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Short Communication

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Preparation of dense/spherical fine particle by spray dryer

Abstract

Fine particle granulation using a spray dryer was performed to prepare with a high drug content, a spherical shape, and a smooth surface. Since the target particle size was less than 200 µm, a rotary disk atomizer was adopted and a slurry was chosen as the spray liquid. When 5-aminosalicylic acid used as a model drug, hydroxypropyl cellulose, and sodium chloride were added in the slurry and was spray dried, the desired size of particles were obtained. Then, the obtained particles were coated with an enteric polymer, no dissolution of the drug in the 1st solution was observed, indicating no disruption occurred during coating.

Keywords: spray dryer, fine particle, 5-amino salicylic acid, enteric coating, dissolution test

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Introduction

Core particles for fine particle coating are generally prepared by wet granulation or layered granulation. Although the wet granulation method has the advantage of increasing the drug content, it is difficult to control the particle size for the fine particle coating. Furthermore, particles obtained by wet granulation often have wide size distribution and irregular shapes, there are not suitable for fine particle coating. In the layered granulation method, it is relatively easy to control the particle size by selecting core particles such as spherical sucrose particles (NONPAREIL™)[1] or crystalline particles like lactose, but on the other hand, it is difficult to increase the drug content. Since the coating on fine particles has a large specific surface area due to the small size of each particle, core particles having a spherical shape and smooth surface as well as the development of an appropriate coating material are desired. Therefore, this time, we focused on spray dryers and succeeded in designing particles with a high drug content, a spherical shape, and a smooth surface. The choice of atomizer is one of the important factors in the particle design of spray dryers.[2] Since the target particle size is less than 200 µm, considering the subsequent coating process, we selected a rotary disk atomizer useful for the preparation of the particle size. Droplets that can be applied to the spray dryer include solutions, slurries, pastes, gels, suspensions, oil and fat melts, among which the most suitable slurry was selected to increase the drug content. 5-aminosalicylic acid was used as a model for poorly soluble drugs.

Materials and method

Chemicals

5-aminosalicylic acid (5-ASA) was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Sodium chloride (NaCl) was purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Hydroxypropyl cellulose (HPC, SSL) and ethylcellulose (EC, #10) were purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Eudragit L100 was purchased from Higuchi Inc. (Japan). Stearic acid was purchased from Kao Corporation (Tokyo, Japan). Sodium starch glycolate (DST-SF) was purchased from YUNG ZIP Chemical IND. Co., Ltd (Taiwan). Polyethylene oxide (PEO 205) was purchased from Sumitomo Seika Chemicals Co., Ltd. (Tokyo, Japan). All other reagents were used special grade products commercially available.

Spray dry

HPC-SSL, NaCl, and PEO 205 were dissolved in purified water with a mixer, 5-ASA and a dissolution excipient (DST-SF) were added, thoroughly stirred, and then filtered to prepare a slurry with the formula shown in Table 1. The viscosity of the prepared slurry was measured using a C-type viscometer. Since 5-ASA is unstable to light, the prepared slurry was stored in a light-shielding container until the experiment. The spray dryer was performed using an Anhydro® pilot spray dryer with rotary disc atomizer (PSD58) of MATSUBO Corporation (Tokyo, Japan). The operating conditions are as shown in Table 2.

Table 1 Composition of slurry containing 5-ASA for spray drying

Component	Ex1	Ex2	Ex3
5-ASA	60	95	75
DST-Sf[a]	30	-	-
PEO 205	-	5	-
HPC-SSL[b]	10	-	20
NaCl	-	-	5
Total	100	100	100

a, sodium starch glycolate; b, hydroxyl propyl cellulose

Table 2 Operational conditions during spray drying of fine particles

Operation condition	Ex1	Ex2	Ex3
Solbent	water	water	water
Solid concentration (%)	13.1	17.3	32
Viscosity(cpm)	300	440	130
Disk roatation speed(rpm)	7000	6000	8000
Inlet temperature(°C)	140	140	140
Outlet temperature(°C)	79	77	86
Sulluly feed speed(L/h)	8.6	8.45	8.6

