A Technical Feasibility of Aqueous Aerosol Generation Based on the Flashing Jet: Impact of Surfactant, Electrolyte, and Drug Concentration

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Abstract

This study aimed to investigate the atomization mechanism of a flashing jet (FJ), focusing on the potential factors that influence the atomization performance of the device. Those factors include surfactant, electrolyte, and drug concentration. In this work, Tween 80, sodium chloride (NaCl), and salbutamol sulfate (SBS) were used for the study. The aerosol's mass median aerodynamic diameter (MMAD) was investigated for analysis. The drug delivery ability of the FJ prototype was compared with the Pari nebulizer. Our data suggested that the MMAD of aerosol decreased as the concentration of Tween 80 increased, but the critical micelle concentration point was not influenced. Upon adding NaCl to pure water, with the increase of NaCl concentration, the MMAD of aerosol initially decreased significantly and then increased, reaching the lowest point when 0.05% NaCl was used. A higher concentration of SBS was beneficial for the atomization performance. When the SBS concentration was 5 mg/mL, the MMAD values of the FJ prototype and Pari nebulizer were 2.28 ± 0.15 and 1.03 ± 0.21 µm, respectively, and the fine particle dose (%TDD) of the FJ prototype and Pari nebulizer was 50.99 ± 5.88 and $53.51 \pm 4.58\%$, respectively. Interestingly, the concentration of SBS has no effect on the residual dosage level of the FJ prototype, indicating that it can be applied in atomizing high-concentration solutions. In summary, surfactant, electrolyte, and drug concentration played an important role in the atomization performance of the FJ prototype and these ingredients are also crucial factors that should be considered in future formulation studies.

Keywords
► inhalation drug delivery
► flashing jet
► inhaler prototype

Introduction

Inhalation drug delivery is a method of administration whereby medications in aerosolized form are inhaled into the respiratory tract and subsequently the pulmonary system for topical or systemic applications.[1,2] The efficiency of inhalation drug delivery is determined by the atomization performance of the aerosol device, the physicochemical characteristics of the formulation, and the inhalation skill of the patient.[3–6] Flashing is an instantaneous boiling process that occurs when the external pressure of a liquid drops below its saturated vapor pressure.[7] When overheated liquid is forced through an orifice, flashing happens after the orifice, resulting in a flashing jet.[8,9] The expansion and rupture of flashing bubbles break the flashing jet into droplets.[8,10–13] Our previous study established a flashing

jet inhaler prototype (FJ prototype) and recovered the potential effects of flashing and jetting parameters on the atomization performance of the device.[14] In terms of the FJ prototype, when normal saline is used as the atomized liquid, fine droplets ($<5\,\mu m$) can be obtained. However, when drugs and surfactants are introduced, there will be significant changes in the aerodynamic particle size distribution (APSD). Therefore, further research is necessary to investigate the potential effects of formulation ingredients on the atomization performance of the FJ prototype.

Evidence suggests a variety of factors that affect the atomization performance of the flashing jet, and those factors may be surface tension, ion concentration, and viscosity.[10,15–18] In addition, several theoretical formulas have been proposed to elucidate the relationship between these factors and the droplet size.[7,15,19,20] However, these theoretical formulas mainly consist of empirical equations. The mechanism through which these factors affect the flashing jet remains unclear.

The primary objective of this study is to investigate the impact of surfactant, electrolyte, and drug concentration on the atomization performance of the FJ prototype. In this work, Tween 80 was employed as a surfactant, sodium chloride (NaCl) was used as an electrolyte, and salbutamol sulfate (SBS) was chosen as a model drug used in pulmonary drug delivery. The mass median aerodynamic diameter (MMAD) and APSD of the aerosol produced were measured to compare the atomization performances. Additionally, the drug distribution was evaluated to assess the drug delivery capacity at different SBS concentrations. The study is helpful to explore the formulation of the FJ prototype with improved atomization performance.

Material and Methods

Instruments and Materials

The following instruments were used in this study: high-performance liquid chromatography (HPLC; Shimadzu, LC-20AT), aerodynamic particle sizer (APS; TSI, Model 3321), impactor inlet for pharmaceutical research (IIPR; TSI, Model 3306), vacuum pump (SH-Deying Vacuum & Lighting Equipment Co., Ltd., 2XZ(s)-2), air flow meter (QF-meter, LZB-10), glass microfiber filter (Whatman GF/F), analytical balance (Mettler Toledo, XS205DU), Pari nebulizer, and Flashing Jet prototype.

The following reagents were used in this study: Tween 80 (Sigma-Aldrich, BCBR8595V), sodium chloride (Sinopharm Chemical Reagent Co., Ltd., 20161207), SBS (SPH Sine Pharmaceutical Laboratories Co., Ltd., cpc-007–1712005), methanol (CNW Technologies GmbH, 16891140), phosphoric acid (Sinopharm Chemical Reagent Co., Ltd., 20120920), and sodium dihydrogen phosphate dihydrate (Sinopharm Chemical Reagent Co., Ltd., 20170209). Methanol was of chromatographically pure grade, while the other reagents were analytical grade. The water used in the experiments was purified water.

FJ Prototype

The FJ prototype is illustrated in ►**Fig. 1A**, and the atomization process of the FJ prototype (►**Fig. 1B**) was conducted according to a reported study.[14]

The FJ prototype was operated using an overheat temperature of 150°C, an initial chamber pressure of 150 kPa, and a jetting rate of 25 µL/s. The jetting volume was set at 150 µL, which approximates the atomized volume at the Pari nebulizer in 60 seconds.

Pari Nebulizer

The Pari nebulizer is globally recognized as one of the most commonly used jet nebulizers. Jet nebulizers employ compressed air or oxygen to transform liquid into aqueous aerosol. During the atomization process, the compressed air generates a localized area of negative pressure around the nozzle, causing the liquid from the reservoir to be drawn and fragmented into droplets (►**Fig. 2A**).[21]

The Pari nebulizer was used as a reference device in the study due to its fundamental atomization mechanism, which involves using an air jet to break the liquid jet. In contrast, the atomization mechanism of the FJ prototype relies on using flashing bubbles to disrupt the liquid jet (►**Fig. 2B**). By observing the distinct patterns of changes in atomization performance at different solvent concentrations, it is possible to discern whether these variations are related to the flashing process.

