E. (2009). Tenoxicam-Methylparaben cocrystal formation in aqueous suspension formulation. In *Proceedings of 2009 AAPS Annual Meeting and Exposition*. Los Angeles.

Yu, L. X., Amidon, G. L., Polli, J. E., Zhao, H., Mehta, M. U., Conner, D. P., … Hussain, A. S. (2002). Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions. *Pharmaceutical Research*, *19*(7), 921–925.

6.4 Bibliografía

Collins, M. N., & Birkinshaw, C. (2007). Comparison of the Effectiveness of Four Different Crosslinking Agents with Hyaluronic Acid Hydrogel Films for Tissue-Culture Applications. *Journal of Applied Polymer Science*, *104*(5), 3183–3191.

Florey, K. (1987). *Analytical Profiles of Drug Substances Volume 16*. *Analytical Profiles of Drug Substances* (Vol. 16). Orlando: Academic Press, Inc.

Hao, H., Wang, J., & Wang, Y. (2004). Solubility of Dexamethasone Sodium Phosphate in Different Solvents. *Journal of Chemical & Engineering Data*, *49*(6), 1697–1698. doi:10.1021/je0498412

Lai, J.-Y., Ma, D. H.-K., Cheng, H.-Y., & Sun, C.-C. (2010). Ocular Biocompatibility of Carbodiimide Cross-Linked Hyaluronic Acid Hydrogels for Cell Sheet Delivery Carriers. *Journal of Biomaterials Science*, *21*(3), 359–376.

Lavik, E., Kuehn, M. H., & Kwon, Y. H. (2011). Novel drug delivery systems for glaucoma. *Eye (Lond)*, *25*(5), 578–586. doi:10.1038/eye.2011.82

Lu, P., Lai, J., Ma, D. H., & Hsiue, G.-H. (2008). Carbodiimide cross-linked hyaluronic acid hydrogels as cell sheet delivery vehicles : characterization and interaction with corneal endothelial cells. *Journal of Biomaterials Science, Polymer Edition*, *19*(1), 1–18.

Tomihata, K., & Ikada, Y. (1997). Preparation of cross-linked hyaluronic acid films of low water content. *Biomaterials*, *18*(3), 189–195.

7.7 Bibliografía

Abd EL–Gawad, A. E. H., Gawad, E. L., Soliman, O. A., Barker, S. A., & Girgis, G. N. S. (2012). Formulation and Evaluation of Gel Forming Ocular Minitablets Containing Piroxicam. *British Journal of Pharmaceutical Research*, *2*(3), 141–167.

Bordallo Sanroma, L. J. (1994). *Determinación por HPLC de 4-epianhidro-tetraciclina como producto de degradación en formas orales de tetraciclina condicionada por nuevos diseños galénicos*. Universidad Complutense de Madrid.

Costa, P., & Sousa Lobo, J. M. (2001). Modeling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences*, *13*(2), 123–133.

Duffel, M. W., Silwai Ing, I., Segarra, T. M., Dixson, J. A., Barfknecht, C. F., & Schoenwald, R. D. (1986). N-Substituted sulfonamide carbonic anhydrase inhibitors with topical effects on intraocular pressure. *Journal of Medicinal Chemistry*, *29*(8), 1488–1494. doi:10.1021/jm00158a028

Farmacopea Nacional Argentina. (2003) (7th ed.).

Fassihi, A. R., & Kanfer, I. (1986). Effect of Compressibility and Powder Flow Properties on Tablet Weight Variation. *Drug Development and Industrial Pharmacy*, *12*(11-13), 1947–1966. doi:10.3109/03639048609042619

Florey, K. (1993). *Analytical Profiles of Drug Substances and Excipients Volume 22*. (H. G. Brittain, Ed.). San Diego: Academic Press, Inc.

Gallo, L., Llabot, J. M., Allemandi, D., Bucalá, V., & Piña, J. (2011). Influence of spray-drying operating conditions on Rhamnus purshiana (Cáscara sagrada) extract powder physical properties. *Powder Technology*, *208*(1), 205–214. doi:10.1016/j.powtec.2010.12.021

Kaur, I. P., Smitha, R., Aggarwal, D., & Kapil, M. (2002). Acetazolamide : future perspective in topical glaucoma therapeutics. *International Journal of Pharmaceutics*, *248*(1-2), 1–14.

Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. *International Journal of Pharmaceutics*, *15*, 25–35.

Lee, P. I. (1985). Kinetics of drug release from hydrogel matrices. *Journal of Controlled Release*, *2*, 277–288.

Llabot, J. M. (2007). *Sistemas Bioadhesivos de Administración de Fármacos*. Universidad Nacional de Córdoba.

Llabot, J. M., Manzo, R. H., & Allemandi, D. a. (2004). Drug release from carbomer:carbomer sodium salt matrices with potential use as mucoadhesive drug delivery system. *International Journal of Pharmaceutics*, *276*(1-2), 59–66.

Mortazavi, S. A., Jaffariazar, Z., & Damercheli, E. (2010). Formulation and In-Vitro Evaluation of Ocular Ciprofloxacin-Containing Minitablets Prepared with Different Combinations of Carbopol 974P and Various Cellulose Derivatives. *Iranian Journal of Pharmaceutical Research*, *9*(2), 107–114.

Odeniyi, M. A., Babalola, A. O., & Ayorinde, J. O. (2013). Evaluation of Cedrela gum as a binder and bioadhesive component in ibuprofen tablet formulations. *Brazilian Journal of Pharmaceutical Sciences*, *49*, 95–105.

Palma, S. D., Tartara, L. I., Quinteros, D., Allemandi, D. A., Longhi, M. R., & Granero, G. E. (2009). An efficient ternary complex of acetazolamide with HP-ß-CD and TEA for topical ocular administration. *Journal of Controlled Release*, *138*(1), 24–31.

Peppas, N. A., & Sinclair, G. W. (1984). Analysis of non-fickian transport in polymers using simplified exponential expressions. *Journal of Membrane Science*, *17*, 329–331.

Tártara, L. I., Quinteros, D. A., Saino, V., Allemandi, D. A., & Palma, S. D. (2012). Improvement of Acetazolamide Ocular Permeation Using Ascorbyl Laurate Nanostructures as Drug Delivery System. *Journal of Ocular Pharmacology and Therapeutics*, *28*(2), 102–109.

Weyenberg, W., Bozdag, S., Foreman, P., Remon, J. P., & Ludwig, A. (2006). Characterization and in vivo evaluation of ocular minitablets prepared with different bioadhesive Carbopol-starch components. *European Journal of Pharmaceutics and Biopharmaceutics*, *62*(2), 202–209. doi:10.1016/j.ejpb.2005.08.003

Weyenberg, W., Vermeire, A., Remon, J. P., & Ludwig, A. (2003). Characterization and in vivo evaluation of ocular bioadhesive minitablets compressed at different forces. *Journal of Controlled Release*, *89*(2), 329–40.

Weyenberg, W., Vermeire, A., Vandervoort, J., Remon, J. P., & Ludwig, A. (2005). Effects of roller compaction settings on the preparation of bioadhesive granules and ocular minitablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *59*(3), 527–536. doi:10.1016/j.ejpb.2004.09.012

Anexo: Producción científica

A lo largo del presente trabajo de tesis se han realizado las siguientes comunicaciones en revistas científicas, congresos nacionales e internacionales y presentaciones en concursos de ciencia y tecnología:

Publicaciones:

- Calles, J. A., Tártara, L. I., Lopez-García, A., Diebold, Y., Palma, S. D., & Vallés, E. M. (2013). Novel bioadhesive hyaluronan – itaconic acid crosslinked films for ocular therapy. International Journal of Pharmaceutics, 455(1-2), 48–56.

- Calles, J. A., Palma, S. D., & Vallés, E. M. (2013). Aplicaciones oftalmológicas del ácido hialurónico. Pharmaceutical Technology, 123, 74–82.

- Calles, J. A., Vallés, E. M., Llabot, J. M., & Palma, S. D. (2012). Dispositivos poliméricos sólidos de administración oftálmica. Atención Farmacéutica - European Journal of Clinical Pharmacy, 14(2), 116–122.

