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NANOCAPSULES- A REVIEW

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ABSTRACT

The use of nanotechnology in the medical world offers many exciting possibilities. Many techniques are being used today while others are at various stages of testing and research is still going on every day. Nanotechnology within the field of drugs involves applications of nanoparticles which are currently under development, and research that involves the utilization of manufactured nanocapsules to form repairs at the cellular level, and is sometimes referred to as nanomedicine. The applications of nanotechnology in medicine could create a remarkable change in the diagnosis and treatment of disease in the future. Nanocapsules are having exciting applications not only in medicine, but also in other fields. This review was aimed to highlight the important aspects of nanocapsules.

INTRODUCTION

Nanoparticles are solid, submicron-sized drug carriers that can be either biodegradable or non biodegradable (Patrick Couvreur, Dubernet, and Puisieux 1995). The term nanoparticle is a combination name of both nanospheres and nanocapsules. Nanospheres have a matrix type of structure. Drugs may be encapsulated within the particle or absorbed at the sphere surface. Nanocapsules are vesicular that the drug is confined to a cavity consisting of an inner liquid core surrounded by a polymeric membrane (P. Couvreur 1988). The active substances are usually dissolved in the inner core but may also be adsorbed to the capsule surface (Eric Allemann, Gurny, and Doelker 1993).

Nanocapsules are used as drug delivery systems for several drugs by different ways of administrations such as oral and parental, lessen the toxicity of drugs, improve the stability of the drug (Leite et al. 2007). Nanocapsules are seen as active vectors because of their capacity to release drugs; their subcellular size allows higher intracellular vectors. They can also improve the stability of active substances (Ourique et al. 2008). Nano-encapsulated systems include high drug encapsulation efficiency due to optimized drug solubility in the core, low polymer content when, drug polymeric shell protection against degradation factors like pH and light and the reduction of tissue irritation due to the polymeric shell (Anton, Benoit, and Saulnier 2008). Nanoparticles are under the spotlight for the delivery of therapeutic drugs. The review emphasizes the methods of preparation of nanoparticles and their application. The extremely small size of nanoparticles offers distinct advantages over microparticles, including higher intracellular uptake compared with microparticles. In intestinal uptake, nanoparticle nature and charge properties seem to influence the uptake by intestinal epithelia (Soppimath et al. 2001).

Methods of preparation of nanocapsules

There exist six methods for the nanocapsules preparation: nanoprecipitation, emulsion–diffusion, double emulsification, emulsion-coacervation, polymer-coating and layer by-layer method.

Nanoprecipitation

Nanoprecipitation, also known as solvent displacement method is composed of the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent within an aqueous medium(Fessi et al. 1989)(Barichello et al. 1999)(Galindo-Rodriguez et al. 2004)(Ganachaud and Katz 2005). Precipitation of nanospheres is due to the polymer dissolving in a solvent of intermediate polarity. This phase is injected into an aqueous solution that contains a stabilizer as a surfactant. Polymer deposition on the interface between the water and the organic solvent, caused due to fast diffusion of the solvent, can result in fast formation of a colloidal suspension (Quintanar-Guerrero et al. 1998). To help with that, phase separation is performed with another solvent that is also a non solvent of the polymer (Vauthier et al. 2003). The solvent displacement technique allows the preparation of nanocapsules when a minimal volume of nontoxic oil is incorporated in the organic phase. High loading efficiencies are usually reported for lipophilic drugs when the nanocapsules are prepared (Dimitrova,