The APS/IIPR system was used to measure the APSD and MMAD of the aerosol output. It should be noted that the
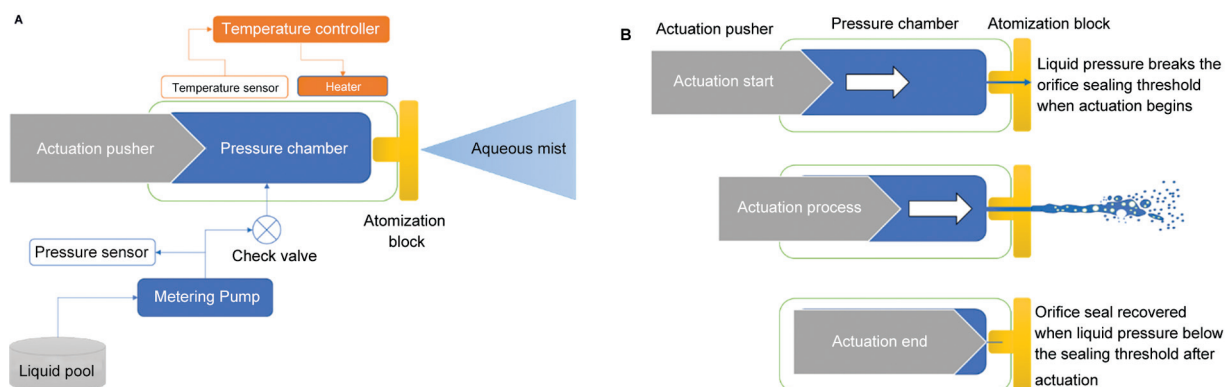

Fig. 1 Diagrammatic view of FJ prototype: (**A**) prototype composition, and (**B**) actuation process.[14]
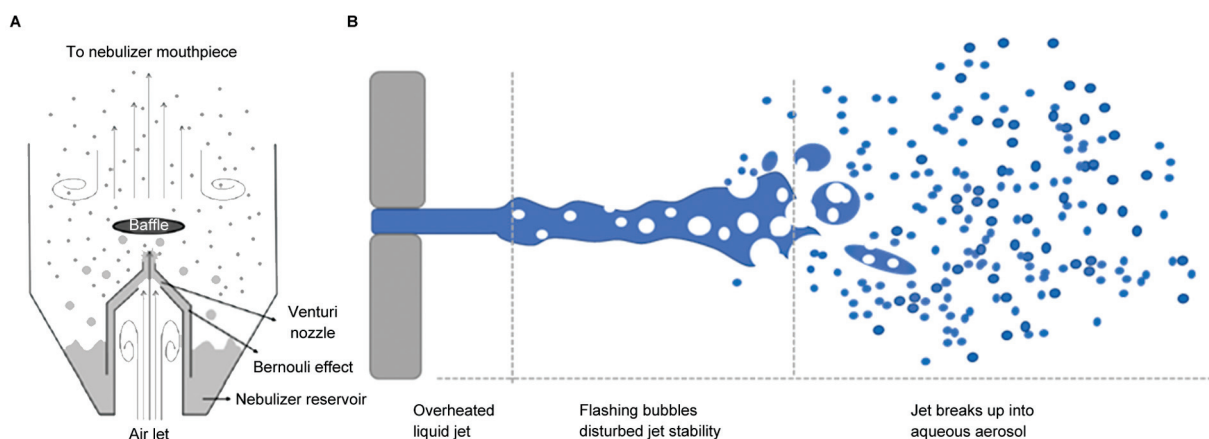
Fig. 2   Diagram view of atomization mechanism of (**A**) Pari nebulizer and (**B**) FJ prototype.

measurement results obtained using this system may deviate from the original droplet size due to potential shrinkage caused by the sampling flow.[22,23] Therefore, the Pari nebulizer was chosen as a reference device since it also produces aqueous aerosol and is subjected to similar evaporation effects within the APS/IIPR system. The APSD and MMAD of the aerosol output from the Pari nebulizer were used as benchmarks to assess the atomization quality of the FJ prototype.

APSD and MMAD Measurement
The particle size of the delivered aerosol was measured by the APS based on the time of flight method. The IIPR, which has a United States Pharmacopeia/European Pharmacopeia (USP/Ph Eur) inlet and an APS sampling probe, was integrat-ed with the APS. APSD and MMAD of the aerosol were measured according to a reported study.[14]

Atomized Volume Measurement
Atomized volume was defined as a 60-second continuous output for the Pari nebulizer and a single spray output for the FJ prototype. The residual gravimetric method was used to measure the atomized volume.[24,25] For the Pari nebulizer, a 2 mL liquid was filled into the nebulizer cup, and the initial weight of the cup before atomization was recorded. After 60 seconds of continuous atomization, the end weight of the cup was recorded. The difference between the initial and end weights, divided by the liquid density, represents the atom-ized volume of the Pari nebulizer.
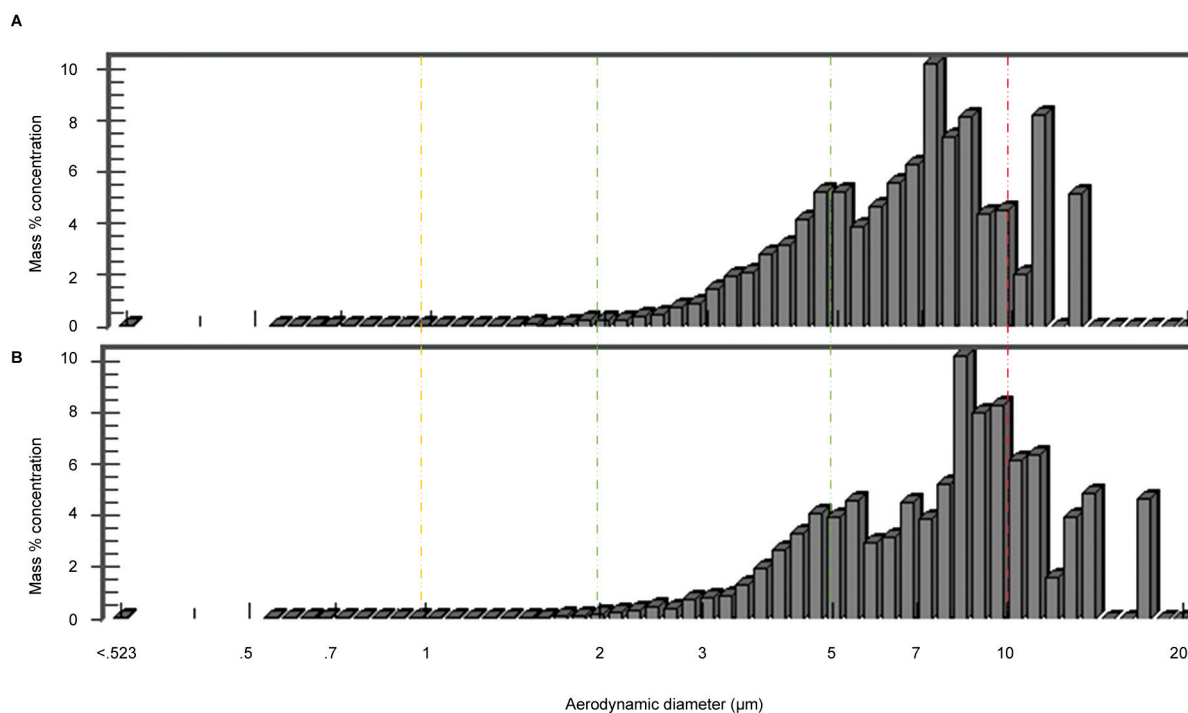

