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Review on SPG membrane emulsification: an efficient approach to prepare uniform microspheric drug carrier

Abstract

During the past decades, Shirasu porous glass (SPG) membrane emulsification, one of the excellent microsphere preparation approaches, has been widely visible within many fields, especially for drug carrier preparation. The microspheres prepared via this method have the advantages of uniform size, excellent stability and high productivity. To date, there were scarcely any reviews available to give a systemic and overall summary on preparation, performance and application of such microspheres. It is necessary to give a review on predecessors contribution on this method. Based on the background, the paper is focused on the following aspects: the development of this method, factors of preparation process and application as drug carriers. It is expected to provide some inspiration on syntheses of uniform microspheric drug carriers via this approach.

Keywords: SPG membrane emulsification, mono disperse microspheres, drug carriers

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Introduction

Mono dispersed polymer microsphere was known as one of unique functional polymer materials with spherical shape and controllable diameters within the scale ranged from nanometer to micron. Due to the advantage of easy modification within its surface, better stability, time saving and homogeneous pharmacokinetics, such materials were extensively accepted as drug carriers by chemists.[1–5] Many conventional methods, involving suspension polymerization,[6] dispersion polymerization,[7] precipitation polymerization and seeded emulsion polymerization,[8–11] have been employed to prepare mono disperse polymer microspheres. These methods have made great contribution to prepare polymer microspheres, however, still lots of problems are existed up to now, such as high consumption of energy, low efficiency and especially, difficult to achieve mono disperse microspheres. During the past decades, Shirasu Porous Glass (SPG) membrane emulsification method has been gradually developed. [12] This method was firstly proposed by Nakashima in Annual Conference of Chemical Engineering held in Japan. Dispersed phase with uniform size was achieved when it entered continuous phase via SPG membrane under certain pressures.[13] The most outstanding feature of this technology is that uniform droplet is easily and swift achieved within the micro porous membrane.[14] Compared with conventional emulsification methods, SPG membrane emulsification technology was highlighted with lots of advantages,[15–18] including facile operation of emulsification process, mild emulsification conditions, emulsion stability, high reproducibility, low requirement on equipment, little energy consumption and in particular, excellent mono dispersity of so–resulted microspheres. So far, it has been extended to scale production for some new drug carriers.

History of SPG membrane emulsification method

The technology of SPG membrane emulsification stemmed from Japan. At first, it is used only to solve the problem of heterogeneity in food emulsion. A large number of uniform emulsion are rapidly obtained via this approach.[19] was one of the pioneers to use this approach in preparing microsphere. They successfully synthesized uniform polymer microspheres and solved the problems of poly dispersity, which were difficult to avoid in traditional emulsification way. Hereafter, researchers have paid more and more attentions to this technology. For example,[20–25] who have given a lot of contributions to the preparation and the formation mechanism of uniform microspheres via this way. Furthermore, microcapsules were also synthesized by in which uniform emulsion droplets was firstly achieved following by cross linking of resultant particles.[26] the formation mechanisms was given that uniform emulsion droplet were obtained when trans membrane pressure and flow rate of continuous phase were lowered to the critical value and interfacial tension between dispersed phase and membrane was promoted up to certain value. Furthermore, they also achieved hollow microspheres via modified SPG membrane emulsification method and also analyze its formation process by control of several key factors, such as initiator amount, molecular weight distribution of polymer and so on. After a series of deep exploration on basic principle of membrane emulsification technology,[27,28] found that, the function of SPG membrane significantly different from traditional emulsification method and it was achieved mainly relying on separation and capillary of membrane pores. As proposed, dispersed phase passed homogeneous membrane pore under designed pressures, stripped from the film, then rapidly entered continuous phase as function of sheer force of continuous phase. Finally, uniform emulsion droplet was formed. The process was shown as Figure 1. Hereafter, adding cross linking agent into the resultant emulsion droplet, leading to the formation of cross linked

