Polymeric Nanocapsules

Subjects: Nanoscience & Nanotechnology | Chemistry, Organic | Others
Contributor: Piera Di Martino

Polymer-based nanocapsules have been widely studied as a potential drug delivery system in recent years. Nanocapsules—as one of kind nanoparticle—provide a unique nanostructure, consisting of a liquid/solid core with a polymeric shell. This is of increasing interest in drug delivery applications. In this review, nanocapsules delivery systems studied in last decade are reviewed, along with nanocapsule formulation, characterizations of physical/chemical/biologic properties and applications. Furthermore, the challenges and opportunities of nanocapsules applications are also proposed.

Keywords: polymeric nanocapsule ; drug delivery system ; encapsulation ; nanotechnology

1. Introduction

Over the past century, nanotechnology has increasingly acquired a crucial role in drug delivery [1][2], diagnostic [3][4], biomedical imaging [5][6] and other medicine-related domains [7][8][9]. Employing nanoparticles as delivery system—currently a hot topic of nanotechnology in medical applications—has been widely studied and developed due to their biocompatibility, controlled- and targeted-release abilities [10][11]. Nanoparticles are generally defined as “solid colloidal particles with nano-dimension size (1–1000 nm)” [12][13]. Nevertheless, in the literature, the most common nanoparticle size referred to is between 100–500 nm, in order to avoid fast clearance upon intravenous administration, prolong circulation half-life, and at the same time, increase the probability of crossing various biologic barriers and preventing accumulation in capillaries and/or other organs [14][15]. Polymeric nanoparticles can not only modulate the pharmacokinetic properties of various active substances due to the subcellular size of nanoparticles, but also affect biocompatibility and/or biodegradability of polymers employed to produce the nanoparticles. Depending on their internal structure, polymeric nanoparticles may be further classified as nanospheres or nanocapsules [16]. As suggested by the name, a polymeric nanosphere has usually a regular sphere structure, which is composed of a solid polymeric matrix. In the other hand, a polymeric nanocapsule consists of a liquid/solid core coated with a polymeric shell, which is absent in the nanosphere [17]. In recent years, polymeric nanocapsules have attracted more interest in drug delivery applications, benefitting from their core-shell microstructure. Compared with polymeric nanospheres, the solid/oil core of nanocapsules can effectively increase drug-loading efficiency, while reduce the polymeric matrix content of nanoparticles [18]. In addition, the encapsulated payload can be isolated from tissue environment by the polymeric shell, thereby avoiding the degradation or burst release induced by pH, temperature, enzymes and other factors. Additionally, the polymeric shell can be functionalized by smart molecules able to interact with targeted biomolecules, thus enabling for targeting drug delivery [19][20][21].

Benefitting from above advantages, polymeric nanocapsules have been increased interest and applied in pharmaceutical field as drug delivery carriers. Since several specialized reviews have already discussed in-depth the nanotechnologies and polymeric materials for the formulation of nanocapsules [22][23], in the present review, we focused our attention on the nanocapsules delivery systems developed in last decade. Furthermore, the challenges and opportunities of nanocapsules applications will be heighted and discussed.

2. Challenge of Nanocapsules as Drug Delivery System

According to a fair amount of theoretical and experimental work, polymeric nanocapsules have demonstrated enormous potentials and wide spaces to be applied as drug delivery systems for various biomedical applications. Nanocapsules are being implemented to overcome limitations of conventional drug delivery approaches by achieving high drug-content loading for both hydrophilic and hydrophobic drugs, as well as targeted and sustained delivery. However, there are still several technical challenges with polymeric nanocapsules that need to be further developed before industrial application.