Fig. 3   APSD of pure water at (**A**) Pari nebulizer and (**B**) FJ prototype. APSD, aerodynamic particle size distribution.

Regarding the FJ prototype, a 2 mL liquid was filled into the liquid pool during preparation. The weight of the pool before and after actuation was recorded. The difference between these two weights, divided by the liquid density, provides the atomized volume of the FJ prototype. For simplification, an approximate density of 1 g/cm³ was used for all solutions in this study during the calculation.

Dosage Measurement
The drug dosage of the delivered aerosol was measured using the USP throat, a 4.7 µm single-stage impactor, and an outlet filter within the APS/IIPR system.[14] Following the atomization process, the atomization block of the FJ prototype, connecter, USP throat, and impact plates were washed by the mobile phase. The lotion of the atomization block was collected as the device residual dosage sample, while the lotions from the connecter and USP throat were combined as a throat residual dosage sample. The lotions from the impact plates were merged to form a large particle dosage (LPD) sample. The glass microfiber filter, situated on the outlet holder in the IIPR, was immersed in the mobile and subjected to ultrasonic cleaning for 30 minutes. The resulting lotion was then filtered through a 0.22 µm membrane and the subsequent filtrate was used as fine particle dose (FPD) samples. All samples were analyzed by HPLC.

The sum of the device residual dosage, throat residual dosage, LPD, and FPD represents the total delivered dosage (TD). The dosage calculated based on the atomized volume and SBS concentration is referred to as the normal dosage.

Chromatographic Conditions
The chromatographic analysis was conducted using a Kromasil C18 column (4.6 × 250 mm, 5 µm particle size). The mobile phase consisted of a phosphate buffer solution prepared by dissolving 12.48 g of sodium dihydrogen phosphate dihydrate in 1,000 mL of purified water and adjusting the pH to 3.1 using phosphoric acid. The mobile phase was mixed with methanol in a ratio of 85:15 (v/v). The detection wavelength was set at 276 nm. A flow rate of 1.0 mL/min was maintained during the analysis. The injection volume was 20 µL, and the column temperature was set to 35°C.

System Cleaning
The Pari nebulizer cup was cleaned after each test. The interior and exterior surfaces of the cup were flushed with a combination of 95% ethanol and pure water. Subsequently, a nonwoven fabric was used to wipe and dry the cup in a shaded area. The net weight difference of the cup was kept within 50 mg. Similarly, the atomization block of the FJ prototype was cleaned after each test. The interior and exterior surfaces of the block were flushed with a mixture of 95% ethanol and pure water. The block was then dried in a shaded area. After each sample group, the pressure chamber, metering pump, and liquid pool were sequentially flushed with 95% ethanol and pure water. For the IIPR system, the

inlet and impactor plates were cleaned after each sample group except for the SBS group. The inlet, upper impact plate, lower impact plate, and outlet holder of the IIPR were successively flushed with 95% ethanol and pure water. Additionally, the exterior surface of the APS probe was cleaned using 75% ethanol wipes, and a nonwoven fabric was used to wipe and dry the probe. In the SBS group, the IIPR system was cleaned after each test.

Statistical Analysis
Data analysis was performed using the SPSSAU data analytics platform. The results were expressed as means ± standard deviation. One-way ANOVA was employed to evaluate data dependency. A statistically significant difference was defined as a p-value less than 0.05.
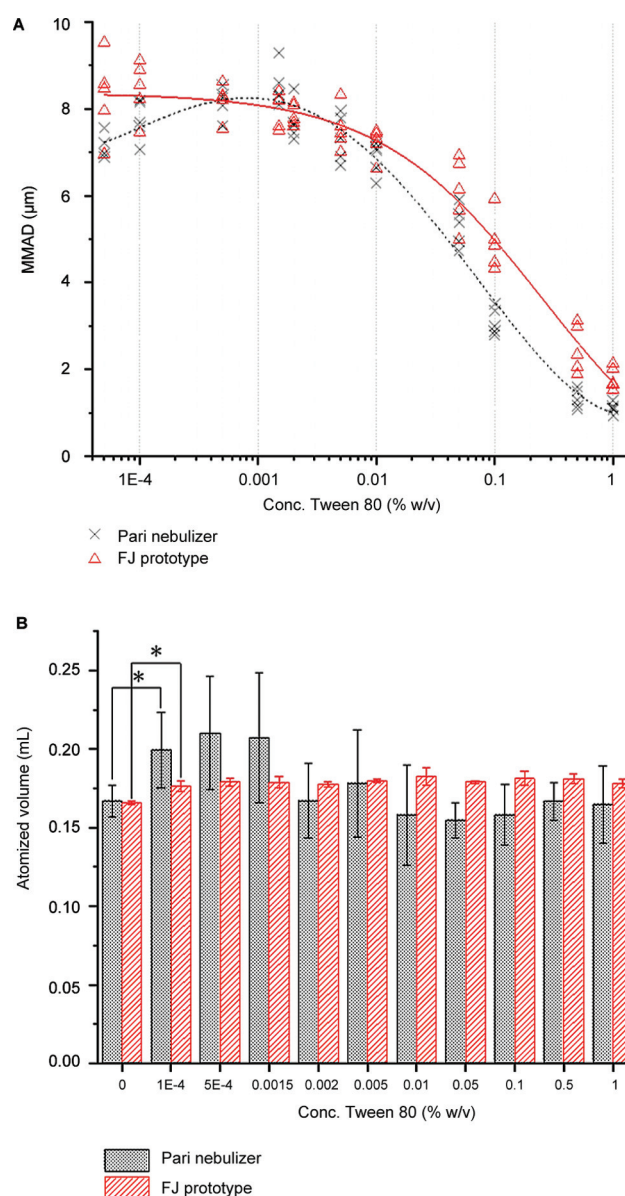

Fig. 4 Effect of different concentrations of Tween 80 on (**A**) aerosol MMAD and (**B**) atomized volume. MMAD, mass median aerodynamic diameter.