Ivanov, and Nakache 1988). However, this technique's effectiveness is restricted to water-miscible solvents, in which the diffusion rate is enough to produce spontaneous emulsification. Spontaneous emulsification is not observed if the coalescence rate of the formed droplets is sufficiently high even when some water-miscible solvents produce a certain instability when mixed in water (Wehrle, Magenheim, and Benita 1995). Even though acetone/dichloromethane (ICH, class 2) are employed to dissolve and increase the entrapment of medicine, the dichloromethane causes increase in mean particle size (Nemati 1996) and is considered toxic. This method can be applied to lipophilic drugs because of the solubility of the solvent with the aqueous phase, and it is not an efficient means to encapsulate water-soluble drugs. This method is applied to various polymeric materials such as PLGA36, PLA43, PCL44, and poly (methyl vinyl ether-comaleic anhydride) (Molpeceres et al. 1996)(Irache et al. 2005). This technique has been well adapted for the incorporation of cyclosporin A, because entrapment efficiencies of 98% were achieved (Arbós et al. 2002). By using the solvent displacement method, highly loaded nanoparticulate systems supported amphiphilic cyclodextrins were prepared to facilitate the parenteral administration of the poorly soluble antifungal drugs Bifonazole and Clotrimazole(E. Allemann 1998).

Emulsification Solvent Diffusion

The preparation of chitosan nanoparticles by emulsification solvent diffusion technology is dependant on the crosslinking between the reactive functional amine groups of chitosan and aldehyde groups, and the partial miscibility of an organic solvent with water. Formaldehyde and glutaraldehyde were widely used as cross-linkers for the preparation of chitosan particles. More Recently, to avoid the toxicity of glutaraldehyde and formaldehyde vanillin was also used as cross-linkers for the preparation of chitosan particles. Vanillin isolated from vanilla pods is widely used in industries such as food, beverage and cosmetic as an important flavouring agent (Memişoğlu et al. 2003). This method involves the injection of an organic phase into a chitosan solution composed of a stabilizing agent under high shearing force, followed by a homogenization under high pressure (Converti et al. 2010)(El-Shabouri 2002). Then a large amount of water was poured to overcome the organic solvent miscibility in water. Upon the diffusion of organic solvent into water, polymer precipitation occurs, which subsequently causes the formation of NPs. A high percentage of drug entrapment could be achieved by this method and is well suited for hydrophobic drugs. But it needs the use of organic solvents and high shearing forces.

Double emulsification method

Double emulsions are complex heterodisperse systems called "emulsions of emulsions", that can be classified into two major types: water-oil-water emulsion and oil-water-oil emulsion (Nagarwal et al. 2009)(Garti 1997). The dispersed phase is itself an emulsion and the inner dispersed droplet is separated from the outer liquid phase by a layer of another phase. Double emulsions are prepared in a two-step emulsification process using two surfactants: a hydrophobic one to stabilize the interface of the internal emulsion and a hydrophilic one to stabilize the external interface of the oil

globules for water-oil-water emulsions. The principle of double emulsion formation, specifically of the water-oil-water emulsion type, is associated with the principles of both nanoprecipitation and emulsion–diffusion methods. Here, in the primary w/o emulsion the oil is replaced by an organic phase composed of a solvent that is totally or partially miscible in water, the film-formed polymer and a water-oil surfactant. The water which has a stabilizing agent is added to the system to obtain the water in organic emulsion. However in this step, particle hardening is obtained through solvent diffusion and polymer precipitation (Bilati, Allémann, and Doelker 2005)(Khoee and Yaghoobian 2009). Water is added to the double emulsion in order to achieve full solvent diffusion. Surfactants play a dual role in emulsions: as a film former and a barrier to drug release at the internal interface, and as a steric stabilizer on the external interface. It was found that drug encapsulation efficiency and average particle size are affected by changing the type and concentration of both the w/o emulsion and the stabilizing agent. On preparing the nanocapsules by double emulsification method, the primary emulsion is formed by ultrasound and the water-oil surfactant stabilizes the interface of the water-oil internal emulsion. The second emulsion is also formed by ultrasound and nanocapsule dispersion is stabilized by adding the stabilizing agent. In the last step, the solvents are removed by evaporation or extraction by vacuum, leaving hardened nanocapsules in an aqueous medium.

