Development of an inhaled ion-paired salbutamol formulation

Bridie Dutton[1], Arcadia Woods[1], Robyn Sadler[2], Nathalie Fa[2], Ben Forbes[1] & Stuart Jones[1]

[1]Institute of Pharmaceutical Science, King's College London, 150 Stamford Street, London, SE1 9NH, UK

[2]GlaxoSmithKline, Park Road, Ware, Hertfordshire, SG12 0DP, UK

Summary

Ion-pairing is a promising technique to control drug delivery that has been shown to be effective for both transdermal and oral medicines. This strategy could also be very interesting for inhaled formulations as it has the potential to control the delivery of a drug without changing the structure of the molecule. Previously, salbutamol has been shown to bind the negatively charged counter ions sodium sulfate, gluconate and octanoate with varying degrees of strength. However, to administer these ion-pairs to the lung an inhalable formulation must be developed. Spray drying is an attractive method to engineer particles for an inhalable formulation as it allows the control of particle size, which influences lung deposition. In this study spray dried ion-pair formulations were developed using lactose, as the bulking agent, PVP, as a physical stabilizer, and l-leucine, to improve powder dispersion. *In vitro* deposition studies with the spray dried formulations using the Next Generation Impactor demonstrated that the gluconate and octanoate ion-pairs improved the dispersibility of the salbutamol microparticles. The addition of PVP to the microparticles generally increased their size except for the octanoate formulation, which produced a smaller particle and better dispersion. The addition of l-leucine generally improved the dispersibility of the powders, but it didn't affect the particle size, hence resulted in a smaller MMAD in comparison to the counter ion/PVP formulations. The results of this study show that it is possible to make an ion-pair formulation that is suitable for inhalation.

Introduction

Oppositely charged ions held together through non covalent interactions have the potential to create a controlled release system for inhaled medicines because the ion-paired complex can display different physicochemical properties compared to the parent drug. Previous studies have showed that salbutamol binds to sulfate, gluconate and octanoate with differing strengths (pK = 1.57, 2.27, and 2.56 respectively) to form biocompatabile complexes [1]. However, the formulation used in this previous work was a simple lactose based microparticle, which is unlikely to covey the stability or aerosolizability suitable for a pharmaceutical product. Spray drying is a method of particle engineering that is commonly used to generate inhalable particles, mainly because it allows precise control of the particle size of the powder [2], but it often creates amorphous particles, which require additional excipients to physically stabilize the powder to prevent agglomeration [3, 4].

The aim of this study was to engineer inhalable particles containing salbutamol ion-pairs in a chemically and physically stable state that could be deposited in the lung. Due to the possibility of amorphous lactose causing the powder to have poor results the inclusion of polyvinylpyyrolidone (PVP) and l-leucine in to the formulation was also studied. PVP has been proven to increase the stability of amorphous lactose over time due to its ability to inhibit crystallization, therefore it was chosen as the excipient to physically stabilize the microparticles [4]. In addition, l-leucine was added to the particles to improve the dispersibility of the powder [5]. The aersolisation and stability of the powders was studied [5].

Methods

Formulations containing 1 % w/w salbutamol and 99% lactose were spray dried using a Buchi B-191 spray dryer with the following settings: aspirator: 80%, feed pump: 10%, inlet temperature: 180 ^{o}C, air flow: 800L/h. The solid content of the feed solution was 3 g/ 100 mL of deionized water. The counter ions were added to the feed solution in a 20:1 counter ion to drug ratio. The PVP (10k) was added as 0.5 % of the total solid content and l-leucine was added as 5% of the total solid content. The spray dried powder was collected and sized using a Helos/Rodos laser diffraction particle-size analyzer. Approximately 100 mg of powder was used to obtain each size distribution. The R1 lens was used (size range 0.1 µm – 35 µm), the dispersion pressure was set at 6.00 bar and the vacuum was set at 30 - 32 mbar. The powders were also sized and surface morphology examined using scanning electron microscopy (SEM). A Zeiss Supra 25 SEM was used. The sample was deposited with a brush on a carbon disc stuck to an aluminium stub. The stub was then coated with platinum for 60 seconds.