2.1. Thickness Characterization of Polymeric Shell

Compared with nanospheres, the core-shell morphologic structure is one of the particular advantages of nanocapsules as drug delivery system. The thickness of the polymer shell plays a critical role in nanocapsule formulation, active substance protection as well as release profiles [24][25]. However, there is little discussion regarding the quantitative measurement of the polymeric shell of nanocapsules in most of studies; only few examples can be here reported. The main characterization method of the thickness is observation via transmission electron microscopy (TEM) [26][27]. For example, a 10-nm polymeric shell has been qualitatively estimated by TEM from argon oil/oleoyl polyoxylglycerides/Eudragit® RS nanocapsules [28].

To obtain more specific values for shell thickness, mathematical calculation has also been carried out. The shell thickness of the nanocapsules formulated based on the scarified core template can be calculated as the different value between the particle radius of the completed nanocapsules and the scarified template. The thickness of polymeric shell of polydopamine/Au hollow nanocapsules was calculated as 70 nm [29].

The surface parameter variation before and after polymer coating can be also applied for the estimation of shell thickness. It has been demonstrated that variation versus salinity of the medium— which may be attributed to the nanoparticle surface—can be calculated through the Eversole and Boardman equation [30]. The thickness of dextran's outer layer of a Miglyol® 810/dextran nanocapsules was estimated as 5 nm by calculating the salinity difference using the Eversole and Boardman equation [31].

2.2. Organic Solvent Free Formation

Organic solvents play a critical role in polymeric nanocapsule formulation. Organic solvents have to be strictly eliminated from the formulation by purification procedure because of their toxicity in humans. Nonetheless, traces of organic solvents that cannot be adequately removed may cause toxic effects in clinical application. Additionally, nanoparticles are usually captured by immune cells—such as macrophages or mononuclear phonotypes—which indicates that the trigger of inflammation and the toxic organic solvent is considered as one of the reason for this inflammatory situation induced by nanoparticles [32]. Despite potential toxic risks, the organic solvent removal step can also influence the stability of nanoparticles [33] Therefore, it is significant and imperative to develop polymeric nanocapsule using solvent-free methods.

There are several studies that report the formulation of polymeric nanocapsules by solvent-free approach. Two formulation strategies are possible: either by using solvent-free organic phase for nanoemulsion preparation or form polymeric shell by polymerization in aqueous environment. A solvent-free protamine nanocapsule was developed as carrier for a model lipophilic anti-inflammatory agent, cyclosporine A. The nanocapsules were prepared by a nanoemulsion method. The organic phase was prepared by mixing Maisine 35–1 and Tween® 80 which acted as oleic compound and surfactant, respectively. Anionic surfactant sodium deoxycholate and polyethylene glycol-40 stearate were added to the water phase. Polyethylene glycol-40 stearate was added to prevent the aggregation of nanocapsules. The organic and inorganic phases were prepared into nanoemulsion and added to protamine aqueous solution [34] along with magnetic stirring to obtain a nanocapsule formulation. Resulted protamine nanoparticles presented a particle size around 160–180 nm with a narrow distribution (PDI = 0.2). This solvent-free method can be considered as a promising strategy for nanocapsule prepared by water-soluble polymers. Another interesting example is that of Steelandt et al. who developed polymeric nanocapsules containing an oleic core and a poly-ε-caprolactone shell [35]. Poly-ε-caprolactone was heated at the glass transition temperature then mixed with oleic compound and surfactant to act as organic phase for emulsion preparation. This method can be considered as potential method for preparation of nanocapsules based on hydrophobic crystalline or amorphous polymer.

The polymeric nanocapsules can also be prepared by monomer polymerization in organic solvent free condition to preform polymeric shell. For example, a nanocapsule was formulated by free radical polymerization of monomers acrylamide and 2-aminoethyl methacrylate hydrochloride in the deoxygenated buffer [36]. However, the polymerization method can also lead new toxic issue by residual monomers, cross linker or other chemical compounds.