Enteric coating to spray-dried particles

A GPCG-1 Wurster (Glatt GmbH, Binzen, Germany) with a spray nozzle of 0.8 mm diameter and a filter with an opening of about 5 µm

was used. Sixty gram of spray dried particles (75 - 150 µm) (Ex.3) was loaded to GPCG-1 and a mixture of HPC-SL and stearic acid (2:98) in ethyl alcohol (5 % solid concentration) was coated. A mixture of EC #10, Eudragit L100, and stearic acid (1:1:2) was dissolved in ethyl alcohol to a concentration of 8% was further coated. The standard operating conditions applied were as follows: spray solution feed, 4 g/min; spray air volume, 60 NL/min; spray air pressure, 2 bar; blower rate, 0.5–2 m^3/min; blower temperature, 20 deg.

Measurement of particle size distribution

Samples (10 g) were measured using a Ro-tap sieve shaker (Iida Seisakusyo Co. Ltd., Osaka, Japan).

Scanning electron microscopy (SEM)

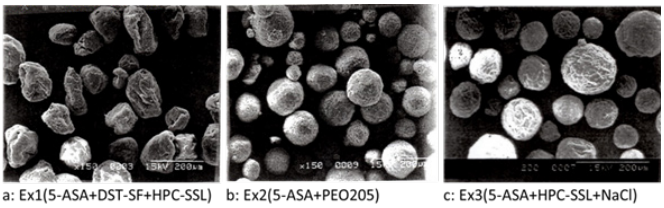
A scanning electron microscope (JSM-T100, JEOL Co., Ltd., Tokyo, Japan) was used to record the spray dried particles. Each sample was coated with gold by ion sputtering (JFC-1100, JOEL Co., Ltd.) for 3 min at an emission current of 15A for SEM studies.

Dissolution studies

Dissolution study was investigated according to the Japan Pharmacopeia 14 paddle method. The paddle speed was 50 rpm. The dissolution medium was 900 mL of first fluid (pH 1.2) and second fluid (pH 6.8) maintained at 37.8 deg. The released amount of drug was determined by a UV spectrophotometer (UV-160, SHIMADZU Co., Ltd., Kyoto, Japan) at 330nm.

Results

Figure 1A shows a SEM photograph of the result of spray-drying a slurry consisting of 5-ASA, DST-SF, and HPC-SSL. Further, the particle size distribution of the obtained particles is shown in Figure 2. The average particle size of spray dry particles to which 5-ASA was added to DST-SF and HPC-SSL was 153.8 µm, and granulate of the target size was obtained. However, the sphericity was low and the surface condition was poor. In addition, the strength of the particles was weak, and when pressed with a finger, the particles were easily broken. For purpose of improving the particle shape, Figure 1B shows a SEM photograph of the result of spray-drying a slurry in which the slurry viscosity has been increased to 440 cps with PEO 205. The average particle diameter was 153.5 µm, and granulate of almost the same size was obtained. In addition, the sphericity has also been improved, but they were not strong enough. The results of adding NaCl to the slurry and spray drying it are shown in Figure 1C. Granulate with an average particle size of 135.0 µm were obtained, which was approximately the same size. The sphericity was also almost satisfactory, and the strength of the particles was significantly improved. Then, using this granulate (Ex.3), an enteric fine particle coating was performed, and the dissolution profile was evaluated. The results are shown in Figure 3. It was clear that the dissolution profile of 5-ASA from enteric-coated particles in 1st fluid was not observed at all. When the dissolution medium was changed to 2nd fluid, sustained release was shown and the coating property as expected was obtained.



a: Ex1(5-ASA+DST-SF+HPC-SSL) b: Ex2(5-ASA+PEO205) c: Ex3(5-ASA+HPC-SSL+NaCl)

Figure 1 SEM photographs of spray dried particles.