With three approaches related to SPG membrane emulsification methods,[29] obtained mono dispersed chitosan microspheres. Varying the membrane with different pore size, they achieved the microspheres with different size and expounded their formation

mechanism. In the report given by,[30] the method was differentiated into conventional membrane emulsification and rapid membrane emulsification due to the difference of emulsification process. Through the conventional membrane emulsification, the latex that has narrow size distribution merely need lower consumption of energy. Droplet size is usually affected by varying pore size of SPG membrane. In general, droplet size is 3–6 times as large as pore size. As for rapid membrane emulsification technology, the initial emulsion is firstly prepared in conventional approach with mechanical stirring and homogenizing, and then under designed pressures, it was quickly passed the membrane pores so as to form the final emulsion droplet. Here mentioned emulsification process of the latter one was shown in Figure 2. Smaller microspheres were obtained through rapid membrane emulsification method. Both technologies were widely applied to prepare mono dispersed microspheres in different fields.[31] Hereafter, SPG membrane emulsification technology was often employed as an effective emulsification approach to prepare mono disperse microspheres with the size varied from nano– to micro–scale. Due to its rapid development and deep application in medicine fields, it has attracted increasing attentions of researchers from university to hospital. In the recent years, the membranes used in the emulsification technology was extended to a much wider scope, including not only the glass membrane, but also some types made of new material, for example, sintered–glass filter–disc membrane,[32] micro porous ceramic membranes,[33] metal membrane,[34] nickel and stainless steel membranes,[35] alumina membrane and polymeric membrane.[36–38] Influence of membrane material on the production of colloidal emulsions was widely explored. The research indicated that the latex size relied scarcely on the structure or thickness of the membrane but the types of membrane material. Wetting ability of the membrane with continuous phase was decisive for achieving emulsions with desired colloidal sizes.

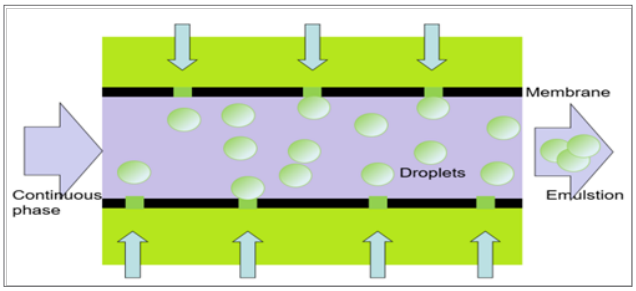

Figure 1 Illustration of SPG Membrane emulsification method.[28]

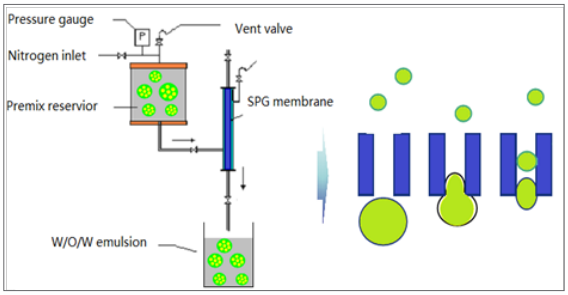

Figure 2 Scheme of rapid membrane of rapid membrane emulsification apparatus and principle of premix membrane emulsification.[30]

Process parameters

There are many factors, which are complicated and often changeable, restricting the formation of polymer microspheres in SPG membrane emulsification process. Up to now, many researchers are still striving for optimizing the process so as to make the preparation approach more simple and efficient.[39] In this paper, the studies on process conditions and influence factors of SPG membrane emulsification, based on large number of reports, involved membrane performance, velocity of continuous phase, membrane surface tension, shear force, nitrogen pressure and emulsifier types.[40] All these factors and relative reports were summarized as following.

Membrane performance

Currently, the used membrane is generally SPG membrane and ceramic membrane with uniform pore size. Reported that homogeneous emulsion could be achieved with SPG membrane as compared with other types.[41,42] adopted new asymmetric SPG membrane in emulsification process, which finally turned out of dried results of mono disperse microspheres of high yield. Hydrophilicity or hydrophobicity is also important parameter for SPG membrane. Commonly used SPG membrane have higher hydrophilicity, which is often used for the preparation of oil in water (O/W) or water in oil in water (W/O/W) emulsion droplets with uniform particle size.

Poly (N–isopropyl acryl amide) (PNIPAM) has been used by,[43] for hydrophobic modification of SPG membrane. Ihe hydrophilicity or hydrophobicity properties of membrane changed along with environmental temperature. Silane coupling agent was used for hydrophobic modification of SPG membrane by Wang et al.[44] Where after, the W/O type emulsion was prepared within so– modified SPG membrane equipment. In this way, liquid droplets including chitosan were prepared followed by cross linking so as to form mono disperses microspheres of chitosan. In addition, methyl silane coupling reagent was also employed by,[45] in order to explore the influence of membrane properties on microspheres particle size. Eventually, W/O droplets with average diameter of 1.8μm and dispersion coefficient of 0.25 were finally obtained. Found that particle size of the emulsions did not depend mainly on the structure or thickness of the membrane but on the combination of emulsifier and membrane material. The results from contact angle measurements demonstrated that the wetting of the membrane with the continuous phase of the emulsion was decisive for obtaining emulsions with colloidal particle sizes.

