Mini-Review

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Harmless and ecologically acceptable fabrication of long-acting injectable microspheres

Akihiro Matsumoto*, Masahiro Murakami

Laboratory of Pharmaceutics, Faculty of Pharmacy, Osaka Ohtani University, Osaka, Japan.

SUMMARY The use of harmful solvents during the preparation of pharmaceutical formulations is restricted to preserve environment and ensure safety of industrial operations. However, harmful solvents must be used to produce certain formulations. For instance, methylene chloride has been used in the fabrication of polylactic acid (PLA) and poly(lactic-co-glycolic) acid (PLGA) microspheres. This review highlights the latest advances in the strategy of PLA or PLGA microsphere production from non-halogenated solvents and describes advantages and limitations of these methods. The study also discusses the development of dry fabrication techniques for microsphere fabrication and the positioning of conventional and dry fabrication in the containment concept for workers' safety.

Keywords polylactic acid, poly(lactic-co-glycolic) acid, substitute solvents, containment, solventless fabrication

1. Introduction

Microsphere formulations play an important role in clinical drug therapy of various disorders. In drug delivery systems, microspheres are primarily used to control drug release. Most microsphere preparations for controlled drug release have particle sizes of several microns. The particle size determines the type of application. Microspheres with a size of 100-1,000 μm or more are mainly used as oral preparations, whereas microspheres with sizes ranging from several to tens of micrometers are used for injections. Long-acting injectable (LAI) microspheres are made of biodegradable polymers, including polylactic acid (PLA) and lactic acid-glycolic acid copolymer (PLGA).

The method for producing microspheres can be categorized based on the target particle size. For microspheres of 100 μm or more, a fabrication method by coating the core particles is mainly adopted, using a coating machine such as fluidized and tumbling fluidized bed coating machine. The conventional coating machine produces microspheres with sizes of several hundred micrometers. Because smaller microspheres tend to aggregate during the fabrication process, for their production, the coating machine needs to be equipped with specific functions. The Wurster method, utilized in one type of fluidized bed coating machines, can be used to produce microspheres of 100 μm (*1*) or smaller; however, it is difficult to obtain primary particles of 20-50 μm (*2*). In contrast, in the production of microspheres of 100 μm or smaller, spray drying and solvent evaporation from emulsion formation are generally performed (*3*). Figure 1 shows the scheme of particle production using an oil-in-water-type emulsion-solvent evaporation method. Low boiling point, water-insoluble solvents, such as methylene chloride, are used to dissolve the polymer and form the oil phase, in which the drug is then dissolved or dispersed. The oil is emulsified in an aqueous solution containing an emulsion stabilizer, such as polyvinyl alcohol, to form an oil-in-water emulsion. The emulsification process determines microsphere particle size, which can be regulated by adjusting the emulsification sheering speed and surfactant concentration, so that oil droplets reach the target size. After the emulsification process, the obtained emulsion is stirred to remove the solvent from the oil droplets, which are solidified as microspheres by heating and pressure reduction, if necessary. The collected microspheres are washed with water and dried by freeze-drying, typically used to ensure good dispersibility. If necessary, the freeze-dried microspheres can be filled into vials by a powder-filling machine.

Fabrication of microspheres using coating machines usually uses water and less harmful solvents, such as ethanol. Some methods require no solvent at all (*4*). In contrast, harmful solvents are commonly used in microsphere fabrication by solvent evaporation, which is a problem that needs to be resolved. In addition,

