Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 298 (2005) 206–210
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Note

Two new plate nozzles for the production of alginate microspheres

Fan Yang, Kang Wang, Zhimin He *

Enzyme Technology Laboratory, Chemical Engineering Research Center, Tianjin University, Tianjin 300072, PR China

Received 20 December 2004; received in revised form 4 April 2005; accepted 5 April 2005
Available online 23 May 2005

Abstract

Combining the Rayleigh-type jet break-up and two new plate nozzles, the alginate microsphere was produced. Spray generators made of syringe needle and laser-drilling nozzle plate and synthetic red stone nozzle plate were fabricated and contrasted. The above two plate nozzles provided lower liquid resistance and yield well. Furthermore, the more uniform microsphere was produced within a wider range of frequency by plate nozzles. Experiments using multiple-nozzle synthetic red stone plate was easy to feasible.

Keywords: Laser-drilling nozzle plate; Synthetic red stone nozzle plate; Alginate microsphere

The immobilization of drugs in the hydrogels has proven to be of great utility in pharmaceutical applications. Alginate-calcium gel has been the most commonly used material in controlled release. The production of alginate microspheres through the Rayleigh-type break up of liquid jets is a well-known technique. This technique uses vibration as a mechanical disturbance to induce the controlled break up of a liquid capillary jet into uniformly sized droplets.

A schematic representation of the production system is shown in Fig. 1. A suspension of Na-alginate solution is held in the feed tank which is a graduated vessel in order to show the remaining quantity. The solution is driven through plate nozzle by air pressure. Because of controlled vibration disturbances provided by magnetic vibrator, uniform microspheres are formed.

In the process, several parameters have fundamental influence over the performance of this system. According to the theory of capillary, the jet velocity must be high enough to create a jet (beyond the jetting point). To avoid the aerodynamic effect, the jet velocity should not be too high. Otherwise, satellite drops are formed and deformation is caused by impact of high-speed beads upon $CaCl_2$ solution. So the jet velocity is extremely important and should be carefully controlled by adjust the air pressure.

Conventionally, syringe needle was used to provide the nozzle hole (Dabora, 1967). Compared with this traditional nozzle, two other kinds of plate nozzle are presented in this paper, which have many advantages,

* Corresponding author. Tel.: +86 22 2740 7799; fax: +86 22 2740 4757.
E-mail address: zhe@tju.edu.cn (Z. He).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.04.002

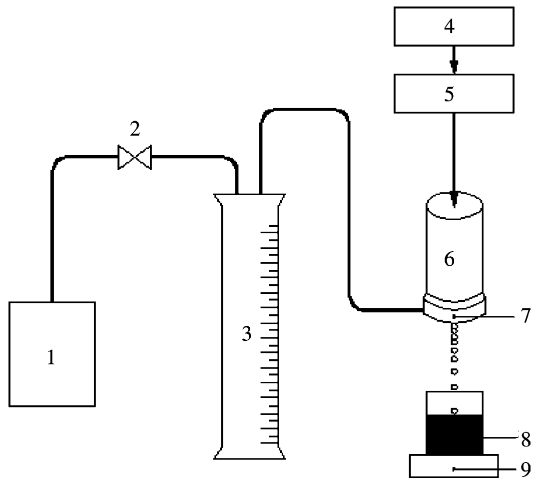

Fig. 1. Schematic of the apparatus for the production of alginate microspheres: (1) air compressor; (2) valve; (3) feed tank; (4) signal generator; (5) signal amplifier; (6) vibrator; (7) nozzle plate; (8) gelling reservoirs; (9) magnetic stirrer.

especially at production scale. Laser-drilling nozzle plate and synthetic red stone nozzle plate were used in my work for these production processes of relatively simple and the high veracity. In the case of multi-nozzle production, plate nozzle is much easier to fabricate and fix with low cost. On the contrary, the preliminary work like the cutting off of all needle tips and adjustment of needles in the process of fixation is not only time consuming but also not accurate because of man-involved factors.

Due to the characteristic of laser-drilling technique, the nozzle hole drilled into the plate has self-formed gradient of about 18° as shown in Fig. 2. The upper end of the hole was comparatively larger. The sodium alginate solution was jetted from the nether end of the hole. This peculiarity not only facilitate the Na-alginate solution to overcome the surface tension thus enter the upper end of nozzle hole much easier, but also help to form smaller jet and smaller microspheres. This 18° gradient is similar to the gradient of spray head widely used in food and pharmaceutical industry.