Pore size

Liquid/liquid multiphase dispersion processes has been studied within porous membrane structures for emulsification. The interior membrane structure was found having a significant impact on the liquid fragmentation as well as on the dispersion process and hence on the resultant droplet size distribution of dispersed phase.[46] Pore size of membrane has also important influence on droplets formation.[47,48] reported that mono dispersity of emulsion droplet depended on the distribution of membrane pore size. The more average the pore size, the better the mono dispersity. Size distribution coefficient of membrane pore is generally about 15% and size of emulsion droplet is linearly related to membrane pore.[49,50] confirmed that size of lipido some can be adjusted by varying channel number and pore size. Porosity, defined as the volume percentage of pore relative to the total membrane, is also a key factor of SPG membrane towards the formation of microspheres. Although in the early report membrane pore distribution and shape did not exert obvious effects on the

formation of emulsification,[51] different observation was later disclosed that microcapsules of size from 1.4μm to 9.6μm were achieved via SPG membrane of varied pore size.[52] According to the report of, [53] the coalescence of droplets occurred as pore size was larger than 1.6μm and porosity closed to 30%.[54] found the upper limit of porosity should be 1.5%, below which dispersed droplets could be prevented from cohesion, and meanwhile, the membrane pore size is closed to 5μm. The results demonstrated that the porosity play an curtail role on formation of microsphere as well as its size uniformity. Therefore, the chemists often chose a SPG membrane with suitable porosity in practical applications. The work of also give the similar conclusion by establishing a linear correlation between the average size of microspheres and the pore size of membranes after the preparation of regular–sized gelatin microspheres via membrane emulsification method.[55]

Trans membrane pressure

As one of the main acting forces to prompt dispersed phase to enter continuous phase through the membrane, trans membrane pressure has been proved having obvious influence on droplet size while less effects on size uniformity.[56] Thus it is necessary to choose appropriate trans membrane pressure in emulsification process with SPG membrane as shown in Figure 3.[57,58] has taken out an investigation on the effects of trans membrane pressure on the drug–loaded poly (lactic acid–co–glycolic acid) (PLGA) microspheres. According to their reports, the greater the pressure, the smaller the particle size. However, the uniformity of particle size will be lowered if the pressure is excessively raised. A two–step emulsification method was explored by to prepare glucagon–like peptide–1 – poly (lactic acid–co–glycolic acid) (GLP–1–PLGA) microspheres, in which the effects of trans membrane pressure upon microspheres size and uniformity were both explored.[59] The results showed that uniform (GLP–1–PLGA) microspheres with size of about 350 nm and poly dispersity coefficient of less than 0.050 were obtained when the pressure is raised to 1000kpa. In another case, under trans membrane pressure of 250kPa, poly (N–isopropyl acryl amide–co–acrylic acid) (P(NIPAM–co–AA)) microspheres of size at 5.2μm and narrow size distribution was prepared by,[60] They found micro–scaled particles could be achieved but the size distribution was also kept at a narrow level. No matter that trans membrane pressures are high or low, it will not be helpful to emulsification process. On the one hand, emulsification process will be extended if membrane pressure is too low. Emulsification efficacy will become especially poor within a high Trans membrane pressure, on the other hand. Furtherly,[61] investigated the influence of trans membrane pressure on size distribution of emulsion droplet. They found stable emulsion was achieved under trans membrane pressure of 30Pa. Although the resultant latex has been stored for 159 days, the size distribution of emulsion droplet did not change obviously.