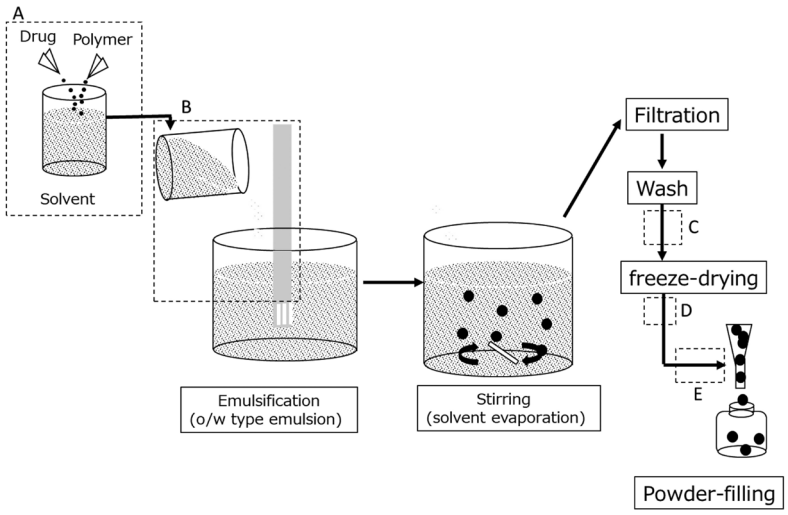

Figure 1. Solvent evaporation procedure for fabricating LAI microspheres. Dash line frame indicates the example of the risk points for workers' exposure to harmful ingredients or products; **(A)** charging ingredients in the oil phase preparation process, **(B)** charging oil phase in an emulsification process, **(C)** discharging the collected microspheres in a microspheres collection process, **(D)** charging and discharging the collected microspheres into a freeze dryer in the freeze-drying process, and **(E)** charging freeze-dried microspheres in a powder filling process.

workers' exposure to active pharmaceutical ingredients (API) can occur (Figure 1). This review mainly discusses the solutions proposed to solve the problems of the solvents used for the fabrication process of LAI microsphere formulations. The containment concept for workers' safety is explored in the microencapsulation of compounds with high pharmacological activity or toxicity. We hope that this review will promote further research into harmless and ecologically sound fabrication methods for LAI microsphere formulations.

2. Reduction of residual solvent content in PLGA microspheres

For the solvent evaporation method, it is instructed that a solvent should meet the following criteria: i) ability to dissolve the chosen polymer, ii) poor solubility in the continuous phase, iii) high volatility and low boiling point, and iv) low toxicity (*5*). In general, when PLGA microspheres are prepared by an oil-in-water-type emulsion-solvent evaporation method, it is common to use a halogen-based water-insoluble volatile organic solvent, such as methylene chloride, to dissolve PLGA because such solvents meet the criteria i), ii), and iii). However, halogen-containing organic solvents are highly toxic to the human body and have a significant impact on the environment. In the pharmaceutical industry, the use of such solvents is not prohibited, but the amount of the residual solvent in pharmaceuticals is regulated. For example, methylene chloride is categorized as a class 2 solvent, and its concentration limit was set at 600 ppm by ICH Q3C (R6) guideline of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), organized by the regulatory authorities of Japan, Europe, and the United States, and the 18th edition of the Japanese Pharmacopoeia (*6*).

In the oil-in-water-type emulsion-solvent evaporation method, the solvent removal process includes solvent extraction from the oil phase into the water phase and solvent evaporation from the water phase into the vapor phase (*5*,*7*). Solvent extraction occurs at the beginning of the process to reach the saturated solubility of the solvent in the water phase immediately before solvent evaporation occur simultaneously (*8-11*). The state of the dispersed phase that includes PLGA changes from liquid to gel as the solvent extraction/evaporation process progresses (*7*). As the state of the oil phase changes from liquid to gel and solid, the diffusion coefficient of the solvent decreases in the dispersed phase. The speed of solvent extraction from the liquid state of the oil phase varies negligibly at the start of the emulsification process, despite the differences in oil phase sizes. In fact, it has been reported that the solvent was extracted in approximately 10 s during fabrication of microparticles with mode diameters of 2 μm and 20 μm (*7*). However, the speed of solvent extraction from the oil phase in gel state depends on the size of the oil phase and temperature. In our preliminary study, the residual methylene chloride in PLGA microspheres of approximately 10 and 40 μm, which were fabricated at 25°C for 3 h using the solvent evaporation method, was 500-700 and 2,000-3,000 ppm, respectively. For the encapsulation of water-insoluble drugs, reduction of the microsphere size is an effective approach to decrease the concentration of the residual solvent. Increasing the temperature during solvent evaporation is another effective approach. However, for the microencapsulation of water-soluble drugs, the reduction of particle size and solvent evaporation/extraction at higher temperatures are

