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Uniform-sized particles in biomedical field prepared by membrane emulsification technique

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HIGHLIGHTS

- Membrane emulsification possesses advantages on preparing uniform-sized particles.
- Uniform-sized particles have beneficial effect on investigating their properties.
- Particles show high potential as drug delivery system and vaccine adjuvants.

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ABSTRACT

Particles have been investigated intensively in recent years. However, the broad size distribution of particles limited their application in biomedical field and also brought difficulty in studying the effect of particle properties. It is necessary to develop techniques which could be utilized to fabricate uniform-sized and size-controllable particles. Membrane emulsification technique is one of them which have been reported frequently for preparing various particles with narrow size distribution. Our research group carried out much work on the utilization of membrane emulsification technique in preparing particles for biomedical application. In this review, these studies were introduced in brief. The effect of particle properties on their application mainly as drug delivery system and vaccine adjuvant would also be introduced.

1. Introduction

It is not a novel idea using particles in biomedical field. As early as in the 1980s, particles have been used for pharmaceutical formulation. The French company Ipsen developed the first commercialized Triptorelin acetate loaded particle system for long-term drug release, which trade name is Decapetyl. Triptorelin acetate is water soluble peptide and unstable in vivo, which tends to be eliminated from the body rapidly. After being encapsulated in biodegradable poly (lactide-co-glycolide) (PLGA) particles, the drug would be released constantly during one month, which largely erases the pain of patients. At present, Ipsen developed several marketed formulations of Decapetyl including daily, one-month, three-month and six-month formulations. In 2013, the sales of Decapetyl achieved €298.6 million.

Since the success of Decapetyl, other long-effective drug release systems based on particles were reported and licensed for clinical application, including Leuprorelin (Okada, 1997), Calcitonins (Diaz et al., 1999), Octreotide (Stewart et al., 1995) and Buserelin (Kranz and Bodmeier, 2007) etc. Moreover, besides the sustained release system, with the development of materials and pharmaceutics, particles have been investigated and applied more intensively, such as for local drug delivery, target drug delivery and vaccine adjuvant (Morçöl et al., 2004; Pawar et al., 2013; Wei et al., 2013). For all of these systems, the choice of particle compositions, preparation methods and structure are important. Many literatures studied and reviewed the effect of these influencing factors (Liu et al., 2008; Bysell et al., 2011; Leleux and Roy, 2013). However, due to the broad size distribution of particles prepared by conventional dispersing methods, such as stirring or homogenizing, the investigation on effects of single factor is difficult if not impossible and sometimes the results from different literatures are contradictory. Moreover, the wide size distribution of particles would bring the negative impact on preparation repeatability and treatment efficiency

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(Santos et al., 2013). Thus, in order to intensively and systematically study the effect of process conditions and properties of those particles used in the biomedical field, it is necessary to obtain uniform-sized particles at first.

Membrane emulsification technique is a unique technique which is especially useful in preparing uniform-sized particles (with average size from tens of nano-meters to one hundred of micro-meters). By this technique, in recent years our research group fabricated various particles with narrow size distribution and investigated their application in biomedical field (Wang et al., 2005; Hao et al., 2008; Zhou et al., 2009; Lv et al., 2009). The advantages of the membrane emulsification technique mainly includes: (1) the size of prepared droplets and formed particles is easy to control and the size distribution is narrow; (2) break-up and coalescence between droplets rarely occur due to the monodispersity of droplets; (3) the preparation process is mild because no high shear force needs to be used (Ma 2003a).

In this review, we mainly focus on our studies about the utilization of the membrane emulsification technique for preparing particles and the effect of prepared uniform-sized particle properties on their application especially as drug delivery system and vaccine adjuvants.

2. Utilization of membrane emulsification for preparing uniform-sized particles

The main component of the membrane emulsification technique is the micro-porous membrane, especially Shirasu Porous Glass (SPG) membrane, which is a special glass membrane with uniform pore size (the commercial available pore size range from 0.1 to 50.2 μm). According to the preparation mechanisms, SPG membrane emulsification technique has been mainly divided into two types, general membrane emulsification (GME) and pre-mix membrane emulsification (PME).

2.1. General membrane emulsification

The typical preparation process by using the GME technique is as follows: under critical pressure, the dispersed phase was slowly pressed through the tunnels of the SPG membrane into a continuous phase and formed droplets under the action of external dispersing forces. The representative miniature kit of GME is shown in Fig. 1 (Liu et al., 2005a). For GME, the formation and detachment of droplets on the SPG membrane are related to multiple influencing factors as shown in Fig. 2 (Hao et al., 2008). Among all of these parameters, the nature of the used membrane is the key factor for preparing particles with narrow size distribution, such as pore size distribution, thickness and hydrophilicity–hydrophobicity of membrane. At present, most of the commercial SPG membranes were provided by SPG Technology Co. Ltd. (Japan) with similar thickness (around 0.8 mm) and narrow pore size distribution (CV% less than 15%, porosity around 50–60%). Because the main ingredient of the SPG membrane is Al_2O_3–SiO_2, the membrane is highly hydrophilic, which is beneficial for preparing hydrophobic particles by oil in water (o/w) emulsion, such as polystyrene particles (Ma et al., 2004), polyurethane urea–vinyl particles (Ma et al., 2003b).