2.3. Aggregation and Storage

Based on fabrication procedure, nanocapsules are in general yielded into aqueous dispersion. However, it has been highlighted that nanocapsules tend to be unstable and aggregate in water suspension, thereby inducing leaking of payload. In this case, to store nanocapsules into dried form is generally preferable to improve the stability of nanocapsules and also prolong the store term [37]. Moreover, to adapt preparations of particular pharmaceutical dosage forms, such as oral tablet, it is necessary to manufacture the polymeric nanocapsules suspension into dry state for further preservation and usage [38][27][39]. Spray drying as one of the common drying method has been applied for recovery of

nanocapsules into solid dry state. To enhance the stability of nanocapsules by avoiding their aggregation during the drying process, protectants such as inulin or polyvinyl alcohol were used [40][41]. But the application of spray drying method may induce thermal degradation of polymeric nanocapsules and also drug loading [42]. Lyophilization carried out in presence of a lyoprotectant is another strategy for desiccation of nanocapsules [43]. However, thin polymeric shell of nanocapsules may compromise the stability of the whole delivery system because of the low working pressure, especially when nanocapsules are characterized by an oil or a hollow core [44]. After all, lyophilization is considered an expensive technique due to the experimental conditions, time and equipment need [45]. Therefore, optimization for an appropriate desiccation procedure for the stabilization and storage of polymeric nanocapsules is most urgent needed.

2.4. Sterilization

Sterilization of polymeric nanocapsules is also a major challenge in the development of appropriate drug delivery system for clinical trials and commercial manufactures. Several approaches have been studied to sterilize nanoparticles for in vivo experiments. Membrane filtration is a physical method to sterilize nanoparticles by using 0.22 μm filters: this method allows for the removal of microorganisms from nanocapsules water suspension [46]. This method does not need extraneous heat, radiation or chemicals which could induce damage or degradation of polymeric nanocapsules [47][48]. However, membrane filtration presents the limitation for the nanocapsules possessing particle size higher 200 nm. In addition, it could cause decrease of product yield due to filter clogging by nanocapsules. Autoclaving is another effective technique that has been applied for polymer nanoparticles sterilization via controlled temperature and pressure [49][50]. However, aggregation, morphology deformation and also chemical degradation were observed for several polymeric nanoparticles [51][52]. Additionally, size increasing was detected for nanocapsules with an oil core Miglyol®-based. The size increased depended either on swelling of polymeric shell or expansion of oil core under the harsh environment of temperature and pressure [53]. Gamma irradiation can provide homogeneous sterilization to inactive the microorganisms and avoid the risk of high temperature or pressure [54][55]. However, it may cause physical or chemical degeneration of either polymeric nanocapsules or loaded drugs. As a conclusion, at the present, to maintain a contaminant-free fabrication procedure of polymeric nanocapsules is the most optimal strategy for the preparation of sterilized nanocapsules. Additionally, novel and advanced strategies for sterilization of polymeric nanocapsules are imperative.

Furthermore, more novel polymeric materials, surfactants and also chemical ingredients have been used to formulate functional polymeric nanocapsules in order to meet applications in demand which are bringing more opportunities but also challenges for the polymeric nanoparticles as drug delivery systems.

3. Conclusion

Research of polymeric nanoparticles has widely attracted attention recently. This minireview has reported the studies and progress of polymeric nanocapsules as drug delivery system in pharmaceutical field, in last decade. To perform the specific core-shell nanostructure, various materials were used for polymeric nanocapsule formulation via the interfacial deposition method, nano-emulsion template method or lay-by layer method. The selection of polymers and formulation methods mainly depends on the characteristics of pharmaceutical ingredient and application purpose. Polymeric nanocapsules as drug delivery systems can improve the bioavailability of payloads and achieve sustained and targeted delivery. Likewise, they can also effectively reduce the harmful effects between payload and tissue environments. By loading the drug inside polymeric nanocapsules, it can protect the drug from failure or degradation caused by biologic environment. Meanwhile, it can also reduce the side-effect induced by drug to health tissue. To date, many studies have mainly focused on the development and characterization of bioactive substance-loaded polymeric nanocapsules. However, the storage and sterilization methods of formed drug-loaded polymeric nanocapsules are needed attentions and researches. Additionally, future perspectives in polymeric nanocapsules should focus on studies of using new and most performing polymers to develop advanced delivery system, thereby extending the applications of polymeric nanocapsules in pharmaceutical fields.