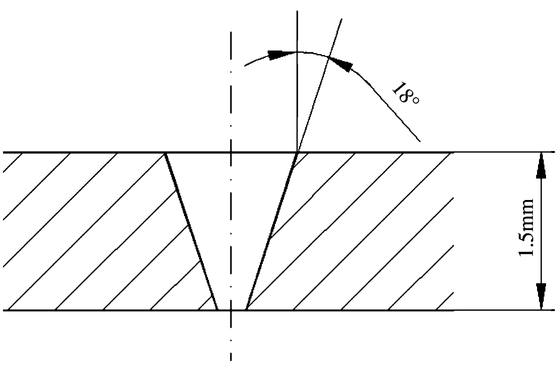

Fig. 2. Sectional view of laser drilled nozzle plate.

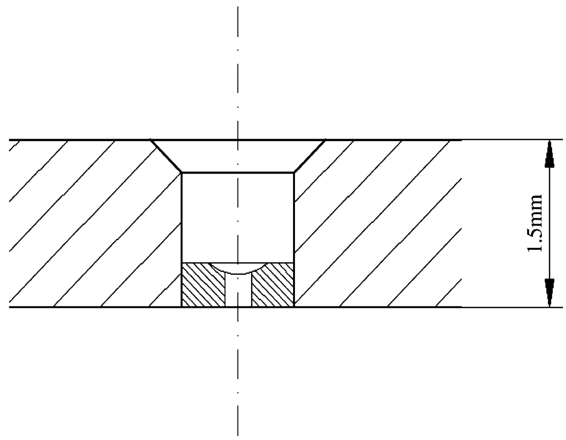

Fig. 3. Sectional view of synthetic red stone nozzle plate.

In the case of synthetic red stone nozzle plate, the precisely drilled synthetic red stone is fixed on the tip of plate nozzle as shown in Fig. 3. This special material enables the formation of perfectly round and uniform outlet with which laser-drilling technique cannot compete. Therefore, synthetic red stone is chosen to fabricate multiple-nozzle plate. The nozzle spacing on the plate should be large enough to prevent collision, and a minimum mutual distance between the nozzles should be around three times the nozzle hole diameter (Karasawa et al., 1988).

The microsphere diameter was determined microscopically with a vernier scale micrometer. The mean microsphere diameter and standard deviation (S.D.) were calculated from a sample population of at least 20 microspheres randomly selected from the population.

The sizes and the S.D. of microspheres produced by a single syringe needle (0.3 mm inner diameter) were presented in Table 1. The stainless steel hypodermic needle was shortened to 3 mm length to avoid and excessive pressure drop. The stable liquid and the small S.D. were obtained within the operation pressure

Table 1
Alginate (2%) microsphere size and S.D. as a function of jet velocity and frequency of the imposed disturbance using a single syringe needle (0.3 mm)

Frequency (Hz)	Flux			
	4.0 ml/min		5.3 ml/min	
	Diameter (mm)	S.D. (%)	Diameter (mm)	S.D. (%)
0	0.82	24.9	0.85	24.3
100	0.85	10.0	0.91	5.5
200	0.62	14.3	0.77	12.4
300	0.65	9.6	0.77	9.3
350	0.58	5.3	0.73	13.1

of $0.04–0.06 \times 10^6$ Pa and the sodium alginate flux of 4.0–5.3 ml/min. It was apparent that the average microsphere size decreased with increasing frequency. For low flux system (4.0 ml/min), more uniform microspheres was gained using high frequency (350 Hz). On the contrary, for high flux system (5.3 ml/min), microspheres of small S.D. was obtained using low frequency (100 Hz). Furthermore, the size of microsphere was increased when the flux was enhanced.

Table 2 illustrated the size and the S.D. of microsphere using a single laser-drilled nozzle (0.3 mm outer diameter). It was obvious that the feasible pressure and liquid flux were $0.02–0.04 \times 10^6$ Pa and 10.9–12.2 ml/min, respectively. Comparing with the syringe needle system, the higher liquid flux was achieved under lower operation pressure due to the small resistance of liquid. During 100–250 Hz, the small S.D. was appeared. Using the high flux, the size of microsphere was decreased slightly, which was different from the syringe needle system.