Results

Reference Output

When pure water was atomized by the Pari nebulizer, the MMAD of output aerosol was 7.12 ± 0.27 μm ($n = 5$), and the atomized volume in 60 seconds was 166.9 ± 9.8 μL. In comparison, when the FJ prototype was used, the MMAD of output aerosol was 8.30 ± 0.94 μm ($n = 5$), and the single spray volume was 165.7 ± 1.03 μL. Typical APSD of output aerosol is shown in ►**Fig. 3**.

MMAD was significant difference between the Pari nebulizer and the FJ prototype ($p = 0.0284$). To facilitate the follow-up work in this study, the single spray volume of the prototype was adjusted to an approximate volume (150

μL) as the average 60-second output volume of the Pari nebulizer. Therefore, there is no significant difference in the atomized volume between the two devices.

Effect of Surfactant Concentration

Tween 80 was chosen for this study due to its ability to induce significant changes in surface tension while causing minimal alterations in viscosity. Tween 80 concentrations ranging from 0.0001% to 1.0% were used to compare the atomization performances of both the Pari nebulizer and the FJ prototype.

The aerosol MMAD decreased as Tween 80 concentrations increased and no abnormal changes were found around the critical micelle concentration (CMC) point at the FJ prototype
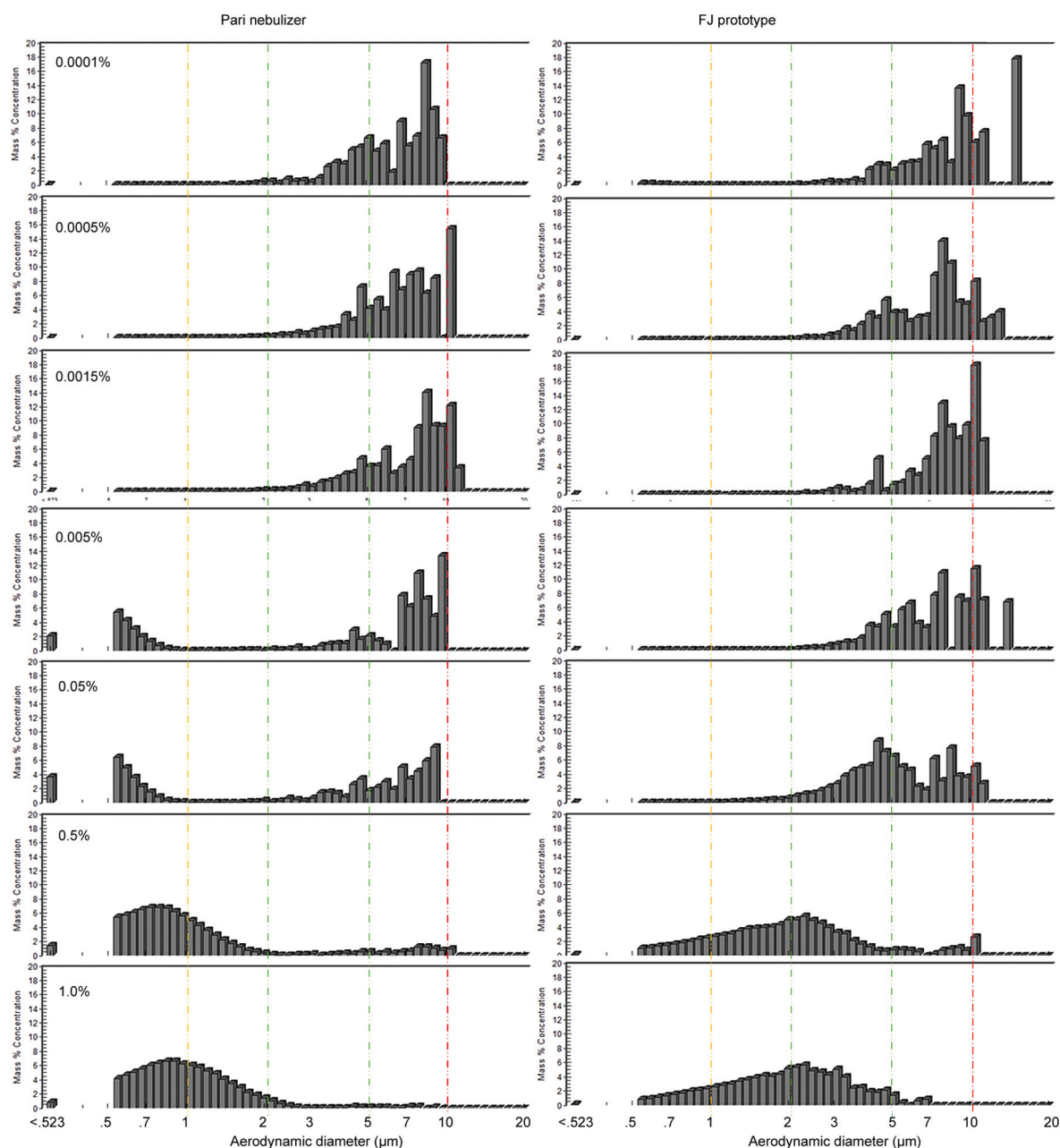

Fig. 5 Effect of different concentrations of Tween 80 on APSD. APSD, aerodynamic particle size distribution.

(►**Fig. 4A**). At the Pari nebulizer, the aerosol MMAD first increased, but then decreased when Tween 80's concentration increased above the CMC (►**Fig. 4A**).

The addition of Tween 80 to pure water resulted in a significant increase in the atomized volume. However, as the concentrations of Tween 80 increased, no significant changes in atomized volume were observed in the two devices (►**Fig. 4B**). In addition, the influence of different Tween 80 concentrations on the APSD of aerosol is shown in ►**Fig. 5**.