References

1. Omid C. Farokhzad; Robert Langer; Impact of Nanotechnology on Drug Delivery. *ACS Nano* **2009**, *3*, 16-20, 10.1021/nn900002m.
2. Mehrdad Hamidi; Amir Azadi; Pedram Rafiei; Hajar Ashrafi; A pharmacokinetic overview of nanotechnology-based drug delivery systems: an ADME-oriented approach.. *Critical Reviews™ in Therapeutic Drug Carrier Systems* **2013**, *30*, 435-467, 10.1615/critrevtherdrugcarriersyst.2013007419.

3. M Cheng; Giovanni Cuda; Y Bunimovich; Marco Gaspari; J Heath; H Hill; C Mirkin; A Nijdam; Rosa Terracciano; Thomas Thundat; et al. Nanotechnologies for biomolecular detection and medical diagnostics. *Current Opinion in Chemical Biology* **2006**, *10*, 11-19, 10.1016/j.cbpa.2006.01.006.

4. Kewal K. Jain; Nanodiagnostics: application of nanotechnology in molecular diagnostics. *Expert Review of Molecular Diagnostics* **2003**, *3*, 153-161, 10.1586/14737159.3.2.153.

5. Amr El-Sayed; Mohamed Kamel; Advances in nanomedical applications: diagnostic, therapeutic, immunization, and vaccine production.. *Environmental Science and Pollution Research* **2019**, , 1-14, 10.1007/s11356-019-06459-2.

6. Otilia M. Koo; Israel Rubinstein; Hayat Önyüksel; Role of nanotechnology in targeted drug delivery and imaging: a concise review. *Nanomedicine: Nanotechnology, Biology and Medicine* **2005**, *1*, 193-212, 10.1016/j.nano.2005.06.004.

7. L Zhang; Frank X. Gu; Jm Chan; Az Wang; Rs Langer; Oc Farokhzad; Juliana Chan; Andrew Z. Wang; Omid C. Farokhzad; Nanoparticles in Medicine: Therapeutic Applications and Developments. *Clinical Pharmacology & Therapeutics* **2007**, *83*, 761-769, 10.1038/sj.clpt.6100400.

8. R Jurgons; C Seliger; A Hilpert; Lutz Trahms; S Odenbach; C Alexiou; Drug loaded magnetic nanoparticles for cancer therapy. *Journal of Physics: Condensed Matter* **2006**, *18*, S2893-S2902, 10.1088/0953-8984/18/38/s24.

9. Ilaria Tocco; Barbara Zavan; Franco Bassetto; Vincenzo Vindigni; Nanotechnology-Based Therapies for Skin Wound Regeneration. *Journal of Nanomaterials* **2012**, *2012*, 1-11, 10.1155/2012/714134.

10. Dwaine F. Emerich; Christopher G. Thanos; Targeted nanoparticle-based drug delivery and diagnosis. *Journal of Drug Targeting* **2007**, *15*, 163-183, 10.1080/10611860701231810.

11. С. Э. Гельперина; Kevin Kisich; Michael D. Iseman; L. Heifets; The Potential Advantages of Nanoparticle Drug Delivery Systems in Chemotherapy of Tuberculosis. *American Journal of Respiratory and Critical Care Medicine* **2005**, *172*, 1487-1490, 10.1164/rccm.200504-613PP.

12. D. Moinard-Checot; Y. Chevalier; S. Briançon; H. Fessi; S. Guinebretière; Nanoparticles for drug delivery: review of the formulation and process difficulties illustrated by the emulsion-diffusion process.. *Journal of Nanoscience and Nanotechnology* **2006**, *6*, 2664-2681, 10.1166/jnn.2006.479.