not always possible in a proper approach. For smaller microspheres, extraction of a water-soluble drug into the water phase during the process increases, resulting in low encapsulation efficiency (*12*). In addition, the initial burst release was reported to increase during fabrication at higher temperature (*12-14*). The reduction in particle size and high-temperature fabrication can be a disadvantage for the properties of microspheres, although residual solvents can be reduced. Heating the dried (water removed) hardened microspheres with mannitol is an effective approach to solve the problem of residual solvents and improve other properties of microspheres, as this procedure guarantees the maintenance of encapsulation efficiency. Heating over the glass transition temperature of a base ingredient increases the diffusion coefficient in solidified microspheres, thereby reducing residual solvent. However, heating over the glass transition temperature can induce aggregation and deformation of the microspheres. Mannitol is a commonly used inactive ingredient in the lyophilization process that prevents aggregation. Co-heating with mannitol also suppresses aggregation. For example, co-heating microspheres with mannitol at a temperature 3-5°C higher than glass transition temperature for 24-120 h reduced the low level of residual methylene chloride (< 100 ppm) without microspheres aggregation or deformation and suppressed an initial burst release (*15*).

3. Development of a PLGA microsphere manufacturing method using low toxicity solvent

As we mentioned above, halogenated organic solvents have restricted industrial use owing to their toxicity and potential damage to the environment. Several less harmful solvents have been investigated as substitute solvents for the fabrication of PLGA microspheres. These solvents are classified as low toxicity solvents and are regulated by Good Manufacturing Practice or other quality standards described in guideline Q3C (R6) of the ICH and the 18th edition of the Japanese Pharmacopoeia. Ethyl acetate is a class 3, non-halogenated, low toxicity solvent, which is most used for the fabrication of PLGA microspheres as a substitute for halogenated solvents (*16-21*). Ethyl acetate has a boiling point of 77°C and a water solubility of 8.7 g/100 mL at 20°C, which are higher than those of methylene chloride. Therefore, in the case of ethyl acetate, solvent extraction rather than evaporation is the dominant mechanism of solidifying PLGA microspheres during fabrication. Although methylene chloride can contain very little water, ethyl acetate contains more, which leads to the immersion of water-in-oil phase of ethyl acetate during the emulsification process and formation of microspheres with a rough surface. PLGA microspheres prepared with the use of methylene chloride have high transparency, whereas those prepared using ethyl acetate often have low transparency during optical microscopic observation. The immersion of water in the oil phase causes the formation of micropores in the fabricated microspheres, which explains their low transparency. The porosity caused by the immersion of water also often decreases the efficiency of water-soluble drug encapsulation (*22*). Ethyl formate (*23*,*24*) and methyl propionate (*25*) have also been proposed as candidates to substitute methylene chloride for microsphere fabrication. A report shows that ethyl formate surpasses ethyl acetate in relation to volatility and water miscibility, which improves microsphere manufacturing process, helping to produce PLGA microspheres with better quality in terms of drug crystallization, drug encapsulation efficiency, microsphere size homogeneity, and residual solvent content (*23*,*24*).

Among other low toxicity solvents, acetone is another good option for PLGA and PLA microsphere production (*26-28*). Acetone is a popular solvent in industrial applications. Because acetone is miscible with water, it cannot form an emulsion, so the method of solvent evaporation from an oil-in-water emulsion is not applicable. However, phase separation occurs in the aqueous glycerin solution, when glycerin concentration is above a certain level (Figure 2A). Therefore, if a glycerin solution containing polyvinyl alcohol is used as the continuous phase, a polymer acetone solution can be emulsified as a dispersed phase. Microspheres can then be obtained by extracting the solvent from the dispersed phase by increasing the water content in the continuous phase. Figure 2B shows the dissolution of cyanocobalamin from PLGA microspheres. The dissolution was confirmed to be equivalent to that from conventional microspheres prepared using methylene chloride. Encapsulation efficiency of the resultant microspheres was also equivalent to that of the microspheres prepared with methylene chloride (*26*,*27*).