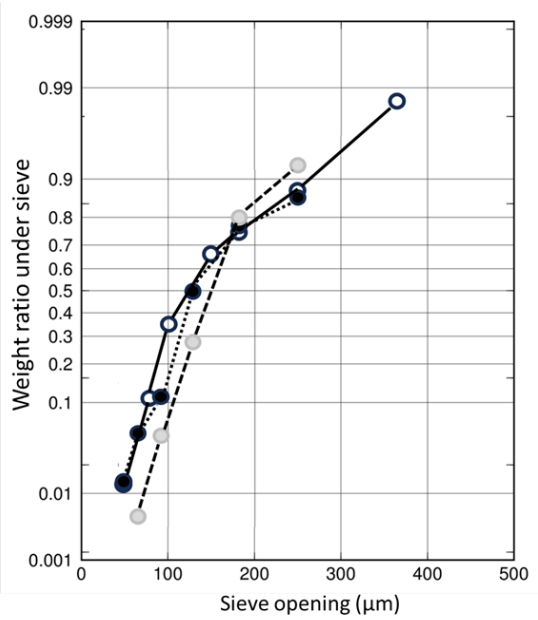


Figure 2 Size distribution of spray dried particles.

●Ex1(5-ASA+DST-SF+HPC-SSL), ●Ex2(5-ASA+PEO205), ○:Ex3(5-ASA+HPC-SSL+NaCl)

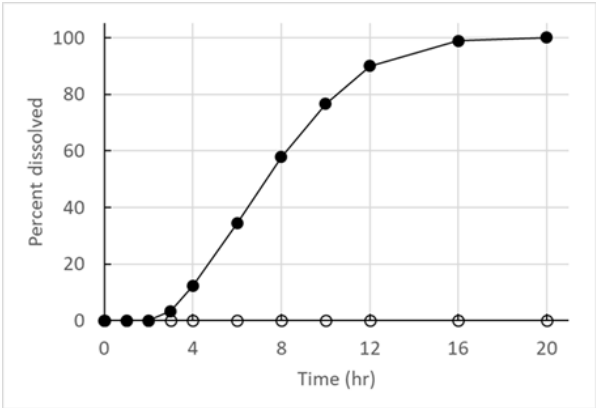


Figure 3 Dissolution Profile of 5-ASA from enteric coated particles (JP paddle method, 900mL, 50 rpm).

○, 1st fluid; ●, 2nd fluid

Discussion

In this study, we focused on the spray drying method for the preparation of fine particles that are dense/spherical and have good surface condition, and examined the preparation of particles that do not disintegrate in the coating process. In a spray dryer, slurry discharged from a nozzle takes on a spherical shape due to its surface tension, and undergoes a drying process in a chamber to prepare particles. It is known that during the drying process, if the balance between water evaporation and particle agglomeration is disrupted, the shape becomes distorted. First, 5-ASA and DST-ST were used as a model drug and a dissolution excipient respectively, and a slurry mixed with HPC-SSL was prepared for particle binding and shape maintenance. Granulation using a spray dryer was attempted, but the shape of the resulting particles was poor and the strength of the particles was not sufficient. Then, PEO 205 as a thicker which is known to be able to obtain dense particles[3] was added and spray granulation was performed. The resultant particles were spherical, but

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they were not strong enough. Therefore, NaCl, which is known to precipitate crystals and form a hard shell when the droplets dry, and to increase the surface roughness, reduce the adhesion of particles to each other[4] is added and spray granulation was performed. As a result, particles with a size of 200 μm or less, a spherical shape, a smooth surface, and, no mechanical strength problems were obtained.

Further, when these spray-dried particles were applied an enteric coating, there was almost no corruption during the coating. When the dissolution medium was changed to 2nd fluid, the sustained release profile was found, indicating the coating properties as expected were obtained. From these results taken together suggest that the combination of a spray dryer and the addition of NaCl to the slurry was able to form each particle ideal for microparticle coating. Future studies will include the optimal amount of NaCl added, the possibility of application to other drugs, and the detailed mechanism of the particle formation process.

Conclusion

For purpose of designing particles with a spherical shape and a smooth surface, granulation by spray drying was attempted, and by blending NaCl in the slurry formulation, we succeeded in preparing particles with a spherical shape, smooth surface, and sufficient mechanical strength. According to this method, since it is also possible to increase the drug content, it seems that it can be applied to drugs with a large dosage.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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