

PHARMACEUTICAL NANOENCAPSULATION STRATEGIES: A MECHANISTIC REVIEW

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ABSTRACT

Colloidal solid particulates of size in nano range with an upper size limit of approximately 1000 nm are called as nanoparticles which include nanospheres (matrix systems) and nanocapsules (reservoir systems). Literature reveals numerous advantages and successful application of nanoparticles in drug therapy. Nanoparticles has proven as active vectors due to their capacity to release drugs; their subcellular size allows relatively higher intracellular uptake than other particulate systems; they can improve the stability of active substances and can be biocompatible with tissue and cells when synthesized from materials that are either biocompatible or biodegradable. Polymeric nanoparticles have been significantly exploited as drug carriers. This review is an attempt to provide summarized information on the various approaches for fabrication of drug loaded nanocapsules.

KEYWORDS

Nanocapsules, nanoparticles, polymer, drug delivery, Stabilization.

INTRODUCTION

Solid colloidal particles of size around 5–10nm (with an upper size limit of ~1000 nm) are called as nanoparticles which include nanospheres and nanocapsules (Quintanar et al., 1998). Literature reveals numerous advantages and successful application of nanoparticles in drug therapy. Nanoparticles has proven as active vectors due to their capacity to release drugs (Cruz et al., 2006; Amaral et al., 2007); their subcellular size allows relatively higher intracellular uptake than other particulate systems (Furtado et al., 2001a,b); they can improve the stability of active substances (Ourique et al., 2008) and can be biocompatible with tissue and cells when synthesized from materials that are either biocompatible or biodegradable. Polymeric nanoparticles have been significantly exploited as drug carriers (Chaubal, 2004; Sinha et al., 2004; Letchford and Burt, 2007). This review is an attempt to provide summarized information on the various approaches for fabrication of drug loaded nanocapsules.

FABRICATION OF NANOCAPSULES

Precipitation/Solvent displacement method

This method needs both solvent and non-solvent phases. The solvent phase essentially consists of a film former such as a polymer in a solvent or in a mixture of solvents, the active ingredient, oil, a lipophilic tensioactive and an active substance

solvent or oil solvent (Fessi et al., 1988). The non-solvent phase consists of a non-solvent or a mixture of non-solvents for the film-forming substance and surfactants. Usually the solvent is an organic medium and the non-solvent is mainly water. However, it is possible to use either two organic phases or two aqueous phases as long as solubility, insolubility and miscibility conditions are satisfied.

The polymers commonly used are biodegradable polyesters, especially poly-ε-caprolactone (PCL), poly(lactide) (PLA) and poly(lactide-co-glicolide) (PLGA). Synthetic polymers have higher stability, purity and better reproducibility than natural polymers (Khoee and Yaghoobian, 2008). Poly ethylene glycol copolymerized polymers has also been used to decrease nanocapsule recognition by the mononuclear phagocyte system (Nogueira de Assis et al., 2008).

In the precipitation method, the nanocapsules are obtained as a colloidal suspension formed when the organic phase is added slowly and with moderate stirring to the aqueous phase. The process variables include organic phase injection rate, aqueous phase agitation rate, the method of organic phase addition and the phase ratio (Legrand et al., 2007; Lince et al., 2008). The process of particle formation in the precipitation method comprises three stages: nucleation, growth and aggregation (Lince et al., 2008).

It has already been established that rapid nanoparticle formation is a process due to differences in surface tension (Quintanar et al., 2005). Since a liquid (aqueous phase) with a high surface tension pulls more strongly on the surrounding liquid than one with a low surface tension (organic phase). This difference between surface tension causes interfacial turbulence and thermal inequalities in the system which lead to the continuous formation of eddies of solvent at the interface of both liquids. Consequently, violent spreading is observed due to mutual miscibility between the solvents, the solvent flows away from regions of low surface tension and the polymer tends to aggregate on the oil surface and forms nanocapsules.