13. Chen Fu; Chizhu Ding; Xianchao Sun; Ailing Fu; Curcumin nanocapsules stabilized by bovine serum albumin-capped gold nanoclusters (BSA-AuNCs) for drug delivery and theranosis. *Materials Science and Engineering: C* **2018**, *87*, 149-154, 10.1016/j.msec.2017.12.028.

14. Elvin Blanco; Haifa Shen; Mauro Ferrari; Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology* **2015**, *33*, 941-951, 10.1038/nbt.3330.

15. Marie Gaumet; Angelica Vargas; Robert Gurny; Florence Delie; Nanoparticles for drug delivery: The need for precision in reporting particle size parameters. *European Journal of Pharmaceutics and Biopharmaceutics* **2008**, *69*, 1-9, 10.1016/j.ejpb.2007.08.001.

16. Sylwia Łukasiewicz; Krzysztof Szczepanowicz; Karolina Podgórna; Ewa Błasiak; Nather Majeed; Sven Ove Ögren; Witold Nowak1; Piotr Warszyński; Marta Dziedzicka-Wasylewska; Encapsulation of clozapine in polymeric nanocapsules and its biological effects. *Colloids and Surfaces B: Biointerfaces* **2016**, *140*, 342-352, 10.1016/j.colsurfb.2015.12.044.

17. Luiza Abrahão Frank; R.P. Gazzi; P. De Andrade Mello; A. Buffon; Adriana Raffin Pohlmann; Silvia S. Guterres; Imiquimod-loaded nanocapsules improve cytotoxicity in cervical cancer cell line. *European Journal of Pharmaceutics and Biopharmaceutics* **2019**, *136*, 9-17, 10.1016/j.ejpb.2019.01.001.

18. Adriana Raffin Pohlmann; Valeria Weiss; Omar Mertins; Nádya Pesce Da Silveira; Sílvia Stanisçuaski Guterres; Spray-dried indomethacin-loaded polyester nanocapsules and nanospheres: development, stability evaluation and nanostructure models.. *European Journal of Pharmaceutical Sciences* **2002**, *16*, 305–312, .

19. Izabel Cristina Trindade; Gwenaelle Pound-Lana; Douglas Gualberto Sales Pereira; Laser Antônio Machado De Oliveira; Margareth Spangler Andrade; José Mário Carneiro Vilela; Bruna Bueno Postacchini; Vanessa Carla Furtado Mosqueira; Mechanisms of interaction of biodegradable polyester nanocapsules with non-phagocytic cells. *European Journal of Pharmaceutical Sciences* **2018**, *124*, 89-104, 10.1016/j.ejps.2018.08.024.

20. Maribel Teixeira; María José Alonso; Madalena Pinto; Carlos Maurício Barbosa; Development and characterization of PLGA nanospheres and nanocapsules containing xanthone and 3-methoxyxanthone. *European Journal of Pharmaceutics and Biopharmaceutics* **2005**, *59*, 491-500, 10.1016/j.ejpb.2004.09.002.

21. Sílvia S. Guterres; Marta P. Alves; Adriana Raffin Pohlmann; Polymeric Nanoparticles, Nanospheres and Nanocapsules, for Cutaneous Applications. *Drug Target Insights* **2007**, *2*, 147-157, 10.1177/117739280700200002.

22. Mona Abdel-Mottaleb; Dirk Neumann; A. Lamprecht; Lipid nanocapsules for dermal application: A comparative study of lipid-based versus polymer-based nanocarriers. *European Journal of Pharmaceutics and Biopharmaceutics* **2011**, *79*,

36-42, 10.1016/j.ejpb.2011.04.009.