Layer-by-Layer

The Layer-by-Layer self-assembly method has many advantages for making thin polymeric layers on surfaces and hence capsules. This method is easy and cheap and is capable of employing various different materials. The basic principle of the Layer-by-Layer (LbL) method is to utilise electrostatic interactions between oppositely charged polyelectrolytes, or other materials, to fabricate thin uniform multilayers onto the original substrates. In 1941, Langmuir discussed the idea of adsorption of ions onto a surface to form a single layer, and also demonstrated the experiment by adsorbing a single layer of thorium ions onto a monomolecular layer of barium stearate(Ariga et al. 2019). In the 1960s, Iler utilised this strategy to build up alternating layers of positively charged alumina fibrils and negatively charged silica colloids onto smooth glass surfaces (Iler 1966). In the early 1990s, Decher and colleagues exploited this method and prepared multilayers of thin films by immersing a charged planar surface (silicon wafer or quartz) alternately into anionic and cationic polyelectrolyte or bipolar ampholyte solutions (G. Decher and Hong 1991)(G. Decher and Hong 1991). They used macroscopic planar silicon wafers and quartz surfaces, which are negatively charged, as the templates, and immersed the substrate initially into a solution containing a cationic polyelectrolyte. After that, a monolayer of polyelectrolyte was found to be adsorbed onto the surface of the solid. After rinsing, the solid was then immersed into another solution with an anionic polyelectrolyte. Again a monolayer was absorbed and the original surface charge was restored (Gero Decher et al. 1991).

Emulsion-coacervation method

The emulsion-coacervation process is mainly presented for nanocapsules preparation from naturally occurring polymeric materials. Till now, sodium

alginate and gelatin have been used though synthetic polymeric materials could be used for this purpose. The procedure involves the o/w emulsification of an organic phase with an aqueous phase by just stirring or using ultrasound. A coacervation process is then performed with the help of either electrolytes with a sodium alginate–calcium chloride system, by adding a water miscible non-solvent (Lertsutthiwong et al. 2008) or a dehydration agent with a gelatin–isopropanol–sodium sulfate system (Krause and Rohdewald 1985) or by temperature modification with the application of triblock terpolymer in gold nanocapsule synthesis (Lutter et al. 2008). Finally, the coacervation process is complemented with extra crosslinked steps that allows it to obtain a rigid nanocapsule shell structure.

Polymer-coating method

Prego et al. proposed a method called polymer coating in which the first step is to prepare the nanoemulsion template and then coat it by polymer deposition on the water/oil nanoemulsion surface. The polymers are added in the continuous phase and their precipitation onto the nanoemulsion droplets is triggered by solvent evaporation, as opposed to the emulsion coacervation method. In their procedure, they start from an organic phase composed of the active substance, oil, surfactant (lecithin) and acetone as solvent; an aqueous phase containing the stabilizing agent and an aqueous polymer-coating solution. The organic and aqueous phases are mixed under moderate stirring and the o/w nanoemulsion is formed by solvent displacement. The solvents are subjected to evaporation under vacuum till it reaches a specific volume. Finally nanoemulsion is coated by the polymer by simple incubation in the polymer solution (Prego et al. 2006).

Drug Release

The goal of pursuing nanotechnology is to deliver drugs, and subsequently understanding the manner and extent to which the drug molecules are released is important. Majority of the release methods require that the drug and its delivery vehicle should be separated. The drug loading of the nanoparticles is defined as the amount of drug bound per mass of polymer, which is usually expressed as moles of drug/ mg polymer or mg drug / mg polymer. This analysis utilizes either classical analytical methods like UV spectroscopy or high performance liquid chromatography (HPLC) after ultracentrifugation, ultrafiltration, gel filtration, or centrifugal ultrafiltration. Quantification is performed with the UV spectroscopy or HPLC. Drug release assays are also similar to drug loading assay which is assessed for a period of time to analyze the mechanism of drug release (Kreuter 1983)(Magenheim, Levy, and Benita 1993).

Applications:

Drug delivery

Nanocapsules can be coated with an antibody on the surface, and is carried along the bloodstream directed to an induced tumor. After reaching the tumor, the capsules open up in a blast and discharge their therapeutic contents. On the surface of the polymer, there are tiny gold particles in the range of 6 nm which stick across and are specific to the laser light and lead the capsules to locate their drug load capacity at the desired time. The near infrared light causes

rupturing of the capsule when it hits the gold spots and they undergo instantaneous melting with no harm to the content.