Table 2
Alginate (2%) microsphere size and S.D. as a function of jet velocity and frequency of the imposed disturbance using laser-drilled plate with single-nozzle (0.3 mm)

Frequency (Hz)	Flux			
	10.9 ml/min		12.2 ml/min	
	Diameter (mm)	S.D. (%)	Diameter (mm)	S.D. (%)
0	0.93	20.4	0.89	22.5
100	1.10	2.0	1.04	7.7
150	1.02	3.5	1.09	5.7
200	1.10	2.0	0.92	3.9
250	1.10	3.6	0.82	4.4
300	1.08	10.8	0.82	10.6

Table 3
Alginate (2%) microsphere size and S.D. as a function of jet velocity and frequency of the imposed disturbance using synthetic red stone nozzle plate with a single nozzle (0.3 mm)

Frequency (Hz)	Flux			
	8.6 ml/min		10.7 ml/min	
	Diameter (mm)	S.D. (%)	Diameter (mm)	S.D. (%)
0	1.12	25.9	1.00	23.0
100	1.21	3.6	1.12	5.4
150	1.01	3.0	0.98	3.2
200	0.90	2.4	0.84	4.3
250	0.73	7.3	0.71	8.5
300	0.71	6.1	0.70	7.6
350	0.71	9.2	0.67	10.8

It can be seen from Table 3 that the optimum operation pressure and liquid flux were $0.02–0.04 \times 10^6$ Pa and 8.6–10.7 ml/min, respectively, when the microspheres made by a single synthetic red stone nozzle plate (0.3 mm outer diameter). It was similar to the result from the syringe needle and the laser-drilled nozzle that the average microsphere size of synthetic red stone nozzle system was reduced when frequency was increased. The more uniform microsphere was produced within a wider range of frequency, 100–300 Hz. It was also found that the average microsphere size decreased slightly with increasing liquid flux.

The particle size distribution curve was shown in Fig. 4. A certain range of wavelengths produced uniform microspheres. At the optimum wavelength, the jet was the most unstable, as indicted by its short jet length, and usually produced the most uniform microsphere population. It was clearly that the optimum wavelength was easily achieved for plate nozzles.

As a result, above two plate nozzles had lower liquid resistance and higher liquid flux, which was of benefit to yield well. Moreover, the device using plate nozzle was easy to handle because the more uniform microspheres were appeared during a wide range of frequency.

It was found from Fig. 5 that the very resemblance size and S.D. of microsphere made by plate with single-nozzle and plate with four nozzles, which indicated that multiple-nozzle synthetic red stone plate was feasible. However, with the laser-drilling technique it is