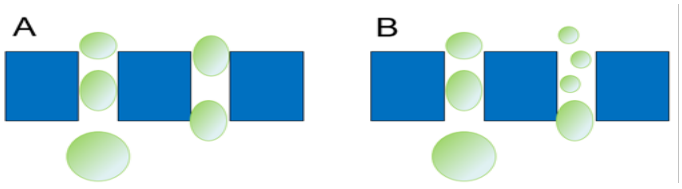

Figure 3 Schematic diagrams of premix membrane emulsification (A) The operating pressure is greater than the critical pressure, (B) The operating pressure is much greater than the critical pressure).[57]

Continuous phase

In SPG membrane emulsification, the function on tiny droplets, which stems from the flow of continuous phase and makes it strip from membrane surface, is called shear force. The change of droplet size are feasible due to the adjusting the flowing speed of continuous phase. According to the report of droplet size was significantly changed by lowering velocity of continuous phase. Further results demonstrated that verifying the velocity of continuous phase could change the size of emulsion droplet within a certain scope. Usually, continuous phase velocity was limited in 0.8–8 ms^{-1}. The observation was further explained by,[62] Shear strength will be increased when flowing of continuous phase speeds up, which makes the droplet secedes easily from membrane surface. The droplet size will decrease till the flow velocity of continuous phase could not be increased any more.[63] Also, accelerated the flow velocity of continuous phase in order to achieve droplets of even smaller size. Additionally, effect of continuous phase temperature on both microsphere size and size distribution was also highlighted.[64]

Surfactants

To enhance the stability of emulsion or to prevent the aggregation between emulsion droplets, various kinds of surfactants are often adopted in SPG membrane emulsification. The function was achieved mainly by reducing surface tension and increasing repulsion between the droplets.[65] The amount and the type of surfactants both make a difference on droplet size and drug loading. The reports of ,[59–67] indicated that surfactants of different types could change solution viscosity and surface tension of O–W interface.[68] prepared poly (styrene– acrylic ester) latex at average size of 0.09μm–1.3μm, and explored the effect of surfactants of different type on latex size. They found the size was easily adjusted by changing surfactants types and its structure. In order to improve the efficiency of drug loaded in PLGA microspheres,[69] attempted to adjust the proportion of oil–soluble surfactants, water and organic solvents. Finally they obtained microspheres of high stability and high drug encapsulation. To investigate the effect of surfactant, wetting ability was anal sized via contact angles tests. The surfactant in continuous phase has double functions: to enhance the wetting of continuous phase on membrane and to increase the stability of the droplets formed at the surface of the porous membrane during membrane emulsification.

Viscosity of dispersed phase and continuous phase

Viscosity have not only act on the droplet size, but change the dispersity of emulsion droplets.[70] Believed that it can improve the stability and the mono dispersity of emulsion by increasing viscosity of dispersed phase and continuous phase or reducing solubility of dispersed phase in continuous phase. Varying proportion and composition of dispersed phase and continuous phase frequently be used as a way to adjust the viscosity. According to the reports of mono disperse droplets was finally achieved when the volume proportion of petroleum ether and liquid paraffin was fixed at 1:2. The reason why increasing viscosity could significantly change droplet size is that the flowing viscosity of continuous phase is easy to reduce the stripping velocity of droplet in membrane pore, so as to extend the period of droplet formation and then form even larger droplet. As the viscosity of dispersed phase is promoted, the flux of dispersed phase will be decreased, so the droplet is more easily and rapidly stripped from membrane and the size of droplet will become smaller.[71] changed

the viscosity of dispersed phase by adjusting the concentration of PLGA in methylene chloride. Along with the increase of viscosity of dispersed phase, the peak of size distribution becomes narrow and high, which indicated that mono dispersity of droplet was achieved.

The application as drug carriers

Up to now, microspheres prepared by SPG membrane emulsification are widely applied in drug delivery system, owning to its good mono dispersity and stabilities of particle size.[62–64] Such application was also investigated in the following.