Emulsion-Diffusion Method

This method facilitates encapsulation of both hydrophilic and lipophilic active ingredients as core materials. For nanoencapsulation of a lipophilic active substance, the organic phase contains the polymer, the active substance, oil and an organic solvent partially miscible with water. This organic medium acts as solvent for the different components of the organic phase. If it is required, the organic phase can also include an active substance solvent or oil solvent. The aqueous phase comprises the aqueous dispersion of a stabilizing agent that is prepared using solvent-saturated water while the dilution phase is usually water.

For preparation of nanocapsules using the emulsion-diffusion method, the organic phase is emulsified under vigorous agitation in the aqueous phase. The subsequent addition of water to the system causes the diffusion of the solvent into the external phase, resulting in nanocapsule formation. This can be eliminated by distillation or cross-flow filtration depending on the boiling point of the solvent. It has been shown that nanocapsule size is related to the shear rate used in the emulsification process, the chemical composition of the organic phase, the polymer concentration, the oil-to-polymer ratio and the drop size of the primary emulsion (Guinebretière, 2001; Moinard-Chécot et al., 2008).

The mechanism suggested to explain nanocapsules formation is based on the theory that each emulsion droplet produces several nanocapsules and that these are formed by the combination of polymer precipitation and interfacial phenomena during solvent diffusion (Quintanar et al., 1998a). Consequently, solvent diffusion from the globules carries molecules into the aqueous phase forming local regions of supersaturation from which new globules or polymer aggregates are formed and

stabilized by the stabilizing agent that prevents their coalescence and the formation of agglomerates. Then, if the stabilizer remains at the liquid-liquid interface during the diffusion process and if its protective effect is adequate, the nanocapsules will be formed after the complete diffusion of the solvent.

Double emulsification method

Double emulsions are complex heterodisperse systems that can be classified into two major types: water in oil in water emulsion (w/o/w) and oil in water in oil emulsion (o/w/o). Thus the dispersed phase is itself an emulsion and the inner dispersed globule/ droplet is separated from the outer liquid phase by a layer of another phase. In this method, for the primary w/o emulsion, the oil phase is an organic phase containing a solvent that is totally or partially miscible in water, the film-forming polymer and a w/o surfactant. Then the water containing a stabilizing agent is added to the system to obtain the water in oil in water emulsion. However in this step, particle rigidization is through solvent diffusion and polymer precipitation (Khoee and Yaghoobian, 2008). It has been established 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.

Emulsion-coacervation method

The emulsion-coacervation process involves emulsification of an organic phase with an aqueous phase by mechanical stirring or ultrasound. Then, a simple coacervation process is performed by using either electrolytes, by the addition of a water miscible non-solvent or a dehydration agent or by temperature change (Lutter et al., 2008; Krause and Rohdewald, 1985). Cross linking step follows coacervation to obtain a rigid nanocapsule shell structure. The coacervating agents induce thin solvated shell (Gander et al., 2002).

Polymer-coating method

Methodologically diverse strategies can be used to deposit a thin layer of coating (film forming) polymer on the nanoparticle surface. This can be achieved by adsorbing the polymer onto the uncoated nanoparticles when the latter are incubated in polymer dispersion under stirring (Calvo et al., 1997). Recently, Prego et al. (2006) proposed a coating method which involves preparation of the nanoemulsion template and then subsequent coating it by polymer deposition on the water/oil nanoemulsion surface. Polymeric materials are added in the continuous phase and their precipitation onto the nanoemulsion droplets is triggered by solvent evaporation. In an another

method nanocapsules were fabricated by sonication of a w/o nanoemulsion followed by coating with a solution composed of polymer and dichloromethane gradually added in the continuous organic phase of the nanoemulsion (Anton et al., 2008). The polymeric materials used were poly methyl methacrylate (PMMA), polymethacrylate (PMA) and polycaprolactone (PCL).