4. Development of a dry, solventless method for microsphere manufacturing

The manufacturing method introduced in the previous section uses a low toxicity organic solvent. In the fabrication of microspheres releasing controlled drugs, using an organic solvent is considered fundamental to PLGA microsphere fabrication because water-insoluble PLGA is required to dissolve in order to encapsulate the drug. However, because these organic solvents still have some negative effect on the environment despite their low toxicity, their use requires setting up the equipment for solvent recovery. Nonetheless, social demand for the development of fabrication methods that do not use organic solvents is increasing.

Mechanofusion is a dry manufacturing method used in fine particle design, whereby composite particles are obtained by attaching guest particles on the surface of core (host) particles for surface modification purposes (*29-31*). There are many commercially available

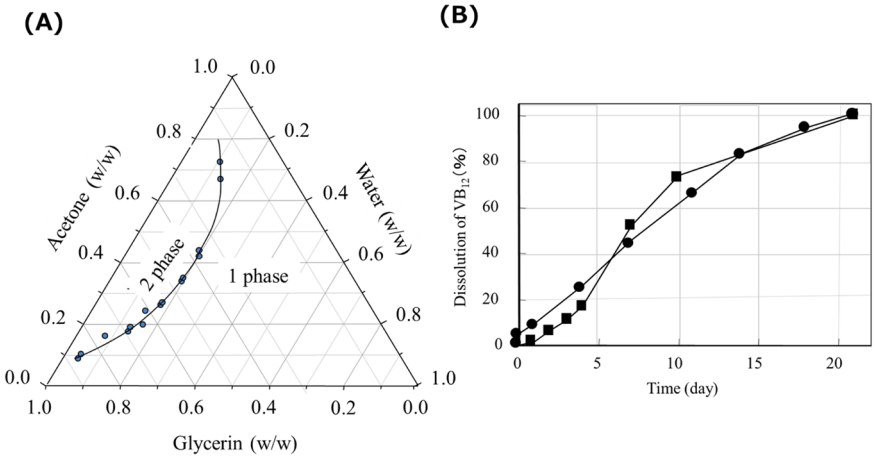

Figure 2. Microsphere fabrication using acetone as solvent in the oil phase. (A) Phase diagram of the acetone-glycerin-water ternary system (*26*). **(B)** Dissolution profiles of cyanocobalamin from poly(lactic-co-glycolic) acid microspheres fabricated using the acetone-glycerin-water ternary system: ●, microspheres fabrication using acetone; ■, microspheres fabrication using methylene chloride (conventional method) (*26*).