- Calles, J. A., Tártara, L. I., Palma, S. D., & Vallés, E. M. (2011). El ácido hialurónico y sus aplicaciones oftalmológicas. Oftalmología Clínica Y Experimental, 5(1), 28–32.

Patentes:

- Calles, J. A., Palma, S. D., & Vallés, E. M. (2013). Dispositivo para evaluar la disolución o liberación de fármacos. Argentina-INPI (Instituto Nacional de la Propiedad Industrial). Exp nº 20130100220 (en trámite).

Concursos de ciencia y tecnología:

- Calles, J. A., Palma, S. D., & Vallés, E. M. (2013). Dispositivo para evaluar la disolución o liberación de fármacos. Seleccionado para la categoría Investigación Aplicada en el Concurso Nacional de Innovaciones INNOVAR, 9na edición, ID nº: 14348. Catálogo INNOVAR 2013, pág. 120.

Resúmenes de congreso:

- Calles, J. A., Mora, M. J., Lopez-García, A., Palma, S. D., Vallés, E. M., Longhi, M. R., … Diebold, Y. (2013). In vitro ocular biocompatibility of novel hp-β-cd acetazolamide complexes. Xth Spanish-Portuguese Conference on Controlled Drug Delivery (p. 78). Valencia: Controlled Release Society Spanish-Portuguese Local Chapter.

- Calles, J. A., Palma, S. D., & Vallés, E. M. (2012). Films de ácido hialurónico entrecruzado como sistemas de liberación de fármacos oftálmicos. IX Congreso de la Asociación de Investigación en Visión y Oftalmología - AIVO. Buenos Aires.

- Calles, J. A., Palma, S. D., & Vallés, E. M. (2012). Novel hyaluronan films in ocular therapy. II Reunión Internacional de Ciencias Farmacéuticas - RICIFA 2012. Rosario.

- Calles, J. A., Lopez-García, A., Palma, S. D., Vallés, E. M., & Diebold, Y. (2012). Cross-linking modification of hyaluronan-itaconic acid films to prepare platforms with potential application to drug delivery systems. 7th MoDeSt Conference - Abstract Book (pp. 445–446). Prague: Institute of Macromolecular Chemistry Academy of Sciences of the Czech Republic.

- Lopez-García, A., Calles, J. A., Soriano Romaní, L., Palma, S. D., Vallés, E. M., & Diebold, Y. (2012). Estudio de tolerancia in vitro de películas de ácido hialurónico-ácido itacónico diseñadas para la administración tópica ocular de fármacos. XXV Congreso Nacional de Técnicos Superiores en Laboratorio de Diagnóstico Clínico y Técnicos Superiores en Anatomía Patológica y Citología (pp. 6–7). Santiago de Compostela.

- Calles, J. A., Palma, S. D., Vallés, E. M., & Diebold, Y. (2011). In Vitro Corneal Compatibility of Cross-Linked Hyaluronan-Itaconic Acid Films. The International Symposium on Ocular Pharmacology and Therapeutics - ISOPT (pp. 43–47). Viena: MEDIMOND s.r.l.

- Calles, J. A., Ressia, J. A., Llabot, J. M., Palma, S. D., & Vallés, E. M. (2011). Novel Hyaluronan-Itaconic Acid-Glutaraldehyde Crosslinked Biofilms. IX Simposio Argentino de Polímeros - SAP 2011. Proceedings (pp. 235–238). Bahía Blanca: Ediuns.

- Calles, J. A., Ressia, J. A., Llabot, J. M., Chetoni, P., Palma, S. D., & Vallés, E. M. (2011). Improved Properties of Cross-Linked Sodium Hyaluronate Films. Proceedings of the European Polymer Congress (p. 1318). Granada.

- Calles, J. A., Ressia, J. A., Llabot, J. M., Allemandi, D. A., Palma, S. D., & Vallés, E. M. (2010). Rheological and tensile properties of sodium hyaluronate hydrogels and films. Primera Reunión Internacional de Ciencias Farmacéuticas – RICiFa 2010 (pp. 207–208). Córdoba.