NANOCAPSULES: CONCENTRATION, PURIFICATION AND STABILIZATION

The different methods used for preparation of nanocapsules frequently produce dispersions with different concentrations and low drug carrying contents which is a serious disadvantage. Hence concentration of the nanocapsules dispersion is an essential step during production. Evaporation under reduced pressure, water washing, ultracentrifugation and lyophilization are undoubtedly the methods of interest. However, they have often limited application due to the aggregates formed (Duclairoir et al., 1998; Vauthier et al., 2008a) and they are currently only adapted for purifying small batches (Limayem et al., 2004).

The initial nanocapsule dispersions may be contaminated by residual solvents, salts, stabilizers and cross-linking agents that must be eliminated in order to guarantee the purity. Among the strategies used for nanocapsule purification, the literature reports the use of dialysis against water, dialysis against a polymer solution, ultrafiltration, cross-flow microfiltration and diafiltration (Schaffazick et al., 2003; Stella et al., 2007; Vauthier et al., 2008b; Limayem et al., 2004). Nevertheless, it is important to note that techniques such as filtration, dialysis, and ultracentrifugation do not provide efficient separation for small nanocapsule sizes (80–150 nm). In these cases, methods such as gel permeation chromatography have proved to be efficient (Ma et al., 2001).

Although nanocapsule dispersions are considered as stable systems due to Brownian motion, they can be subjected to instability due to, among other reasons, polymer degradation, migration of the active substance from the inner liquid and microbiological contamination of aqueous systems. Indeed, one of the things limiting the industrial development of polymeric nanocapsule suspensions as drug delivery systems is the problem encountered in maintaining the stability of suspensions (Pohlmann et al., 2002). Stabilizers during spray drying or lyophilization are essential. The use of cryoprotectants and lyoprotectants is necessary since the thin polymeric envelope of the nanocapsules may not withstand the

stress. Nanocapsules can be destabilized by the crystallization during freezing, dessication or storage of certain cryoprotectants such as mannitol, sucrose or glucose (Abdelwahed et al., 2006a). However, the behaviour of other protectants such as povidone and colloidal silicon dioxide appears to be acceptable (Schaffazick et al., 2003; Abdelwahed et al., 2006b).

CONCLUSION

Nanocapsules used as drug carriers can mask unpleasant tastes, provide controlled release properties and protect vulnerable molecules from degradation by external factors such as light or by enzymatic attack in their transit through the digestive tract (Furtado et al., 2001b; Whelan, 2001; Ourique et al., 2008). They can increase the therapeutic efficacy of active molecules because their biodistribution follows that of the carrier, rather than depending on the physicochemical properties of the active molecule itself (Barratt, 2000). The nanosize range obtained for nanocapsules produced by all methods (between 250 and 500 nm) allows their administration feasible by different routes: oral, rectal, transdermal, ocular, nasal, subcutaneous, intraperitoneal and intramuscular and they can be injected directly into the systemic circulation without the risk of blocking blood vessels (Letchford and Burt, 2007). Moreover, it has been asserted that nanocapsules reduce the systemic toxicity of active substances (Whelan, 2001) and numerous reviews focusing on the state of knowledge of their behavior and interaction with biological systems have been published.

Though there are different alternatives for nanocapsule synthesis by using preformed nanoparticles, the choice of a specific method is usually determined by the drug's physicochemical characteristics, particularly its solubility and the therapeutic objective. It is of paramount importance to take into account that the method chosen should also consider other aspects such as active substance stability under operational conditions, particularly stirring, encapsulation efficiency, method feasibility, the generation of contaminants, the need for subsequent purification steps, solvent nature, the water volume required and time consumption.