Oral delivery of peptides and proteins

Nanocapsules are used as carriers for oral administration of peptides and proteins, particularly biodegradable nanocapsules (Puglisi et al. 1995). However, the development of suitable carriers remains as a challenge due to the characteristic bioavailability of these molecules. Gastrointestinal barriers of the epithelium and by their degradation of digestive enzymes restrict the molecules. Using the technique of encapsulation which provides the bioactive molecules from enzymatic and hydrolytic degradation e.g., the loaded insulin nanoparticles, the impact has been observed in diabetic rats following the oral administration. (Hildebrand and Tack 2000).

Treatment of cancer

The study of Jack et al (2008) showed that specific siRNAs encapsulated in nanocapsules can be used to target estrogen receptor alpha (ERα). There is a significant decrease in tumour growth and ERα expression in tumour cells. by the intravenous injection of these nanocapsules into estradiol stimulated MCF-7 cell xenografts. This indicates that a novel strategy, based on ERα−siRNA delivery, could be developed for the treatment of hormone dependent breast cancers (Damgé et al. 1990)**.**

Food Science and agriculture

The spherical bilayer vesicles liposome form the dispersion of polar lipids in hydrophilic solvents. They are very efficient drug delivery vehicles by protecting most reactive and sensitive compounds immediate to release. Liposomal entrapment has resulted in the stabilization of encapsulated therapeutic materials against the wide range of chemical and environmental changes, including their enzymatic and chemical modifications, as well as changes in buffering against the levels of extreme pH, conditions of temperature, and the ionic strength.

Diagnosis and bioimaging

A number of molecular imaging techniques are available, such as optical imaging (OI), magnetic resonance imaging (MRI), ultrasound imaging (USI), positron emission tomography (PET) and others have been reported for imaging of in vitro and in vivo biological specimens (Margolis et al. 2007)(Weissleder 2002). The current development of luminescent and magnetic nanoparticles advances bio imaging technologies (Sharma et al. 2006). For imaging two different types of nanoparticles have been widely used: luminescent nanoprobes for OI and magnetic nanoparticles for MRI.

Future opportunities and challenges

There exists numerous challenges in developing the following techniques: Virus-like systems for intracellular systems, Architecting of biomimetic polymers, control of sensitive drugs, functions of active drug targeting, bioresponsive triggered systems, systems interacting with smart delivery, nanochips for nanoparticle release, carriers for advanced polymers for the delivery of therapeutic peptide / proteins. Drug delivery techniques were

developed to deliver or control the rate and amount of delivery. Major scientific research programmes aimed at drug delivery are focussed on formulations and dispersion containing components down to nano sizes (Patra et al. 2018)(Chatterjee et al. 2019).

CONCLUSION

There are remarkable applications for nanocapsules in the fields of agrochemicals, wastewater treatments, genetic engineering, cleaning products, cosmetics as well as in adhesive components. Nanocapsules are also used in encapsulation of enzymes, adhesives, catalysts, polymers, oils, inorganic micro and nanoparticles, latex particles, and even the biological cells. To conclude, nanocapsules can be exploited in the delivery of active pharmaceutical ingredients. They provide novel effective drug delivery systems in the up-coming future.

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CONFLICTS OF INTEREST

None declared

REFERENCES

ReAllemann, Eric, Robert Gurny, and Eric Doelker. 1993. “Drug-Loaded Nanoparticles: Preparation Methods and Drug Targeting Issues.” European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V 39 (5): 173–91.

Anton, Nicolas, Jean-Pierre Benoit, and Patrick Saulnier. 2008. “Design and Production of Nanoparticles Formulated from Nano-Emulsion templates—A Review.” Journal of Controlled Release: Official Journal of the Controlled Release Society 128 (3): 185–99.