Physical stability of the powders was assessed using differential scanning calorimetry (DSC). Experiments were performed on a TA Q2000 modulated DSC. A sample of 2 – 5 mg was used in a non-hermetically sealed aluminium pan. The spray dried powder components were heated from 25 to 180 ^{o}C at a heating rate of 10 ^{o}Cmin^{-1} before the temperature was brought back to 25 ^{o}C. The instrument was calibrated using indium prior to the experiments. DSC thermograms were analysed using TA Instruments Universal Analysis 2000 software.

In-vitro drug deposition was studied using a next generation impactor (NGI). The powders were fired into the system using a Pheonix monodose dry powder inhaler. A total of three assessments were carried out for each

spray dried formulation and 5 capsules were used per assessment. Capsules were prepared by manually loading 12.5 (± 0.5) mg of spray dried powder in to a size 3 hard gelatin capsule. The NGI was set up according to USP[21]. The NGI collection cups were coated with 19.25 % PEG200 in Acetone, 4 mL for stage 1, and 2 mL for all other stages. The formulations were tested at 100 L/min for 2.5 seconds. After testing the throat, all stages and the external filter paper were washed with 80 % (v/v) water-methanol mixture. HPLC was used to quantify the amount of salbutamol deposited at each stage. Data were represented as a mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), emitted dose (ED), and fine particle fraction (FPF).

The ED of the formulation was calculated as the mass deposited in the throat and stages 1-8 of the NGI as a percentage of the mean content of salbutamol found in the content uniformity analysis. The FPF was determined as the percentage of the ED that has a particle size less than 5 μm and it was calculated from a plot of the cumulative mass deposited vs. effective cut off diameter. MMAD and GSD were calculated by plotting the inverse normal of the cumulative % under the stated aerodynamic diameter versus the log effective cut off diameter at 100 L/min. The MMAD was taken as the value at which the trend line for this data intersects with 50 % cumulative % value. GSD was calculated as the 84th percentile/16th percentile from this data.

Results and Discussion

The effect of adding counter ions

The spray drying process produced a white powder with a good yield for all the test formulations. The median particle size was generally around 3 μm with each counter ion apart from sodium gluconate, which produced a significantly smaller particle size of around 2.5 μm ($p < 0.001$). DSC results showed a glass transition (Tg) for the base and sulfate formulations at around 120 ^{o}C, however none was seen for the gluconate or octanoate. SEM pictures of all formulations showed smooth circular particles, which suggests that the particles were amorphous.

The NGI results showed that addition of the sulfate to the salbutamol in the microparticles had no effect on the aerosolisation of salbutamol from the inhaler device. The addition of the gluconate counterion resulted in a significantly smaller MMAD ($p = 0.024$) and higher FPF value compared to base and sulfate, presumably due to its smaller particle size. The octanoate formulation displayed a similar MMAD value ($p = 0.032$) to that of the gluconate, despite its larger particle size, suggesting that the addition of the counter ion improved the dispersion of the powder.

The effect of adding PVP

The addition of PVP in to the spray drying mixtures resulted in a larger particles being generated for all the counter ion drug mixtures apart from the octanoate formulation, which was significantly smaller than the counter ion formulation. SEM pictures show that the PVP had an effect on the surface morphology of the particles; it generated “dimples” which suggested that the polymer had migrated to the particle surface during the spray drying process. The DSC results showed no glass transition for any of the formulations, which was presumably a consequence of the complex mixture containing four components resulting in signal overlap.

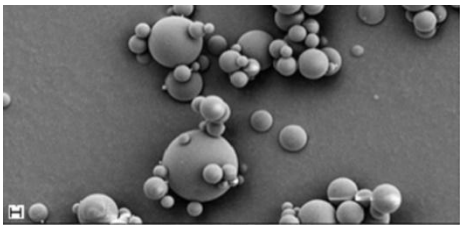
NGI results show that due to the larger size of particle the general trend is that the MMAD for each formulation is higher and the FPF lower. The ED remains the same. This trend is not followed by the octanoate formulation which exhibits a much smaller MMAD value and higher FPF; however it also has a smaller ED. This could be due to the fact that the sodium octanoate has its own effect on the surface properties of the particles, and creates a more aerosolisable particle.