REFERENCES

- Abdelwahed, W., Degobert, G., Fessi, H., 2006b. Freeze-drying of nanocapsules: impact of annealing on the drying process. *Int. J. Pharm.* 324, 74–82.
- Abdelwahed, W., Degobert, G., Fessi, H., 2006c. Investigation of nanocapsules stabilization by

- amorphous excipients during freeze-drying and storage. *Eur. J. Pharm. Biopharm.* 63, 87–94.
- Amaral, E., Grabe-Guimarães, A., Nogueira, H., Machado, G.L., Barratt, G., Mosqueira, V., 2007. Cardiotoxicity reduction induced by halofantrine entrapped in nanocapsule devices. *Life Sci.* 80, 1327–1334.
 - Anton, N., Benoit, J.P., Saulnier, P., 2008. Design and production of nanoparticles formulated from nano-emulsion templates—a review. *J. Control. Release* 128, 185–199.
 - Barratt, G.M., 2000. Therapeutic applications of colloidal drug carriers. *PSTT* 3, 163–171.
 - Calvo, P., Vila-Jato, J.L., Alonso, M.J., 1997. Evaluation of cationic polymer-coated nanocapsules as ocular drug carriers. *Int. J. Pharm.* 153, 41–50.
 - Chaubal, M.V., 2004. Application of formulation technologies in lead candidate selection and optimization. *DDT* 9, 603–609.
 - Cruz, L., Soares, L.U., Costa, T.D., Mezzalana, G., da Silveira, N.P., Guterres, S.S., Pohlmann, A.R., 2006. Diffusion and mathematical modeling of release profiles from nanocarriers. *Int. J. Pharm.* 313, 198–205.
 - Duclairoir, C., Nakache, E., Marchais, H., Orecchioni, A.M., 1998. Formation of gliadin nanoparticles: influence of the solubility parameter of the protein solvent. *Colloid Polym. Sci.* 276, 321–327.
 - Fessi, H., Puisieux, F., Devissaguet, J.P., 1988. Procédé de préparation de systems colloïdaux dispersibles d'une substance sous forme de nanocapsules. European Patent 274961 A1, 20 July.
 - Furtado, V.C., Legrand, P., Gulik, A., Bourdon, O., Gref, R., Labarre, D., Barratt, G., 2001a. Relationship between complement activation, cellular uptake and surface physicochemical aspects of novel PEG-modified nanocapsules. *Biomaterials* 22, 2967–2979.
 - Furtado, V.C., Legrand, P., Morgat, J.L., Vert, M., Mysiakine, E., Gref, R., Devissaguet, J.P., Barratt, G., 2001b. Biodistribution of long-circulating PEG-grafted nanocapsules in mice: effects of PEG chain length and density. *Pharm. Res.* 18, 1411–1419.
 - Gander, B., Blanco-Prieto, M.J., Thomasin, C., Wandrey, Ch., Hunkeler, D., 2002. Coacervation/phase separation. In: Swarbrick, J., Boylan, J.C. (Eds.), *Encyclopedia of Pharmaceutical Technology*. Marcel Dekker, New York, pp. 481–496.
 - Guinebrelière, S., 2001. Nanocapsules par emulsion—diffusion de solvant: obtention, caractérisation et mécanisme de formation. Ph.D. Thesis. Université Claude Bernard-Lyon 1, Francia.
 - Khoei, S., Yaghoobian, M., 2008. An investigation into the role of surfactants in controlling particle size of polymeric nanocapsules containing penicillin-G in double emulsion. *Eur. J. Med. Chem.*, doi:10.1016/j.ejmech.2008.09.045.
 - Krause, H.J., Rohdewald, P., 1985. Preparation of gelatin nanocapsules and their pharmaceutical characterization. *Pharm. Res.* 5, 239–243.
 - Legrand, P., Lesieur, S., Bochot, A., Gref, R., Raatjes, W., Barratt, G., Vauthier, C., 2007. Influence of polymer behaviour in organic solution on the production of polylactide nanoparticles by nanoprecipitation. *Int. J. Pharm.* 344, 33–43.
 - Letchford, K., Burt, H., 2007. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes. *Eur. J. Pharm. Biopharm.* 65, 259–269.
 - Limayem, I., Charcosset, C., Fessi, H., 2004. Purification of nanoparticle suspensions by a concentration/diafiltration process. *Sep. Purif. Technol.* 38, 1–9.
 - Lince, F., Marchisio, D.L., Barresi, A.A., 2008. Strategies to control the particle size distribution of poly-ε-caprolactone nanoparticles for pharmaceutical applications. *J. Colloid Interf. Sci.* 322, 505–515.
 - Lutter, S., Koetz, J., Tiersch, B., Boschetti de Fierro, A., Abetz, V., 2008. Formation of gold nanoparticles in triblock terpolymer-modified inverse microemulsions. *Colloid Surf. A* 329, 160–176.
 - Ma, J., Feng, P., Ye, C., Wang, Y., Fan, Y., 2001. An improved interfacial coacervation technique to fabricate biodegradable nanocapsules of an aqueous peptide solution from polylactide and its block copolymers with poly(ethylene glycol). *Colloid Polym. Sci.* 279, 387–392.
 - Moinard-Chécot, D., Chevalier, Y., Brianc, on, S., Beney, L., Fessi, H., 2008. Mechanism of nanocapsules formation by the emulsion–diffusion process. *J. Colloid Interf. Sci.* 317, 458–468.
 - Nogueira de Assis, D., Furtado, V.C., Carneiro, J.M., Spangler, M., Nascimento, V., 2008. Release profiles and morphological characterization by atomic force microscopic and photon correlation spectroscopy of 99mTechnetium-fluconazole nanocapsules. *Int. J. Pharm.* 349, 152–160.
 - Ourique, A.F., Pohlmann, A.R., Guterres, S.S., Beck, R.C.R., 2008. Tretinoin-loaded nanocapsules: preparation, physicochemical characterization, and photostability study. *Int. J. Pharm.* 352, 1–4.
 - Pohlmann, A.R., Weiss, V., Mertins, O., Pesce da Silveria, N., Guterres, S.S., 2002. Spray-dried indomethacin-loaded polyester nanocapsules and nanospheres: development, stability evaluation and nanostructure models. *Eur. J. Pharm. Sci.* 16, 305–312.
 - Prego, C., Fabre, M., Torres, D., Alonso, M.J., 2006. Efficacy and mechanism of action of chitosan nanocapsules for oral peptide delivery. *Pharm. Res.* 23, 549–556.
 - Quintanar, D., Allémann, E., Fessi, H., Doelker, E., 1998a. Preparation techniques and mechanisms of formation of biodegradable nanoparticles from preformed polymers. *Drug Dev. Ind. Pharm.* 24, 1113–1128.