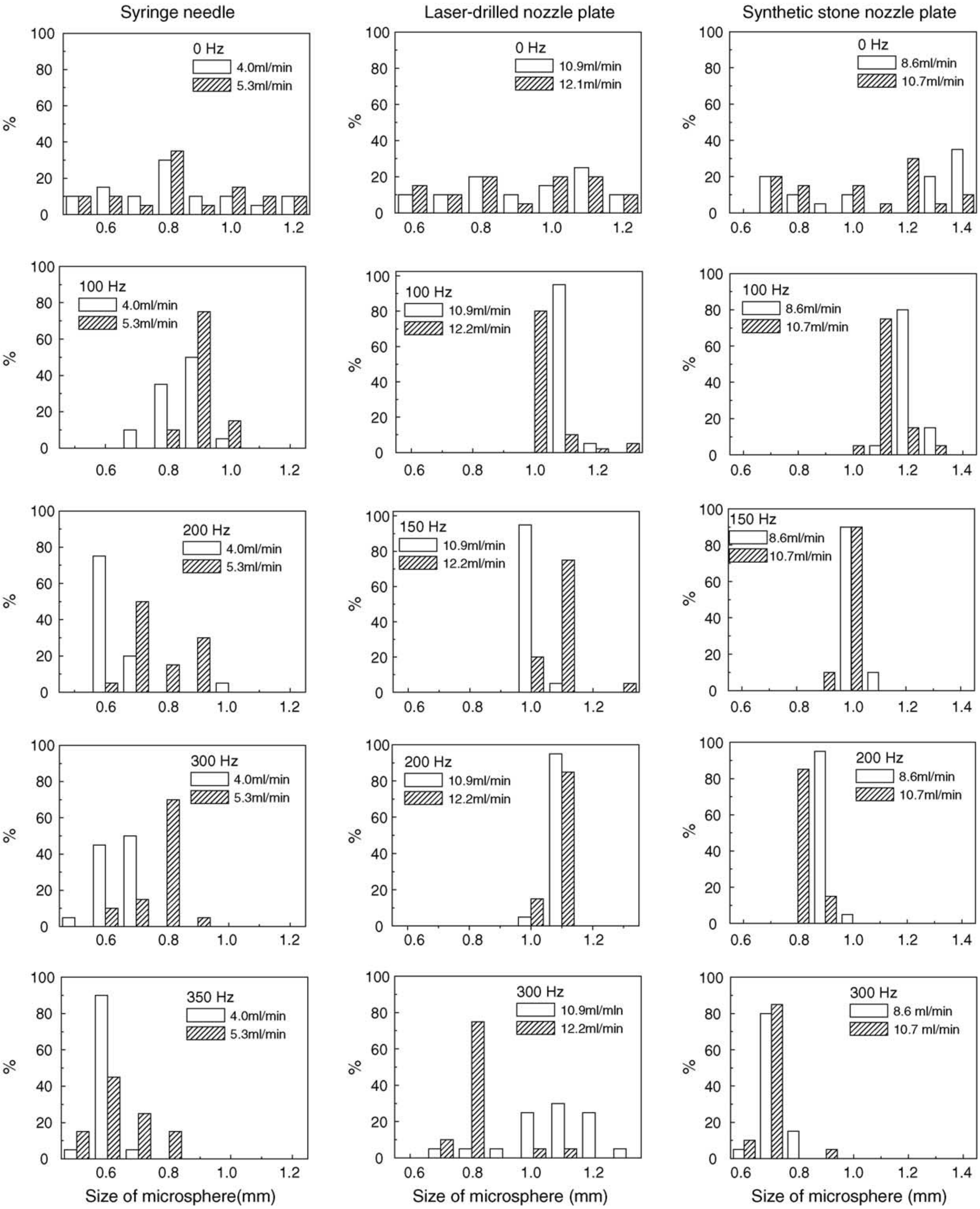

Fig. 4. The microsphere size distribution curve from Tables 1–3.

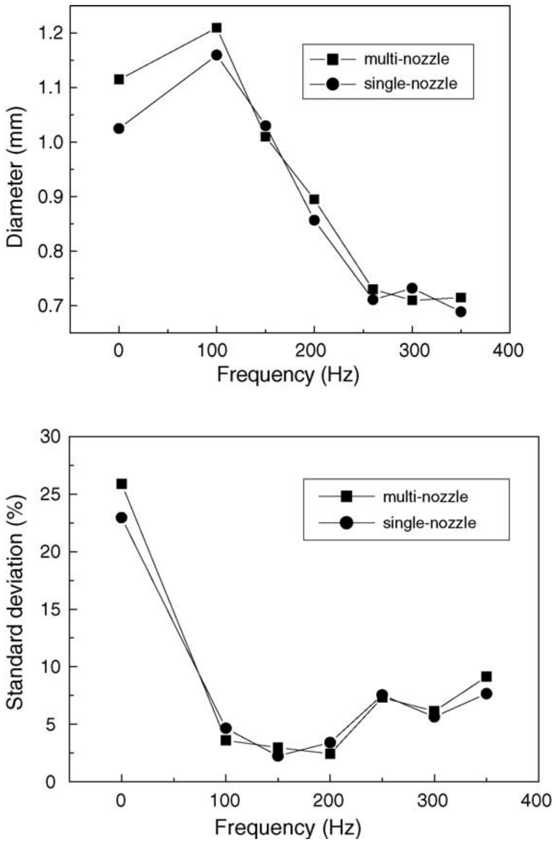

Fig. 5. Alginate (2%) bead size and uniformity as a function of frequency of the imposed disturbance using single-nozzle and multi-nozzle (0.3 mm) sapphire stone plates.

not possible to obtain absolutely uniform nozzle diameters (Brenn et al., 1997). For multiple-nozzle plate of laser drilling, the S.D. of microsphere was relative high. Moreover, the four nozzles were fixed on one plate, which was differential with four-fluid nozzle spray drier with independent nozzle.

In summary, above two new plate nozzles allows reproducible production of microspheres with narrow size distribution and has potential applications in the fields of pharmaceutical industry.

Acknowledgements

We are grateful for the financial support from National Nature Science Foundation of China (No. 50173020) and Tianjin Science and Technology Commission, China (No. 013617011).

References

Brenn, G., Helpio, T., Durst, F., 1997. A new apparatus for the production of monodisperse sprays at high flow rates. Chem. Eng. Sci. 52, 237–244.

Dabora, E.K., 1967. Production of monodisperse sprays. Rev. Sci. Instrum. 38, 502–506.

Karasawa, T., Shiga, S., Kurabayashi, T., 1988. Production of uniform-sied droplets by rectangular nozzles, Proceedings of the Fourth International Conference on Liquid Tomization and Spray Systems, pp. 117–124.