Arbós, P., M. Wirth, M. A. Arangoa, F. Gabor, and J. M. Irache. 2002. “Gantrez AN as a New Polymer for the Preparation of Ligand-Nanoparticle Conjugates.” Journal of Controlled Release: Official Journal of the Controlled Release Society 83 (3): 321–30.

Ariga, Katsuhiko, Eungjin Ahn, Minju Park, and Byeong-su Kim. 2019. “Layer-by-Layer Assembly: Recent Progress from Layered Assemblies to Layered Nanoarchitectonics.” Chemistry – An Asian Journal. https://doi.org/10.1002/asia.201900627.

Barichello, J. M., M. Morishita, K. Takayama, and T. Nagai. 1999. “Encapsulation of Hydrophilic and Lipophilic Drugs in PLGA Nanoparticles by the Nanoprecipitation Method.” Drug Development and Industrial Pharmacy 25 (4): 471–76.

Bilati, Ugo, Eric Allémann, and Eric Doelker. 2005. “Strategic Approaches for Overcoming Peptide and Protein Instability within Biodegradable

Nano- and Microparticles." European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V 59 (3): 375–88.

Chatterjee, Shayeri, School of Pharmacy, Techno India University, EM, Sector-V, Kolkata, West Bengal, et al. 2019. "APPROACHES AND ROLE OF PROTEIN BASED NANOPARTICLES IN DRUG DELIVERY SYSTEM: A REVIEW." Indian Research Journal of Pharmacy and Science. https://doi.org/10.21276/irjps.2019.6.2.8.

Converti, A., B. Aliakbarian, J. M. Domínguez, G. Bustos Vázquez, and P. Perego. 2010. "Microbial Production of Biovanillin." Brazilian Journal of Microbiology: [publication of the Brazilian Society for Microbiology] 41 (3): 519–30.

Couvreur, P. 1988. "Polyalkylcyanoacrylates as Colloidal Drug Carriers." Critical Reviews in Therapeutic Drug Carrier Systems 5 (1): 1–20.

Couvreur, Patrick, Catherine Dubernet, and Francis Puisieux. 1995. "Controlled Drug Delivery with Nanoparticles: Current Possibilities and Future Trends." European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V 41 (1): 2–13.

Damgé, C., C. Michel, M. Aprahamian, P. Couvreur, and J. P. Devissaguet. 1990. "Nanocapsules as Carriers for Oral Peptide Delivery." Journal of Controlled Release. https://doi.org/10.1016/0168-3659(90)90013-j.

Decher, Gero, Joseph Maclennan, J�rgen Reibel, and Ulrich Sohling. 1991. "Highly-Ordered Ultrathin Lc Multilayer Films on Solid Substrates." Advanced Materials. https://doi.org/10.1002/adma.19910031211.

Decher, G., and J. D. Hong. 1991. "Buildup of Ultrathin Multilayer Films by a Self-Assembly Process: II. Consecutive Adsorption of Anionic and Cationic Bipolar Amphiphiles and Polyelectrolytes on Charged Surfaces." Berichte Der Bunsengesellschaft Für Physikalische Chemie. https://doi.org/10.1002/bbpc.19910951122.

Dimitrova, B., I. B. Ivanov, and E. Nakache. 1988. "MASS TRANSPORT EFFECTS ON THE STABILITY OF EMULSION: EMULSION FILMS WITH ACETIC ACID AND ACETONE DIFFUSING ACROSS THE INTERFACE." Journal of Dispersion Science and Technology 9 (4): 321–41.

El-Shabouri, M. H. 2002. "Positively Charged Nanoparticles for Improving the Oral Bioavailability of Cyclosporin-A." International Journal of Pharmaceutics 249 (1-2): 101–8.

Fessi, H., F. Puisieux, J. Ph Devissaguet, N. Ammoury, and S. Benita. 1989. "Nanocapsule Formation by Interfacial Polymer Deposition Following Solvent Displacement." International Journal of Pharmaceutics 55 (1): R1–4.