- Quintanar, D., Fessi, H., Doelker, E., Alleman, E., 2005. Method for preparing vesicular nanocapsules. US Patent 6884438, 26 April.
- Schaffazick, S.R., Pohlmann, A.R., Dalla-Costa, T., Guterres, S.S., 2003. Freeze-drying polymeric colloidal suspensions: nanocapsules, nanospheres and nanodispersion. A comparative study. Eur. J. Pharm. Biopharm. 56, 501–505.
- Sinha, V.R., Bansal, K., Kaushik, R., Kumria, R., Trehan, A., 2004. Poly-ε-caprolactone microspheres and nanospheres: an overview. Int. J. Pharm. 278, 1–23.
- Stella, B., Arpicco, S., Rocco, F., Marsaud, V., Renoir, J.M., Cattel, L., Couvreur, P., 2007. Encapsulation of gemcitabine lipophilic derivatives into polycyanoacrylate nanospheres and nanocapsules. Int. J. Pharm. 344, 71–77.
- Vauthier, C., Bouchemal, K., 2008a. Methods for the preparation and manufacture of polymeric nanoparticles. Pharm. Res. 26, 1025–1058.
- Vauthier, C., Cabane, B., Labarre, D., 2008b. How to concentrate nanoparticles and avoid aggregation? Eur. J. Pharm. Biopharm. 69, 466–475.
- Whelan, J., 2001. Nanocapsules for controlled drug delivery. DDT 6, 1183–1184.
- Xu, J.P., Ji, J., Chen, W.D., Shen, J.C., 2005. Novel biomimetic polymersomes as polymer therapeutics for drug delivery. J. Control. Release 107, 502–512.



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