Mono disperse microsphere

Nakashima et al.[72] attempted to use microspheres resulted from SPG membrane emulsification in drug release system. Their efforts successfully promoted the application of such microspheres in pharmaceutical industry. The microspheres prepared via this way or after modification were frequently employed. These mono disperse microspheres are divided into different types due to the diversity of raw materials, such as the magnetic microspheres with unique advantages in target therapies, the poly(lactic acid) (PLA) microspheres of prominent biodegradability and biocompatibility.[73,74] synthesized biodegradable polymer microspheres with mono disperse size via SPG membrane emulsification. Also, prepared mono disperse chitosan microspheres, where about half of the activity of encapsulated lysozymes was remained during the preparation procedure. Drug carrying microspheres with excellent stability and release properties could be obtained have prepared PLGA microspheres containing dextran blue, a kind of water–soluble drug, by SPG membrane emulsification and the drug loadings were significantly enhanced when compared to those prepared by the other ways. Docetaxel–loaded– poly (lactide)–d–α–tocopheryl polyethylene glycol 1000 Succinate (DTX–loaded PLA–TPGS) microspheres were also achieved via the similar manner by.[75] They confirmed that it has a positive effect on anti–cancer activity with resultant PLA–TPGS nanoparticles.[76] reported the preparation of uniform water–in–oil emulsion by SPG membrane emulsification. It can be used as vaccine formulation to enhance immune response. Also, uniform water–in–oil emulsion of 5.4μm was prepared by,[77] which was used in drug delivery system so as to improve the drug release ratio. A great deal of reports have proved that variation coefficient of mono disperse microspheres prepared by SPG membrane emulsification is very low have prepared particle–stabilized emulsion with uniform size. Variation coefficient of the as–prepared emulsion was shown below 15%, as shown in Figure 4. Moreover,[78,79] obtained poly(methy1 methacrylate)(PMMA) microspheres with variation coefficient of 10% by modifying SPG membrane emulsification. In addition, a novel artificial oxygen carrier composed of bovine hemoglobin (bHb) and bovine serum albumin (BSA) was achieved via this approach by.[80] Variation coefficient of bHb–BSA contained microsphere is around 10%. The uniform pore structure of SPG membranes was believed to be the core factor. More excellent properties can be endowed on uniform microspheres when SPG membrane emulsification method was combined with other methods, successfully synthesized uniform, biodegradable PLA microcapsules with drug–loading up to 92.20% through combination of SPG membrane emulsification method with solvent evaporation. Double emulsion evaporation was also integrated into SPG membrane emulsification method to prepare insulin–loaded PLA/PLGA microcapsules. Drug encapsulation efficiency was improved up to 91.82%, which was obviously higher than that of drug carrier microspheres by traditional methods. Huang et al.[52] obtained the microcapsule containing PLA/PLGA by coupling of membrane emulsification method and complex emulsion solvent evaporation method. The resultant microcapsules were demonstrated having good protective effect on lysozyme.[81–83] have described a novel synthetic route in their report, where SPG membrane emulsification technology and in situ magnetization technology were combined so as to prepare uniform magnetic poly(styrene–co–2–hydroxyethyl methacrylate) (PSt–HEMA) microspheres. By this way, the difficulties in encapsulating magnetic materials by traditional synthesis routes were overcome and it facilitated the enhancement of encapsulation efficiency. Also in this way, Quantum Dot–embedded polymeric micro beads with an average diameter of 24μm were prepared by,[84] which can be used in antibody immunoassay. The combination of suspension and the planar microarray format was found to enable the spatial location of individual micro beads within physically separated regions and thus facilitated the simultaneous determination of different targets that interacted with the corresponding micro beads. In addition, a SPG membrane with a mean pore size of 2.5μm was used to produce mono dispersed micro emulsions of itraconazole consisting of methylene chloride as the dispersed phase, a mixture of Transcutol HP and Span 20 as a stabilizer, and dextran as solid carrier dissolved in water as the continuous phase.[85] The results demonstrated that solubility and bioavailability of itraconazole was enhanced by coupling of membrane emulsification and spray drying solidification technology. In order to develop a long–term sustained release drug delivery system with low burst release, the effect of microsphere size on the drug release from a microsphere/sucrose acetate isobutyrate (SAIB) hybrid depot (m–SAIB) was investigated. Risperidone, employed as model drug, was first encapsulated into PLGA microspheres with different particle sizes. The drug release from m–SAIB goes through two steps: Firstly, the drug diffuses from the microspheres into SAIB matrix, then from the SAIB matrix into the medium. The drug release from the m–SAIB was found able to be tailored by varying microspheres size to reduce the in vivo burst release of SAIB system alone.[86]

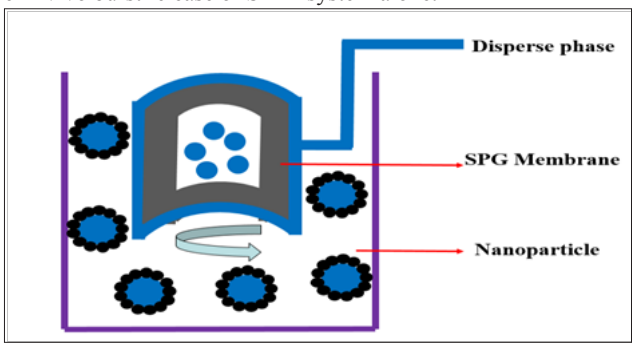

Figure 4 Schematic depiction of SPG membrane emulsification process in the production of uniform Pickering emulsions using soft particles as stabilizers.[78]