Galindo-Rodriguez, Sergio, Eric Allémann, Hatem Fessi, and Eric Doelker. 2004. "Physicochemical Parameters Associated with Nanoparticle Formation in the Salting-Out, Emulsification-Diffusion, and Nanoprecipitation Methods." Pharmaceutical Research 21 (8): 1428–39.

Ganachaud, Fran�ois, and Joseph L. Katz. 2005. "Nanoparticles and Nanocapsules Created Using the Ouzo Effect: Spontaneous

Emulsification as an Alternative to Ultrasonic and High-Shear Devices." ChemPhysChem. https://doi.org/10.1002/cphc.200400527.

Garti, Nissim. 1997. "Double Emulsions — Scope, Limitations and New Achievements." Colloids and Surfaces A: Physicochemical and Engineering Aspects. https://doi.org/10.1016/s0927-7757(96)03809-5.

Hildebrand, Gesine E., and Johannes W. Tack. 2000. "Microencapsulation of Peptides and Proteins." International Journal of Pharmaceutics. https://doi.org/10.1016/s0378-5173(99)00415-9.

Iler, R. K. 1966. "Multilayers of Colloidal Particles." Journal of Colloid and Interface Science. https://doi.org/10.1016/0095-8522(66)90018-3.

Irache, Juan M., María Huici, Monica Konecny, Socorro Espuelas, Miguel Angel Campanero, and Pau Arbos. 2005. "Bioadhesive Properties of Gantrez Nanoparticles." Molecules 10 (1): 126–45.

Khoee, Sepideh, and Morteza Yaghoobian. 2009. "An Investigation into the Role of Surfactants in Controlling Particle Size of Polymeric Nanocapsules Containing Penicillin-G in Double Emulsion." European Journal of Medicinal Chemistry 44 (6): 2392–99.

Krause, H. J., and P. Rohdewald. 1985. "Preparation of Gelatin Nanocapsules and Their Pharmaceutical Characterization." Pharmaceutical Research 2 (5): 239–43.

Kreuter, Jörg. 1983. "Physicochemical Characterization of Polyacrylic Nanoparticles." International Journal of Pharmaceutics. https://doi.org/10.1016/0378-5173(83)90113-8.

Leite, Elaine Amaral, Andrea Grabe-Guimarães, Homero Nogueira Guimarães, George Luiz Lins Machado-Coelho, Gillian Barratt, and Vanessa C. F. Mosqueira. 2007. "Cardiotoxicity Reduction Induced by Halofantrine Entrapped in Nanocapsule Devices." Life Sciences 80 (14): 1327–34.

Lertsutthiwong, Pranee, Khanittha Noomun, Nutthapon Jongaroonngamsang, Pornchai Rojsitthisak, and Ubonthip Nimmannit. 2008. "Preparation of Alginate Nanocapsules Containing Turmeric Oil." Carbohydrate Polymers. https://doi.org/10.1016/j.carbpol.2008.02.009.

Lutter, Stefanie, Joachim Koetz, Brigitte Tiersch, Adriana Boschetti-de-Fierro, and Volker Abetz. 2008. "Formation of Gold Nanoparticles in Triblock Terpolymer-Modified Inverse Microemulsions." Colloids and Surfaces A: Physicochemical and Engineering Aspects. https://doi.org/10.1016/j.colsurfa.2008.07.014.

Magenheim, B., M. Y. Levy, and S. Benita. 1993. "A New in Vitro Technique for the Evaluation of Drug Release Profile from Colloidal Carriers - Ultrafiltration Technique at Low Pressure." International Journal of Pharmaceutics. https://doi.org/10.1016/0378-5173(93)90015-8.

Margolis, Daniel J. A., John M. Hoffman, Robert J. Herfkens, R. Brooke Jeffrey, Andrew Quon, and Sanjiv S. Gambhir. 2007. "Molecular Imaging Techniques in Body Imaging." Radiology. https://doi.org/10.1148/radiol.2452061117.