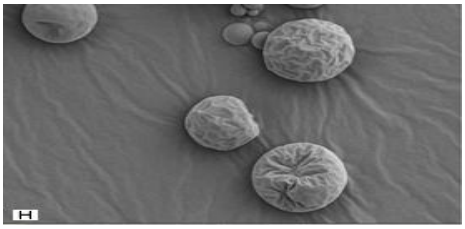
The effect of adding l-leucine

Spray drying with l-leucine created a much more free flowing powder for all apart from the octanoate formulation. The particle size increased for each formulation, however the dispersibility also increased. This resulted in a smaller MMAD value for the sulfate counter ion compared to the equivalent formulations without l-leucine. There was also no significant difference in the MMAD value for the gluconate/leucine formulation compared to the PVP even though the particle size was increased. The addition of l-leucine to the octanoate powder, however did not have the same effect. The resulting MMAD value was significantly higher than either of the 2 previous formulations, however the ED was greatly increased. There were also no Tg seen for any of these formulations.

Table 1 – Particle size, *in vitro* deposition results and SEM pictures (Scale = 1 µm) for all formulations (± standard deviation, n=3)

Formulation	Counter ion	x_{50} (µm)	ED (%)	MMAD (µm)	GSD (µm)	FPF (%)
1% Salbutamol **99% Lactose** **Counter ion**	None	3.68 (± 0.26)	74.24 (± 2.14)	6.30 (± 0.71)	2.31 (± 0.04)	25.34 (± 4.08)
	Sulfate	3.61 (± 0.28)	74.28 (± 1.35)	6.24 (± 0.36)	2.20 (± 0.09)	25.14 (± 1.42)
	Gluconate*	2.57 (± 0.35)	76.57 (± 1.71)	4.85 (± 0.35)	2.09 (± 0.01)	33.52 (± 3.24)
	Octanoate*	3.28 (± 0.06)	79.00 (± 3.06)	4.85 (± 0.73)	2.39 (± 0.18)	27.83 (± 2.84)
1% Salbutamol **98.5% Lactose** **0.5 % PVP** **Counter ion**	Sulfate	3.92 (± 0.07)	68.78 (± 2.41)	5.50 (± 0.11)	2.24 (± 0.03)	22.87 (± 3.41)
	Gluconate	3.36 (± 0.13)	73.91 (± 3.79)	5.15 (± 0.62)	2.30 (± 0.16)	25.74 (± 3.44)
	Octanoate**	3.06 (± 0.12)	64.10 (± 3.54)	4.41 (± 0.21)	2.30 (± 0.11)	36.23 (± 1.45)
1% Salbutamol **93.5% Lactose** **0.5 % PVP** **5 % l-leucine** **Counter ion**	Sulfate	4.21 (± 0.05)	79.38 (± 1.12)	5.19 (± 0.15)	2.51 (± 0.03)	34.93 (± 3.36)
	Gluconate	3.94 (± 0.06)	87.58 (± 2.74)	5.30 (± 0.26)	2.44 (± 0.22)	29.96 (± 5.08)
	Octanoate	3.20 (± 0.04)	84.42 (± 2.09)	5.09 (± 0.38)	2.56 (± 0.04)	33.39 (± 1.21)

A) 

B) 

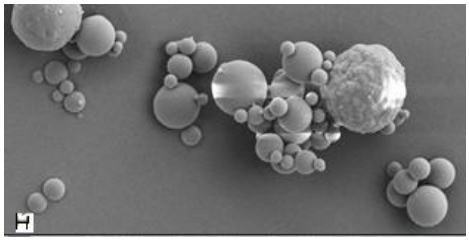
C) 

Figure 1 – Example SEM images of the A) counter ion, B) counter ion/PVP and C) counter ion/PVP/leucine formulations (scale = 1 μm)

Conclusion

In conclusion, addition of the gluconate and octanoate counter ions in to the formulation had a beneficial effect, resulting in a smaller MMAD and larger fine particle fractions. The addition of PVP resulted in a general trend of the powder having larger particles and therefore a larger MMAD value for each formulation except the octanoate. The addition of PVP to the octanoate formulation instead resulted in a smaller particle size and also the lowest MMAD value of the study. Leucine caused a slight increase in particle size for each formulation. Only the sulfate formulation appeared to benefit from the leucine in terms of improved dispersion. The results of this study show that it is possible to create a spray dried ion-pair formulation, but that it is important to understand how the chosen counter ion and excipients interact as this can vary the aerosolisability of the powders.

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