23. Pavankumar Kothamasu; Hemanth Kanumur; Niranjan Ravur; Chiranjeevi Maddu; Radhika Parasuramrajam; Sivakumar Thangavel; Nanocapsules: The Weapons for Novel Drug Delivery Systems. *BioImpacts* **2012**, *2*, 71-81, 10.5681/bi.2012.011.

24. Shi, C.; Zhong, S.; Sun, Y.; Xu, L.; He, S.; Dou, Y.; Zhao, S.; Gao, Y.; Cui, X.; Sonochemical preparation of folic acid-decorated reductive-responsive epsilon-poly-L-lysine-based microcapsules for targeted drug delivery and reductive-triggered release. *Mater. Sci. Eng. C* **2020**, *106*, 110251, .

25. Kawthar Bouchemal; Francoise Couenne; S. Briancon; H. Fessi; M. Tayakout; Polyamides nanocapsules: Modeling and wall thickness estimation. *AIChE Journal* **2006**, *52*, 2161-2170, 10.1002/aic.10828.

26. Sabrina Belbekhouche; Julie Oniszczuk; André Pawlak; Imane El Joukhar; Angélique Goffin; Gilles Varrault; Dil Sahali; Benjamin Carbonnier; Cationic poly(cyclodextrin)/alginate nanocapsules: From design to application as efficient delivery vehicle of 4-hydroxy tamoxifen to podocyte in vitro. *Colloids and Surfaces B: Biointerfaces* **2019**, *179*, 128-135, 10.1016/j.colsurfb.2019.03.060.

27. F.H. Xavier-Jr; C. Gueutin; H. Chacun; C. Vauthier; E.S.T. Egito; Mucoadhesive paclitaxel-loaded chitosan-poly (isobutyl cyanoacrylate) core-shell nanocapsules containing copaiba oil designed for oral drug delivery. *Journal of Drug Delivery Science and Technology* **2019**, *53*, ., 10.1016/j.jddst.2019.101194.

28. Taher Nassar; Alona Rom; Abraham Nyska; Simon Benita; Novel double coated nanocapsules for intestinal delivery and enhanced oral bioavailability of tacrolimus, a P-gp substrate drug. *Journal of Controlled Release* **2009**, *133*, 77-84, 10.1016/j.jconrel.2008.08.021.

29. Bin Shang; Xiaofen Zhang; Ri Ji; Yanbing Wang; He Hu; Bo Peng; Ziwei Deng; Preparation of colloidal polydopamine/Au hollow spheres for enhanced ultrasound contrast imaging and photothermal therapy. *Materials Science and Engineering: C* **2020**, *106*, 110174, 10.1016/j.msec.2019.110174.

30. C. Rouzes; R. Gref; M. Leonard; A. De Sousa Delgado; E. Dellacherie; Surface modification of poly(lactic acid) nanospheres using hydrophobically modified dextrans as stabilizers in an o/w emulsion/evaporation technique.. *Journal of Biomedical Materials Research* **2000**, *50*, 557-565, 10.1002/(sici)1097-4636(20000615)50:4<557::aid-jbm11>3.0.co;2-r.

31. Forero Ramirez, L.M.; Boudier, A.; Gaucher, C.; Babin, J.; Durand, A.; Six, J.L.; Nouvel, C.; Dextran-covered pH-sensitive oily core nanocapsules produced by interfacial Reversible Addition-Fragmentation chain transfer miniemulsion polymerization. *J. Colloid Interface Sci.* **2020**, *569*, 57–67, .

32. D.K. Sahana; G. Mittal; V. Bhardwaj; M. N. V. Ravi Kumar; PLGA Nanoparticles for Oral Delivery of Hydrophobic Drugs: Influence of Organic Solvent on Nanoparticle Formation and Release Behavior In Vitro and In Vivo Using Estradiol as a Model Drug. *Journal of Pharmaceutical Sciences* **2008**, *97*, 1530-1542, 10.1002/jps.21158.