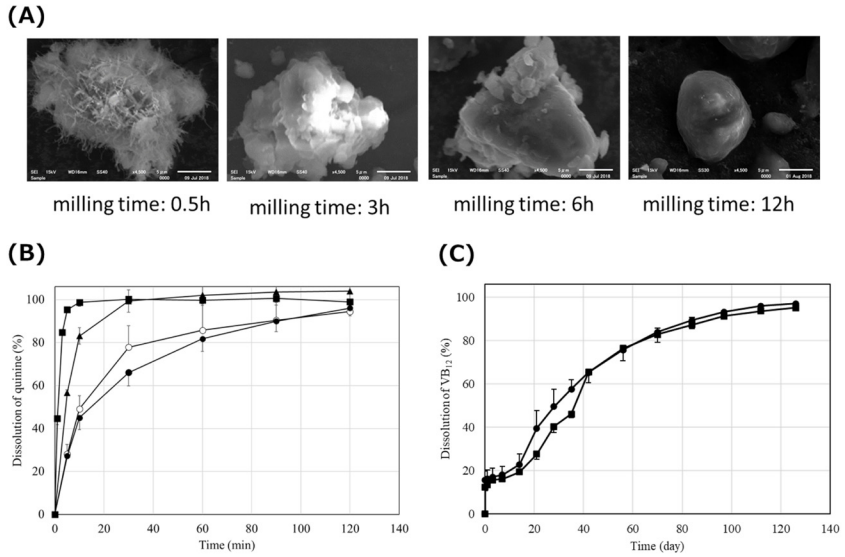

Figure 3. Method of solventless dry microsphere fabrication using a ball mill. (A) Influence of the milling time on the morphology of carnauba wax microspheres (*34*). **(B)** Influence of milling time on the duration of quinine release from carnauba wax microspheres: ■, pulverized quinine; ▲, milling time 0.5 h; ○, milling time 6 h; ●, milling time 12 h (*34*). **(C)** Cyanocobalamin release from poly(lactic-co-glycolic) acid microspheres: ●, solventless dry fabrication method; ■, conventional solvent evaporation method using methylene chloride (*35*).

formulation machines for mechanofusion technology. Following physical impact provided by these machines, van der Waals and electrostatic forces between particles as well as mechanochemical bonding forces are generated when particles collide. In general, the binding force between particles is relatively weak and considered unsuitable for the controlled release of water-soluble drugs. Furthermore, because the guest particles are usually smaller than the host particles, it is necessary to use nanoparticles as guest particles to fabricate particles of several to tens of micrometers using the mechanofusion method. In applying nanoparticles to the mechanofusion method, the preparation of soft-ordered nanocomposite particles with tens of micrometers for inhalation has been reported (*32,33*).

A dry manufacturing method can be introduced to fabricate sustained-release microspheres using a higher physical force than that of the mechanofusion machine (*34-36*). This method can use common manufacturing equipment such as a ball mill (*34*). A characteristic feature of this method is that milling is performed at a relatively low speed for a long time, so that the sample temperature does not become excessively high. An example of ball-milled pulverized quinine hydrochloride powder and carnauba wax is shown in Figures 3A and 3B. The obtained microspheres had an average particle size of approximately 10 μm, and their morphology changed from irregular to rounded particles as milling time increased (Figure 3A). In addition, the drug release time was also prolonged with milling time (Figure

3B). When particles smaller than 10 μm undergo dry pulverization with a ball mill, it is difficult to further decrease their sizes because agglomeration between particles rather than reduction in their size becomes a dominant process. As milling progresses, the coating materials with a large particle size become finer, but particle size of the pulverized drug powder is retained. The fine coating material particles generated during milling collide and become attached to the drug particles, forming agglomerates. When a coating material with a low melting point or a low softening point is used, melting occurs in the limited area at the collision point owing to the thermal energy generated by the collision between the particles and during prolonged processing, the melted part stochastically spreads over the entire particle and, as a result, fills the gaps in the composite particles.

This method also allows for the fabrication of PLGA microspheres (*35*). Figure 3C shows a profile of drug release from microspheres fabricated by ball milling finely ground cyanocobalamin powder and PLGA. Fabrication of conventional microspheres by the oil-in-water emulsion-solvent evaporation method using methylene chloride is accompanied by some drug loss, which was not observed during manufacturing of microspheres by ball milling. In addition, microspheres manufactured by the latter method showed drug release equivalent to microspheres fabricated by the solvent evaporation method. The morphology of the particles obtained by ball milling was irregular, whereas the conventional method generated spherical particles. Unlike carnauba, PLGA has a low plasticity to form a spherical shape. Ball milling is considered inefficient in providing enough energy generated by the collision between the PLGA particles to form a spherical shape.

Technologies using pulverizers other than ball mill were also used for the fabrication of microspheres. The preparation of protein-loaded microparticles using a jet mill has been reported (*36*). This technology produces spherical microparticles owing to the stronger force generated by the jet mill compared to that of the ball mill. The spherical shape allows better redispersion of the microparticles and easier passage through the needle during injection.