Effect of Electrolyte Concentration

Normal saline is generally adopted as a solvent in an inhaled liquid prescription according to the requirement of osmotic pressure equilibrium. Hence, NaCl was used to study the potential effect of electrolyte concentration on atomization performance. Upon adding NaCl to pure water, the MMAD of aerosol significantly decreased for both the FJ prototype and Pari nebulizer (►**Fig. 6**). When NaCl concentration was above 0.1%, the MMAD of aerosol at the FJ prototype was increased dose-dependently, while the MMAD of aerosol at the Pari nebulizer showed almost no change. Moreover, no significant changes in the atomized volume were observed at the Pari nebulizer or FJ prototype. The aerosol APSD at different NaCl concentrations is presented in ►**Fig. 7**.

Effect of Drug Concentration

The effect of different concentrations of SBS on the atomization performance was assessed. Upon adding SBS to the pure water, a significant decrease in the MMAD while an increase in the atomized volume were observed (►**Fig. 8**). At the FJ prototype, the aerosol MMAD continued to decrease with increasing SBS concentration, whereas, at the Pari nebulizer, no significant changes were observed. In addition, the atomized volume fluctuated at the Pari nebulizer, but no significant difference was observed.
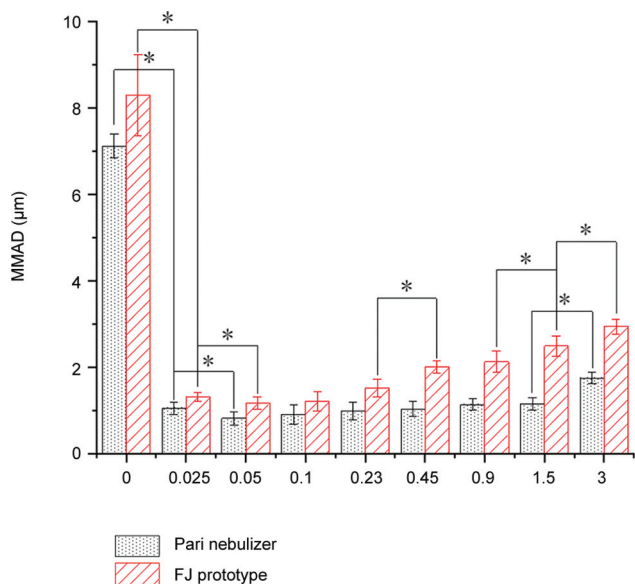
As SBS concentration increased, the fine particle fraction (FPF) at the FJ prototype increased, and FPF at the Pari nebulizer substantially fluctuated (►**Fig. 9**). Also, the APSD of aerosol at different SBS concentrations is presented in ►**Fig. 10**.

Discussion

Surfactant and MMAD

In the Pari nebulizer, changing the surface tension of the liquid may either influence the aerosol size or the atomized volume. Tween 80 has a CMC value of 0.0014% (w/v) at 25° C.[26] Tween 80A increased MMAD to a peak value followed by a decreased value, which was observed in the other three types of jet nebulizers in a previous study.[27] This pattern change is likely caused by the volume change of the primary and satellite droplets.[28,29]

Reducing the surface tension first leads to a larger primary droplet due to decreased flow resistance of the liquid. As a result, the nebulization rate increases,[30] and larger droplets will be generated. This explains the presence of large droplets of Pari nebulizer at low Tween 80 concentrations (►**Fig. 5**). Beyond the CMC point, reducing surface tension theoretically reduces the volume of the primary droplet, which inadvertently increases the volume of the satellite droplet.[31] This is consistent with the displacement of the super-fine droplet (<1 μm) distribution at high Tween 80 concentrations (►**Fig. 5**). This explanation is also suitable for the FJ prototype. Below CMC, the aerosol MMAD did not increase with increasing Tween 80 concentrations at the FJ prototype, because the atomized volume was controlled by a pusher.