33. Varun Kumar; Robert K. Prud'Homme; Nanoparticle stability: Processing pathways for solvent removal. *Chemical Engineering Science* **2009**, *64*, 1358-1361, 10.1016/j.ces.2008.11.017.

34. Paulina Jakubiak; Lungile N. Thwala; Ana Cadete; Véronique Preat; María José Alonso; Ana Beloqui; Noemi Csaba; Solvent-free protamine nanocapsules as carriers for mucosal delivery of therapeutics. *European Polymer Journal* **2017**, *93*, 695-705, 10.1016/j.eurpolymj.2017.03.049.

35. Damien Salmon; Julie Steelandt; Elodie Gilbert; Eyad Almouazen; Marek Haftek; F. Pirot; Laurène Roussel; François Nr Renaud; Antimicrobial nanocapsules: from new solvent-free process to in vitro efficiency. *International Journal of Nanomedicine* **2014**, *9*, 4467-4474, 10.2147/IJN.S64746.

36. María Rocío Villegas; Alejandro Baeza; Alicia Usategui; Pablo L Ortiz-Romero; Jose Luis Pablos; María Vallet-Regí; Collagenase nanocapsules: An approach to fibrosis treatment. *Acta Biomaterialia* **2018**, *74*, 430-438, 10.1016/j.actbio.2018.05.007.

37. P. N. Ezhilarasi; Pothiyappan Karthik; Narayansing Chhanwal; C. Anandharamakrishnan; Nanoencapsulation Techniques for Food Bioactive Components: A Review. *Food and Bioprocess Technology* **2012**, *6*, 628-647, 10.1007/s11947-012-0944-0.

38. Raquel S. Araújo; Giani Martins Garcia; José Mario Carneiro Vilela; Margareth Spangler Andrade; Laser Antônio Machado Oliveira; Eunice Kazue Kano; Carla Christine Lange; Maria Aparecida Vasconcelos Paiva E Brito; Humberto Brandão; Vanessa Carla Furtado Mosqueira; et al. Cloxacillin benzathine-loaded polymeric nanocapsules: Physicochemical characterization, cell uptake, and intramammary antimicrobial effect.. *Materials Science and Engineering: C* **2019**, *104*, 110006, 10.1016/j.msec.2019.110006.

39. Yajie Wang; Katherine Kho; Wean Sin Cheow; Kunn Hadinoto; A comparison between spray drying and spray freeze drying for dry powder inhaler formulation of drug-loaded lipid–polymer hybrid nanoparticles. *International Journal of Pharmaceutics* **2012**, *424*, 98-106, 10.1016/j.ijpharm.2011.12.045.