For biomedical application, our group choose biodegradable hydrophobic poly (lactide) (PLA) as particle matrices, which has been explored extensively for therapeutic applications (Anderson and Shive, 2012). By using GME, PLA particles with an average diameter around 8 μm and low coefficient of variation (CV) value (14.7%) were prepared (Liu et al., 2005a). For GME, the size (d_d) of prepared droplets is in linear relationship with the pore size (d_p) of the used membrane as $d_d = x d_p$. According to the difference of

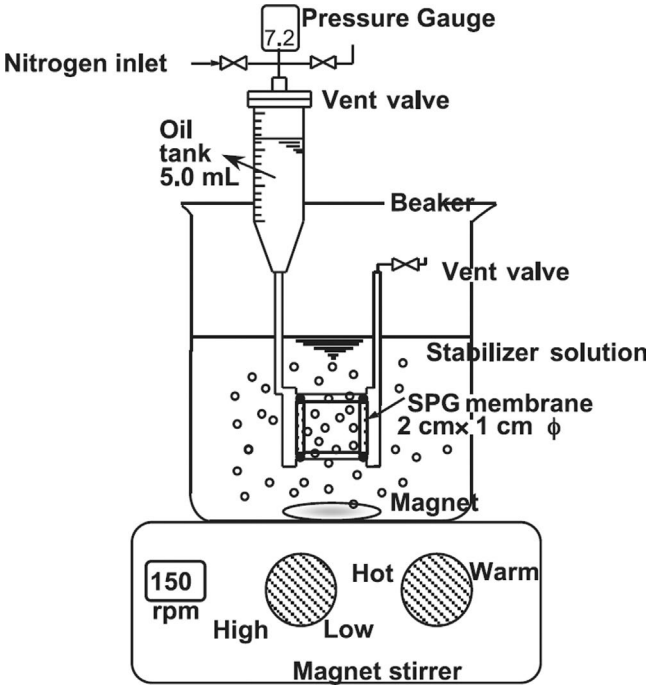

Fig. 1. Schematic diagram of the experimental equipment of GME. (Liu et al., 2005a).

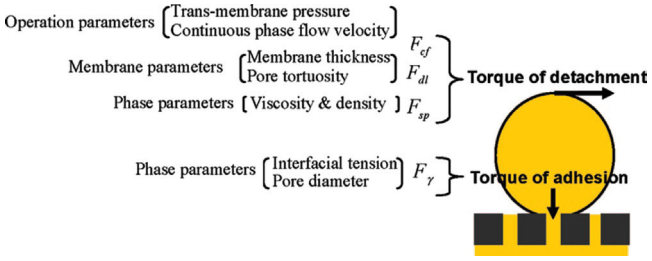

Fig. 2. Action forces on the formation and detachment of droplet (Hao et al., 2008).

processing conditions and properties of the membrane, the value of x is between 2 and 100 (Omi, 1996). In this study, we fabricated PLA particles with different sizes (3.2, 5.8 and 9.0 μm) by using membranes with different pore sizes (1.4, 2.8 and 5.2 μm), and the value of x is between 1.7 and 2.2 (Liu et al., 2005b). The drug loading capacity of these PLA particles were further investigated with insulin as the model drug. With the increase of particle size, the encapsulation efficiency of insulin increased and the burst release decreased. The encapsulation efficiency is 70.80% and the initial release in the first day is 4.5% when using 9.2 μm particles.

However, for particles used as the drug delivery system, the hydrophilic polymers attracted much attention than hydrophobic polymers due to their biocompatibility and weak interaction with proteins (Maderuelo et al., 2011). In order to use the SPG membrane emulsification technique to prepare water in oil (w/o) emulsion, the high interfacial tension between dispersed phase and membrane is the necessary prerequisite to avoid the spread of dispersed phase on the membrane. Due to hydrophilicity of the SPG membrane, we used a silane coupling agent with a C18 hydrophobic chain (KP-18C) to modify the SPG membrane (Wang et al., 2005). After modification, hydrophobicity of the membrane increased and the contact angle between water and membrane was above 130°. By using the modified SPG membrane, the uniformity of prepared hydrophilic chitosan particles were greatly improved than those

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