Dynamic surface tension may be another explanation for the MMAD changes in the FJ prototype. The dynamic surface tension indicates the equilibrium process of surface tension in the liquid surface.[32] The initial surface tension of a newly generated liquid surface is the same as pure water. Soon after, this value is decreased with the diffusion of the surfactants until an equilibrium value is reached. The time required for this equilibrium is the dynamic surface tension depending on the diffusion rate and concentration of the surfactant.[33,34] Same as the surface tension, the dynamic surface tension improves the bubble bursting strength in a flashing jet. The growth of a bubble in a liquid involves balancing three forces: the pressure of the external liquid, the vapor pressure inside the bubble, and the interfacial tension.[7,35] In order for a bubble to expand, its internal pressure must exceed the external pressure and interfacial tension. Therefore, a lower surface tension not only results in a faster expansion process but also leads to more intense bubble formation in the flashing jet. However, since the bubble expansion happens in microseconds, the surface tension on the newly generated bubble interface may not reach the equilibrium value measured in the static conditions. In such cases, a lower dynamic surface tension can effectively decrease the surface tension throughout the entire bubble expansion process, ultimately resulting in a more drastic flashing process and smaller aerosol droplet sizes.
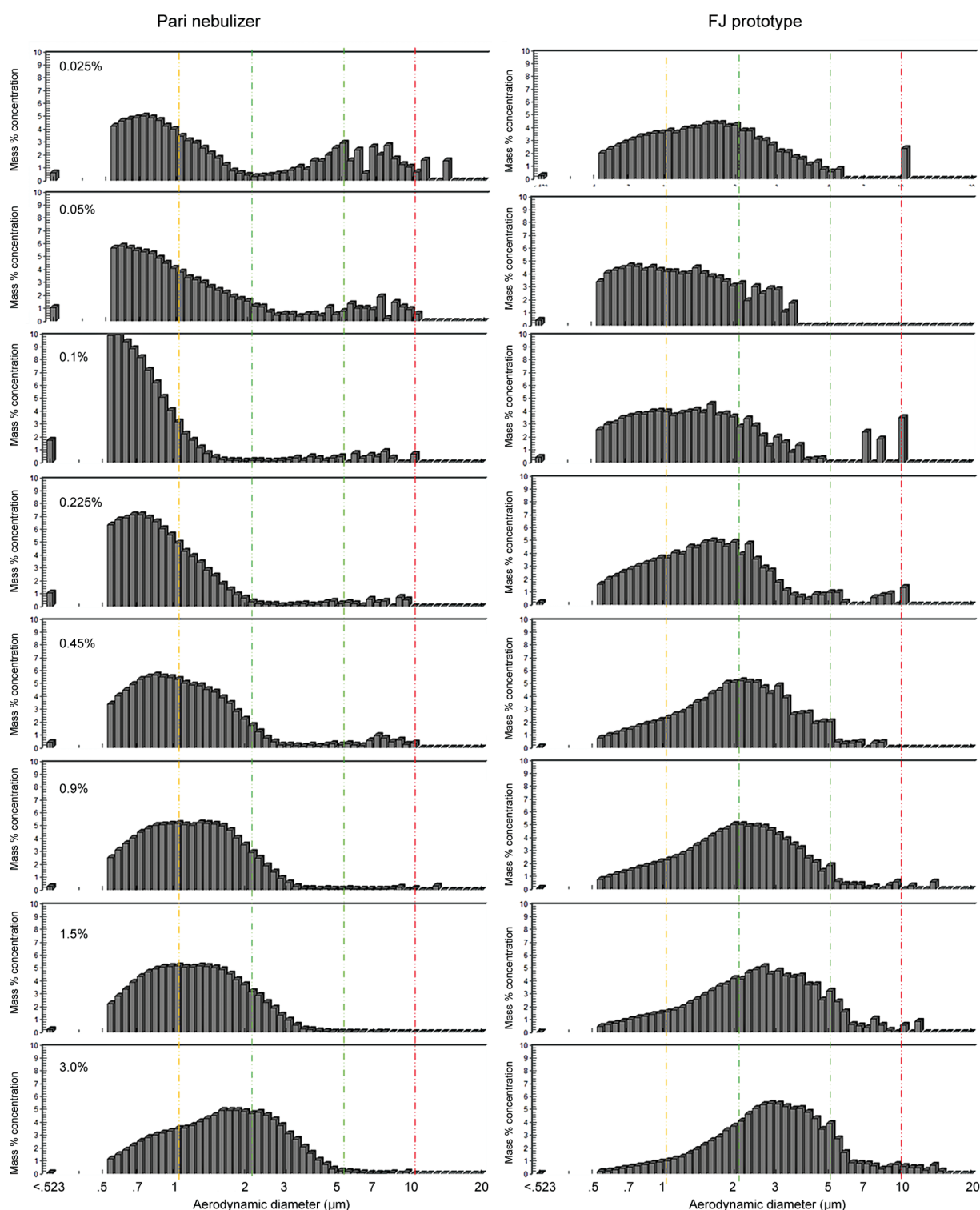

Fig. 6 Effect of different concentrations of NaCl on MMAD of aerosol; $^{*}p < 0.05$. MMAD, mass median aerodynamic diameter.

Fig. 7 Effect of different concentrations of NaCl on APSD. APSD, aerodynamic particle size distribution.

Effects of Electrolyte

The addition of electrolytes, specifically NaCl, has two effects of electrolyte on the atomization performance. First, it leads to a significant decrease in the aerosol MMAD at both the FJ prototype and Pari nebulizer. Second, the aerosol MMAD significantly increased with increased NaCl concentration at the FJ prototype while no significant change was observed at the Pari nebulizer.

The first effect is not caused by the physical properties of the liquid, since the NaCl has not significantly changed the surface tension, viscosity, or density at low concentrations ($<$1.0%). For example, the surface tension, kinematic viscosity, dynamic viscosity, and density of 0.9% normal saline at 20°C are 72.90 mN/m, 10.042 mSt, 1.009 mPa.s, and 1.004 g/cm^3, respectively, which are almost the same as those of pure water (72.88 mN/m, 10.07 mSt, 1.005 mPa.s, and 0.998 g/cm^3, respectively).
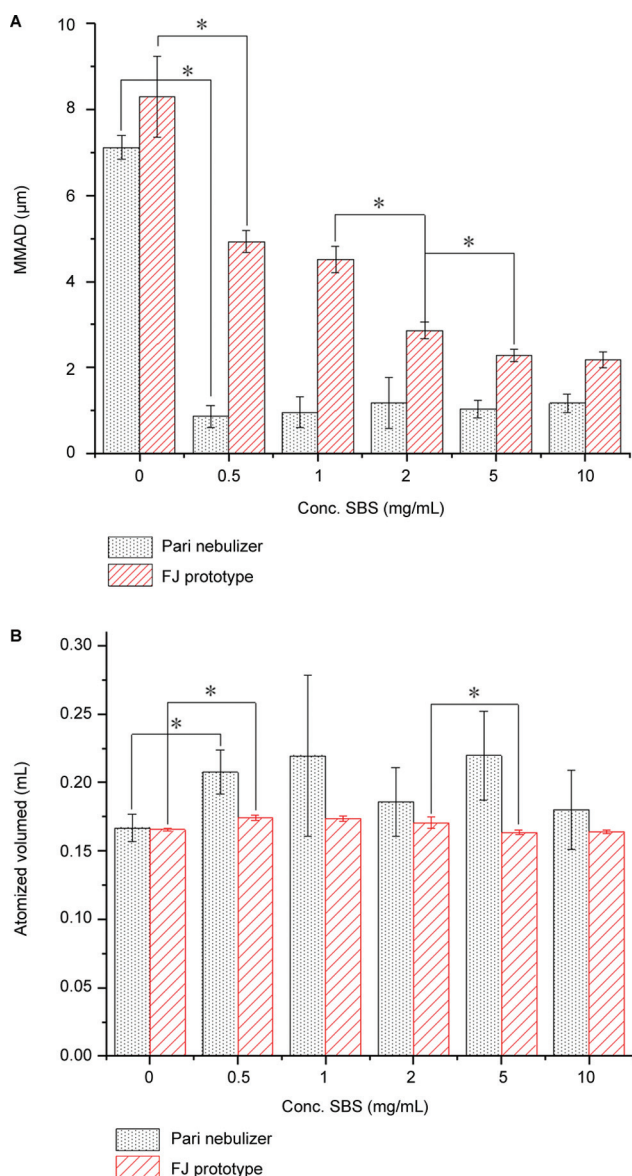
Fig. 8 Effect of different concentrations of SBS on (**A**) aerosol MMAD and (**B**) atomized volume; *$p < 0.05$. MMAD, mass median aerodynamic diameter; SBS, salbutamol sulfate.