Porous microspheres or microcapsule

Porous or hollow microspheres have attractive prospects especially in the area of drug carrier, due to its good effect on sustained and controlled release. However, there were usually tedious, requiring techniques of high energy input or a sacrificial template. Additionally, loading the final capsules with drugs is often associated with low encapsulation efficiency. To this end,[87] explored the use of SPG membrane emulsification to achieve a wide size range of water droplets stabilized with an amphiphilic block copolymer. Polymeric capsules were finally obtained via inverse emulsion periphery RAFT (Reversible Addition–Fragmentation Chain Transfer) polymerization.

Changing the pore size of the SPG membrane (0.2–3μm), resulted in controlling the polymeric microcapsule size from submicron to tens of microns.[88] firstly prepared uniform emulsion by SPG membrane emulsification technology, followed by cross linking to achieve hollow microcapsule. PLGA was also employed as wall material, to encapsulate BSA (Bovine Serum Albumin) by via a composite emulsion method, which contributed largely to improve the encapsulation and avoid the fast onset of release.[89] To prepare menthol contained chitosan microcapsules,[90] employed both SPG membrane emulsification and high–speed dispersion technology. They found that size of microcapsules depends largely on average pore size of SPG membrane and the amount of menthol loaded in dispersed phase, as shown in Figure 5. Liposomes microcapsules were achieved by Hwang T et al [51] through SPG membrane emulsification method, in which the encapsulation efficiency of Adriamycin is improved even up to 94%. The nano–scale liposomes microcapsules can be used as anticancer drug delivery vehicles through intravenous injection owing largely to its smaller particle size where larger surface area enables the quick release of the drug. Micron–sized microcapsule of calcium alginate/sodium cellulose sulfate–water soluble chitosan (CA/NaCS–WSC) was prepared by membrane emulsification method.[91] The CA/NaCS–WSC microcapsules had a spherical shape with average diameter of 62.36±13.87μm. A fluorescent ring was obviously seen on the surface of microcapsules with confocal microscope, when the wall was labeled by fluorescein isothiocyanate. The micro capsules prepared has the potential to develop micron–sized drug delivery carriers. Currently, mono disperse polydopamine capsules with thin shells are prepared by,[92] via dopamine polymerization with toluene emulsion droplets as templates. During the preparation process, aqueous emulsions of mono disperse toluene droplets stabilized by sodium dodecyl sulfate are formed via SPG membrane emulsification. This approach allows easy adjusting of the polydopamine capsule size with choice of the membrane emulsification pore size, providing an access to well–defined capsules with diameters from submicron to micron–size range. In addition, high ion exchange capacity for peptide was also proved to feasible.[93] A high cross–linking porous polystyrene (PSt)–based anion–exchange microsphere with uniformly size and high hydrophilicity was synthesized by membrane emulsion polymerization strategy coupled with surface fictionalization approach. Modified PSt microspheres showed greatly improved hydrophilicity and biocompatibility with 0.387 mmol/mL ion exchange capacity. As a result, eventide can be purified from 42.9% of peptide crudes to 88.6% by modified PSt column with 97.1% recovery yield.

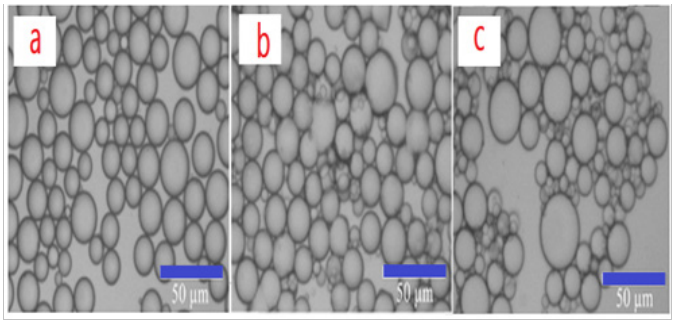

Figure 5 Optical micrographs (a–c) and histograms of the size distribution (d–f) of the o/w emulsion with different amounts of menthol loadings: (a) and (d) without menthol, (b) and (e) 5wt% menthol, and (c) and (f) 10wt% menthol.[90]