Memişoğlu, Erem, Amélie Bochot, Murat Şen, Dominique Duchêne, and A. Atilla Hıncal. 2003. "Non-Surfactant Nanospheres of Progesterone Inclusion Complexes with Amphiphilic β-Cyclodextrins." International Journal of Pharmaceutics. https://doi.org/10.1016/s0378-5173(02)00593-8.

Molpeceres, J., M. Guzman, M. R. Aberturas, M. Chacon, and L. Berges. 1996. “Application of Central Composite Designs to the Preparation of Polycaprolactone Nanoparticles by Solvent Displacement.” Journal of Pharmaceutical Sciences 85 (2): 206–13.

Nagarwal, Ramesh C., Shri Kant, P. N. Singh, P. Maiti, and J. K. Pandit. 2009. “Polymeric Nanoparticulate System: A Potential Approach for Ocular Drug Delivery.” Journal of Controlled Release: Official Journal of the Controlled Release Society 136 (1): 2–13.

Nemati, F. 1996. “Reversion of Multidrug Resistance Using Nanoparticles in Vitro: Influence of the Nature of the Polymer.” International Journal of Pharmaceutics. https://doi.org/10.1016/0378-5173(96)04559-0.

Ourique, A. F., A. R. Pohlmann, S. S. Guterres, and R. C. R. Beck. 2008. “Tretinoin-Loaded Nanocapsules: Preparation, Physicochemical Characterization, and Photostability Study.” International Journal of Pharmaceutics 352 (1-2): 1–4.

Patra, Jayanta Kumar, Gitishree Das, Leonardo Fernandes Fraceto, Estefania Vangelie Ramos Campos, Maria Del Pilar Rodriguez-Torres, Laura Susana Acosta-Torres, Luis Armando Diaz-Torres, et al. 2018. “Nano Based Drug Delivery Systems: Recent Developments and Future Prospects.” Journal of Nanobiotechnology 16 (1): 71.

Prego, C., M. Fabre, D. Torres, and M. J. Alonso. 2006. “Efficacy and Mechanism of Action of Chitosan Nanocapsules for Oral Peptide Delivery.” Pharmaceutical Research 23 (3): 549–56.

Puglisi, G., M. Fresta, G. Giammona, and C. A. Ventura. 1995. “Influence of the Preparation Conditions on Poly(ethylcyanoacrylate) Nanocapsule Formation.” International Journal of Pharmaceutics. https://doi.org/10.1016/0378-5173(95)00142-6.

Quintanar-Guerrero, D., E. Allémann, H. Fessi, and E. Doelker. 1998. “Preparation Techniques and Mechanisms of Formation of Biodegradable Nanoparticles from Preformed Polymers.” Drug Development and Industrial Pharmacy 24 (12): 1113–28.

Sharma, Parvesh, Scott Brown, Glenn Walter, Swadeshmukul Santra, and Brij Moudgil. 2006. “Nanoparticles for Bioimaging.” Advances in Colloid and Interface Science. https://doi.org/10.1016/j.cis.2006.05.026.

Soppimath, K. S., T. M. Aminabhavi, A. R. Kulkarni, and W. E. Rudzinski. 2001. “Biodegradable Polymeric Nanoparticles as Drug Delivery Devices.” Journal of Controlled Release: Official Journal of the Controlled Release Society 70 (1-2): 1–20.

Vauthier, Christine, Catherine Dubernet, Elias Fattal, Huguette Pinto-Alphandary, and Patrick Couvreur. 2003. “Poly(alkylcyanoacrylates) as Biodegradable Materials for Biomedical Applications.” Advanced Drug Delivery Reviews 55 (4): 519–48.

Wehrle, Pascal, Baruch Magenheim, and Simon Benita. 1995. “The Influence of Process Parameters on the PLA Nanoparticle Size Distribution, Evaluated by Means of Factorial Design.” European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V 41 (1): 19–26.

Weissleder, Ralph. 2002. “Scaling down Imaging: Molecular Mapping of Cancer in Mice.” Nature Reviews Cancer. https://doi.org/10.1038/nrc701.