Fig. 9 Effect of different concentrations of SBS on FPF; *$p < 0.05$. FPF, fine particle fraction; SBS, salbutamol sulfate.

A similar effect was observed with mesh nebulizers, where the aerosol MMAD decreased with increased ion concentration.[36] One possible cause of this effect is the streaming potential caused by the electrolyte solution flow. The streaming potential refers to the potential difference produced by the convective flow of charge due to a pressure gradient through a nozzle.[37] When the streaming potential is present, an additional reverse pulling force acts on the jet, and the stability of the liquid interface is significantly disturbed. As a result, the liquid jet can break into finer droplets under the same jetting or flashing strength (►**Fig. 7**). Furthermore, the transfer of electrons makes the jetting liquid positively charged. Electrostatic repulsion in the flashing jet may also help the generation of fine droplets.[38]

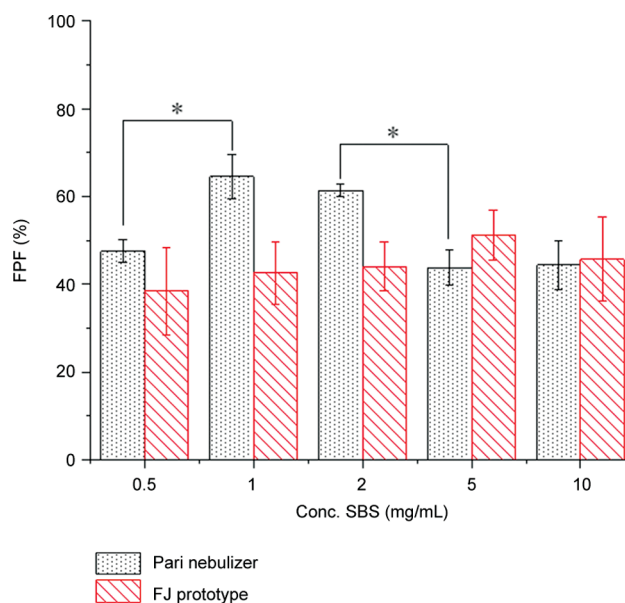The mechanism of the second effect is less clear, as an increased NaCl concentration did not increase the MMAD of aerosol at the Pari nebulizer. The second effect of the FJ prototype is likely associated with the flashing or bubbling process. A bubble-bursting experiment of seawater spray indicated that as salinity increases, the aerosol speed and geometric mean diameter will also increase.[39] However, the underlying mechanism remains unclear.

Effect of Drug Concentration

Evidence suggests that SBS does not greatly influence the surface tension of the solution.[30] In this study, SBS concentration had no effect on the MMAD of aerosol in a Pari nebulizer, however, decreased the MMAD of aerosol in the FJ prototype in a dose-depended manner, which is not caused by changes in the physical properties of the liquid.

A similar effect of drug concentration can be observed in mesh nebulizer and thermal inkjet.[40,41] Possible causes for this effect include the streaming potential and the changes in dynamic viscosity. When liquid viscosity is relatively low, an inter-droplet filament appears in the initial stage of droplet generation.[42] As the droplet separation progresses, the filament breaks into a string of fine satellite droplets. However, when the viscosity becomes higher, the liquid in the filament is pulled back into the main droplet. As a result, fewer fine satellite droplets are produced, and the volume of the main droplet increases. This can be supported by the disappearance of large droplets and the shift in the fine droplet distribution in the APSD induced by a high SBS concentration (►**Fig. 10**).

Besides, the molecular behavior of SBS in solution is another possible cause of the MMAD change. Several thermodynamic parameters of the solution are influenced by the SBS concentration, such as apparent molar volume, partial molar volume, molar expansivity, isobaric thermal expansion coefficient, isentropic compressibility, apparent compressibility, partial molar compressibility, and viscosity coefficient.[43] Apart from the viscosity coefficient, all other
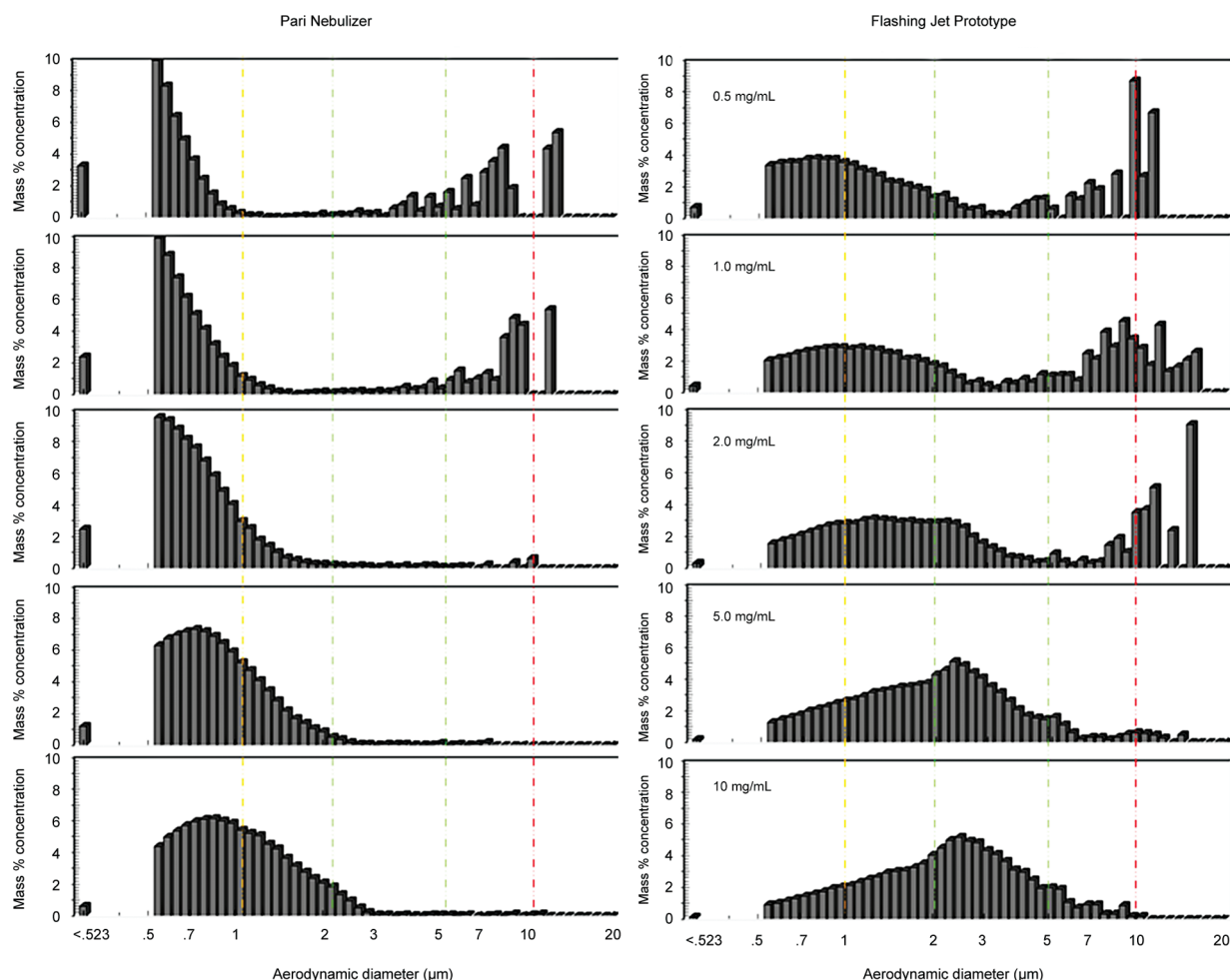
Fig. 10 Effect of different concentrations of SBS on APSD. APSD, aerodynamic particle size distribution; SBS, salbutamol sulfate.