Nano particle

Nano–scaled sphere carrier is of importance for anti–cancer drugs and other goals, which could be endowed excellent targeting property after surface modification with molecules of specific recognition. Uniform PLA nano particles containing water–soluble vitamin E were prepared by,[58] via SPG membrane emulsification method. It provides the opportunity to further conduct the pilot scale test in the near future. With Tween–80 and Brij–35 as complex emulsifier,[94] has prepared nano latex containing vitamin E with the special target towards lungs. Also in this way,[95] have prepared complex latex containing water–soluble drugs (cytarabine, adriamycin, and vancomycin) by SPG membrane emulsification. The results demonstrated that the resultant Nano–scaled spheres have narrower size distribution and higher ratio of encapsulation than those prepared by the two–step emulsification method. It is of significance for boosting the encapsulation efficiency of small molecule drugs. To develop a continuous system in favor of the formulation of polymeric nano particles at industrial scale, SPG membranes with pore diameters of 1 and 0.2μm were used to control the mixing process during the (PLGA–PEG) nano particles preparation.[96] Dexamethasone was successfully encapsulated in a continuous process, with an encapsulation efficiency of 50% and drug loading efficiency of 5%. The dexamethasone was released from the nano particles conforming to Fickian kinetics. The method to produce polymeric nano particles for drug delivery was demonstrated having a high productivity, reproducibility and easy scalability. Particle size of nano–spheres was emphasized on when in vivo release behavior of encapulated drug and its distribution in the body were concerned. Mono disperse PLA nano particles were prepared by[97] via emulsion–solvent removal combined with rapid membrane emulsification. The resultant microspheres showed desired potentials on drug delivery. The flurbiprofen–loaded nano particles were prepared by[98] through membrane emulsification method, which was already proved helpful to load water–insoluble drug, for example, flurbiprofen, while the bioavailability was enhanced by the use of uniform nano–scaled particles. Nano–scaled self–emulsifying drug delivery system with small and uniform emulsion droplets was also achieved using SPG membrane emulsification technique, leading to enhanced solubility, dissolution and oral bioavailability of poorly water–soluble cilostazol.[99] To investigate the feasility of polymeric nano/micro particles as vaccine adjuvants and the impact on specific immune responses, PLGA nano/micro particles with uniform sizes (500 nm, 900nm, 2.1μm, and 4.9μm) were prepared via SPG membrane emulsification method. Finally, nano particles of 900 nm was found to be the optimum choice for PLGA particle–based vaccine adjuvants especially for recombinant antigens.[100]

Non–spherical particles

It has been confirmed that the shape of particles has a profound influence on their functions. However, it is not easy to prepare non–spherical particles by the conventional emulsification method because the minimization of interfacial energy results in the swift formation of spherical emulsions. To this challenge, developed a direct method to fabricate non–spherical particles of PLGA with uniform size. This method employed phosphate buffer saline as the deformation initiator and combined the premix membrane emulsification technique with the solvent evaporation method to prepare uniform non–spherical particles of different shapes with aspect ratios from 2 to 40 and verified sizes ranging from 800 nm to 60μm. Moreover, octreotide acetate as a model drug was successfully loaded into the non–spherical particles.

The results indicated that the deformation process did not disturb the encapsulation efficiency and bioactivity of octreotide acetate, providing the possibility of using non–spherical particles as potential drug delivery systems.

Conclusion

During the past decades, SPG membrane emulsification has experienced a rapid development. The application of the resultant microspheres were swift extended into medicine field because of its unique advantages of uniform size, prominent stability and controllable drug release. As is known that membrane emulsification method was influenced by many factors. Although it was being improved in many aspects, the researchers still encounter many obstacles, such as how to achieve uniform polymer microspheres to embed active drug molecule and to maintain a slow and controllable release of loaded drug. On the other hand, it also needs to develop diversiform membrane with high performance, to meet different requirements coming from various types of diseases and provide even more convenience for therapy. Currently, many new technologies were increasingly incorporated into this method so as to develop the method and provide novel ways for further research in the near future. It is expected that membrane emulsification method will be further applied in medicine field along with its quick development.

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Conflicts of interest

There is no conflict of interests regarding the publication of this paper.

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