An additional feature of the dry fabrication method using a ball mill is its high airtightness owing to the excellent sealing performance of the ball mill. This property is advantageous for the aseptic preparation and containment fabrication of microspheres containing highly pharmacologically active substances.

5. Future prospective for harmless and ecologically acceptable LAI fabrication

To summarize and provide a prospective view, because some organic solvents used in manufacturing affect workers' health and the environment through exposure and leakage, respectively, there is an increasing social demand for harmless and ecologically acceptable fabrication technologies. Concerns are raised not only about solvents, but also about encapsulated drugs. Over the past decade, the impact of biotechnology on the global pharmaceutical industry has led to technological breakthroughs in new manufacturing and formulations. Biopharmaceutical formulations based on new drug delivery technologies are a significant value-added proposition. Although the dose of a drug encapsulated in LAI microspheres is limited, biological drugs with high pharmacological activity show efficacy in very low doses and are considered compatible with such microsphere formulations. Thus, the launch of LAI microsphere-encapsulated biopharmaceuticals is expected to increase. However, their manufacturing often inevitably includes a process that is harmful or environmentally unfriendly owing to their high pharmacological activity. Food and Drug Administration commented the following on workers' safety against exposure; "ICH Q7 does not define high pharmacological activity or toxicity; these characteristics are generally determined by evaluating relevant animal and human data collected during research and development. Important considerations in this evaluation of pharmacological activity or toxicity may include occupational exposure limit (OEL), permitted daily exposure (PDE), acceptable daily exposure (ADE), the threshold for toxicological concerns (TTC), no observed adverse effect level (NOAEL), and the consequences of cross-contamination" (*37*). Among these values, OELs, widely used for categorization, are regulatory values which indicate levels of exposure that are considered safe (health-based) for a chemical substance in the air of a workplace (*38*). Due to strict regulatory definitions, pharmaceutical companies set their own containment strategy by categorizing active pharmaceutical ingredients based on their individual OELs (*39*). The control approach is set using decision tools based on product OEL and exposure potential, such as substance allocated to dustiness or volatility band and a band for the scale of use (*40*). Moreover, the containment pyramid is commonly used as a decision tool (*41*). In general, rigid isolators, ventilated laminar flow cabinets, custom-designed glove bags, and bag-in/bag-out systems are used for the containment control approach (*42*). As the risk categorization increases, the system used to prevent exposure should become rigorous. For example, according to the Health and Safety Executive (HSE) of a United Kingdom government agency, as the categorization levels increase, the system should be selected in the order of general ventilation, local exhaust ventilation, full enclosures and containment, and expert advice (*40*). For LAI microspheres preparation, the containment level will not only be high if a high pharmacological activity drug is microencapsulated, but exposure potential will increase. LAI microsphere preparation by the conventional evaporation method

is inconvenient to these closed systems. In a closed system operation, the risk of breaking the closed system will increase when charging materials and solvents or discharging samples. LAI microspheres preparation includes lots of possible charging/discharging points due to its complicated procedure (Figure 1). The numbers of exposure risk points are considerably more than the ordinary injection formulations prepared by filling the API solution into vials. In addition, a solvent-recovering device for the evaporated solvents should be installed in/with the closed system. In contrast, the techniques that can guarantee containment, such as the dry fabrication method using a ball mill, can reduce the charging/discharging opportunities and the risk of workers' exposure to harmful ingredients or products.

6. Conclusion

In conclusion, harmless and ecologically acceptable fabrication technologies, such as containment and dry fabrication, enable safer and easier manufacturing of PLA or PLGA microspheres and facilitate the development of LAI formulations for biopharmaceuticals, which include microspheres as drug carriers.

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Address correspondence to:
Akihiro Matsumoto, Laboratory of Pharmaceutics, Faculty of Pharmacy, Osaka Ohtani University, 3-11-1 Nishikori-kita, Tondabayashi, Osaka 584-0854, Japan.
E-mail: matumoaki@osaka-ohtani.ac.jp

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