thermodynamic parameters are related to the flashing process. Considering the reduction of large droplet proportion in APSD, the flashing intensity may be enhanced by the SBS concentration. However, the mechanism by which these parameters exert their impact remains unknown. The measurement of boiling point, specific heat capacity, and latent heat of vaporization in different SBS concentrations would be beneficial in further understanding the impact of these changes in thermodynamic parameters.

The mechanism behind the effect of SBS concentration was investigated, and it can be argued that the fine particle dose (FPD) values of the FJ prototype were better at higher SBS concentrations (►**Table 1**). When the SBS concentration was 5 and 10 mg/mL, the FJ prototype demonstrated comparable FPF and FPD (%TDD) in a single actuation (►**Fig. 9**). With increased SBS concentration, the proportion of large droplets (>10 µm) in APSD decreased and nearly disappeared after reaching 5 mg/mL (►**Fig. 10**). No significant change was observed in the device residual dosage level, while the residual ratio in the USP throat decreased with increased SBS concentration. Therefore, the reduced proportion of the large droplet is not caused by more interception in the USP throat or device. The enhanced FPD can be attributed to the further breakup of large droplets.

Research Limits

In this study, the MMAD and FPD were not measured using Next Generation Impactor (NGI) or Andersen Cascade Impactor (ACI). This is because the solution containing Tween 80 and NaCl used in the study is not suitable for the measurement of impactor-based MMAD. Instead, the APS/IIPR system was preferred because its droplet size measurement does not rely on HPLC. However, it should be noted that the MMAD values obtained from the APS/IIPR system represent reference values and are only suitable for studying the trend of influence in different solutions, due to the shrinking effect observed in droplet size. When the design of FJ prototype and liquid prescription is further refined in the future, the NGI or ACI will still be necessary for MMAD measurement.

The Pari nebulizer was chosen as the reference device in this study due to its ability to deliver the same aqueous aerosol as the FJ prototype, and its support for a wide range of atomization liquids. However, the nebulizer is a continuous atomization device, which is different from the FJ prototype. Second, the jetting volume of the FJ prototype was increased to 150 µL to obtain the approximate TD with the nebulizer resulting in a 6-second spray duration, which is too long for single actuation. In future studies, a better comparison option would be the soft mist inhaler Respimat. Not only

Table 1 Drug dosage distribution proportion in different SBS concentrations (n = 3)

	FJ prototype					Pari nebulizer				
	0.5	1	2	5	10	0.5	1	2	5	10
Device (%TD ± SD)	15.51 ± 2.14	13.78 ± 4.21	16.40 ± 2.59	12.80 ± 3.13	16.78 ± 4.12	9.01 ± 3.53	8.58 ± 0.56	9.40 ± 1.22	15.56 ± 2.32	14.09 ± 2.40
Throat (%TD ± SD)	34.57 ± 12.00	31.17 ± 4.75	25.19 ± 4.26	17.67 ± 4.63	22.07 ± 10.26	24.98 ± 2.30	15.80 ± 5.76	16.80 ± 2.59	23.52 ± 2.89	27.28 ± 2.67
LPD (%TD ± SD)	15.73 ± 7.29	13.95 ± 0.67	13.76 ± 6.02	18.55 ± 2.68	12.05 ± 6.50	11.41 ± 8.13	8.52 ± 2.08	8.96 ± 1.65	7.41 ± 0.61	7.90 ± 2.67
FPD (%TD ± SD)	34.18 ± 5.28	41.11 ± 6.01	44.66 ± 4.20	50.99 ± 5.88	49.11 ± 7.95	54.58 ± 4.58	67.0 ± 5.55	64.83 ± 5.40	53.51 ± 4.58	50.73 ± 3.07
TD (%ND ± SD)	111.2 ± 12.1	103.4 ± 3.50	98.8 ± 8.70	100.8 ± 4.6	92.6 ± 4.90	87.6 ± 9.75	96.86 ± 13.06	95.05 ± 6.50	81.93 ± 2.10	87.31 ± 7.05

Abbreviations: ND, normal dosage; SBS, salbutamol sulfate; TD, total delivered dosage.

does it deliver fine aqueous aerosols, but also it is known for its limitation in low delivery doses, whereas the FJ prototype has the potential advantage of high delivery doses.

Conclusion

The atomized volume MMAD decreased at the FJ prototype with increasing concentrations of Tween 80 and SBS. When NaCl was added to pure water, the aerosol MMAD decreased initially and then increased with increasing concentrations. These findings indicate that surfactant, electrolyte, and drug concentration all have significant impacts on atomization performance at the FJ prototype. Higher concentrations of surfactant and drug result in improved performance, while the lowest MMAD is achieved between 0.05% and 0.1% NaCl concentration. However, the mechanisms underlying these effects are not fully understood, thus, it is important to consider the effects of these ingredients on the atomization performance of the device in future studies.

Conflict of Interest
None declared.

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