40. Paula Dos Santos Chaves; Luiza Abrahão Frank; Afra Torge; Marc Schneider; Adriana Raffin Pohlmann; Sílvia Stanisçuaski Guterres; Ruy Carlos Ruver Beck; Spray-dried carvedilol-loaded nanocapsules for sublingual administration: Mucoadhesive properties and drug permeability. *Powder Technology* **2019**, *354*, 348-357, 10.1016/j.powtec.2019.06.012.
41. Yue Wang; Zhaojun Zheng; Kai Wang; Chuanhui Tang; Yuanfa Liu; Jinwei Li; Prebiotic carbohydrates: Effect on physicochemical stability and solubility of algal oil nanoparticles.. *Carbohydrate Polymers* **2019**, *228*, 115372, 10.1016/j.carbpol.2019.115372.
42. Patel, R.; Patel, M.; Suthar, A.; Spray drying technology: An overview. *Indian J. Sci. Technol.* **2009**, *2*, 44–47, .
43. Mohamed Gaber; Mark Hany; Sarah Mokhtar; Maged W. Helmy; Kadria A. Elkodairy; Ahmed O. Elzoghby; Boronic-targeted albumin-shell oily-core nanocapsules for synergistic aromatase inhibitor/herbal breast cancer therapy. *Materials Science and Engineering: C* **2019**, *105*, 110099, 10.1016/j.msec.2019.110099.
44. Marcela A. Moretton; Diego A. Chiappetta; Alejandro Sosnik; Cryoprotection–lyophilization and physical stabilization of rifampicin-loaded flower-like polymeric micelles. *Journal of The Royal Society Interface* **2011**, *9*, 487-502, 10.1098/rsif.2011.0414.
45. Getachew Assegehegn; Edmundo Brito-De La Fuente; José M. Franco; Críspulo Gallegos; The Importance of Understanding the Freezing Step and Its Impact on Freeze-Drying Process Performance. *Journal of Pharmaceutical Sciences* **2019**, *108*, 1378-1395, 10.1016/j.xphs.2018.11.039.
46. C. Verdun; P. Couvreur; H. Vranckx; V. Lenaerts; M. Roland; Development of a nanoparticle controlled-release formulation for human use. *Journal of Controlled Release* **1986**, *3*, 205-210, 10.1016/0168-3659(86)90081-7.
47. Yvette Niamien Konan; R. Cerny; Joselyne Favet; Myriam Berton; R Gurny; Eric Allémann; Preparation and characterization of sterile sub-200 nm meso-tetra(4-hydroxylphenyl)porphyrin-loaded nanoparticles for photodynamic therapy.. *European Journal of Pharmaceutics and Biopharmaceutics* **2003**, *55*, , .
48. Muhammad Saad Khan; Jangsun Hwang; Kyungwoo Lee; Yonghyun Choi; Kyobum Kim; Hyung-Jun Koo; Jong Wook Hong; Jonghoon Choi; Oxygen-Carrying Micro/Nanobubbles: Composition, Synthesis Techniques and Potential Prospects in Photo-Triggered Theranostics. *Molecules* **2018**, *23*, 2210, 10.3390/molecules23092210.
49. H. Heiati; R. Tawashi; N. C. Phillips; Drug retention and stability of solid lipid nanoparticles containing azidothymidine palmitate after autoclaving, storage and lyophilization. *Journal of Microencapsulation* **1998**, *15*, 173-184, 10.3109/02652049809006847.
50. Ali Seyfoddin; Raida Al-Kassas; Development of solid lipid nanoparticles and nanostructured lipid carriers for improving ocular delivery of acyclovir. *Drug Development and Industrial Pharmacy* **2012**, *39*, 508-519, 10.3109/03639045.2012.665460.
51. V. Masson; F. Maurin; H. Fessi; J.P. Devissaguet; Influence of sterilization processes on poly(ε-caprolactone) nanospheres. *Biomaterials* **1997**, *18*, 327-335, 10.1016/s0142-9612(96)00144-5.
52. Özcan, I.; Bouchemal, K.; Segura-Sánchez, F.; Abaci, Ö.; Özer, Ö.; Güneri, T.; Ponchel, G. Effects of sterilization techniques on the PEGylated poly (γ-benzyl-l-glutamate)(PBLG) nanoparticles. Acta Pharm. Sci. 2009, 51.
53. J. M. Rollot; P. Couvreur; F. Puisieux; L. Roblot-Treupel; Physicochemical and Morphological Characterization of Polyisobutyl Cyanoacrylate Nanocapsules. *Journal of Pharmaceutical Sciences* **1986**, *75*, 361-364, 10.1002/jps.2600750408.
54. Dewu Long; Guozhong Wu; Shimou Chena; Preparation of oligochitosan stabilized silver nanoparticles by gamma irradiation. *Radiation Physics and Chemistry* **2007**, *76*, 1126-1131, 10.1016/j.radphyschem.2006.11.001.
55. Melisa Lamanna; Noé J. Morales; Nancy Lis García; Silvia Goyanes; Development and characterization of starch nanoparticles by gamma radiation: Potential application as starch matrix filler. *Carbohydrate Polymers* **2013**, *97*, 90-97, 10.1016/j.carbpol.2013.04.081.