Production and Analysis of a Spray Dried Powder Formulations of a Magnetic Resonance Imaging (MRI) Contrast Agent.

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Summary

This paper describes the production of a spray dried formulation of Gadovist®, a magnetic resonance imaging (MRI) contrast agent.

Gadovist® is typically administered prior to the performance of an MRI to enhance the visual image by increasing the relaxation signal detected by the scanner. However, it is only available as a 1ml solution for iv administration. For our clients study, a dry powder formulation was desired to enhance the image of the lung. To achieve lung deposition, a particle size of less than 3µm would be required. It was agreed that spray drying would be used to produce a micro-particle of Gadovist® as this offered the opportunity to accurately control the micro-particle size.

The Gadovist ® solution was diluted with ethanol and water and spray dried using a Buchi B-191 fitted with a Schlick 2-fluid nozzle with 0.6mm liquid insert. The ethanol was used to reduce the viscosity of the solution and thereby reduce the particle size. The particles produced were of near uniform size and spherical.

In-vitro characterisation of the micro-particles by laser particle sizing using a SympaTec HELOS gave a volume mean diameter (VMD) of 2.9µm. Analysis of the material using a simple device and a multi-stage liquid impinger demonstrated a mean fine particle dose of 33mg (30-37mg) from a mean delivered dose of 69mg (64-76mg).

The material was subsequently used in an *in-vivo* MRI study which benefited from the enhanced visual image provided by the contrast agent being deployed to the deep lung region.

Introduction

Magnetic Resonance Imaging (MRI) contrast agents are routinely administered to patients prior to an MRI scan [1]. They work by increasing the relaxation signal detected by the scanner and in doing so enhance the visual image obtained (known as a contrast effect).

MRI of the lung is difficult [2] since the lungs are primarily full of air with relatively little water/tissue present (hence excitation/relaxation signal is low). This results in images of the lung which lack resolution and appear “black”. To overcome the lack of signal, it was anticipated that a contrast agent depositing on the lung surface might enhance the signal received, thereby improving the visual image.

MRI contrast agents are supplied as solutions containing high concentrations of metal ions (usually gadolinium). These are generally administered to the body by injection or multiple microinjections [3]. However, for this study it was necessary to deliver the agent to the surfaces of the airways of the lung. Spray drying was chosen as a useful technology for producing a dry powder formulation of the MRI contrast agent that could be delivered to this region via the inhalation route.

Materials

- Gadovist ®: A 1ml solution of Gadovist ® contains 604.72mg of gabobutrol, equivalent to 1.0mmol gabobutrol containing 157.25mg of gabolinium. Excipients include calcobutrol sodium, trometamol, 1N hydrochloric acid and water for injection.
- Spray Dried Solution: 5g of Gadovist® solution was diluted with water and 25ml of ethanol and made to 100ml with water to produce a 5% w/v solution. The ethanol was used to reduce the viscosity of the solution.
- AR grade solvents for analysis

Apparatus and Experimental Methods

- Spray drying apparatus: Spray drying was performed in a Buchi B-191 fitted with a Schlick 2-fluid nozzle with 0.6mm liquid insert.
- Spray drying parameters: Liquid feed rate of 3ml/min, atomisation at 3bar pressure, inlet temperature 60^{o}C, outlet temperature maintained at 46^{o}C and aspirator set at 100%

- Laser particle sizing: Laser particle sizing was performed using a SympaTec HELOS particle size analyser with a 4mm RODOS disperser. Approximately 50mg of the spray dried material was placed on the vibrating feeder and fed into the hopper. Dispersal was achieved using 2.0 bar of compressed air. Analysis was triggered when an optical concentration of sample >1% was attained.
- Aerodynamic particle size determination (APSD) apparatus: APSD was performed using an aluminium multi-stage liquid impinger (MSLI) as described in USP Chapter <601> with an integral paper filter for sub 1.7 micron particles. Each stage contained 20ml of water. The apparatus was used at 60 l/min.
- APSD analysis: Approximately 8mg of spray dried material was loaded into the central reservoir of a DP-4 Penn Century experimental delivery device. The powder was dispersed using a syringe filled with 2 x 20ml of air. Dosing was repeated 10 times to obtain sufficient stage loading. Approximately 2mg of spray dried material was retained by the device per actuation.

Results

Physical Characterisation by Laser Particle Sizing

Following the generation of the spray dried particles using the Buchi spray dryer with the parameters previously described, micro-particles were characterised using the SympaTec HELOS system. The results of this analysis are shown in Table 1.

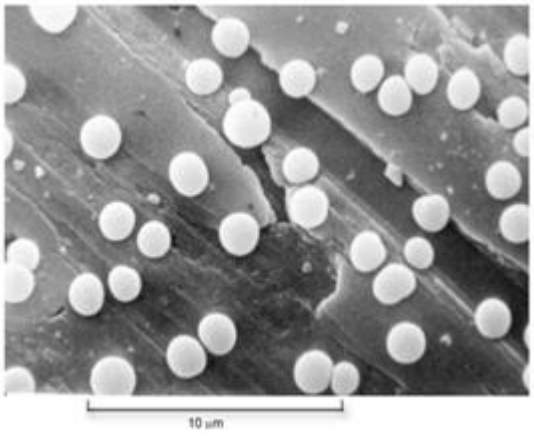
Table 1. The particle size distribution of the Gadovist ® micro-particles.

X_{10} (µm)*	X_{50}(µm)**	X_{95}(µm)***	VMD(µm)****
0.9	2.5	5.2	2.9

* 10% of the micro-particles, by volume, below this figure
** 50% of the micro-particles, by volume, below this figure
*** 95% of the micro-particles, by volume, below this figure
**** Volume mean diameter

Electron microscopy was used to determine particle morphology and as can be seen in Figure 1 the particles are largely spherical and the size (approximately 1-3µm) is consistent with the laser particle size measured by the Sympatec.

Figure 1. Scanning electron micrograph of spray dried Gadovist® micro-particles



***In-Vitro* Performance Characterisation by MSLI**

In this study the spray dried particles were filled into a Penn Century dry powder delivery device which relies on a manual injection of air to disperse the powder from the device.

An accepted method for assessing the aerodynamic particle size diameter (APSD) of the powder once it has been aspirated from the device is to use an impinger. In this case, we used an MSLI fitted with a USP throat, 4 stages and a paper filter.

A total of 4 determinations were performed, each using 10 aliquots of 8mg of spray dried material. The results of each analysis are shown in Table 2. It should be noted that the mean recovery, based on 80mg of spray dried material used per determination was 86% (80-95%).

Table 2: The APSD of spray dried Gadovist®.

Impinger Stage	Determination 1		Determination 2		Determination 3		Determination 4	
	% (of dose ex-device)	mg	% (of dose ex-device)	mg	% (of dose ex-device)	mg	% (of dose ex-device)	mg
USP Throat	15%	10.2	17%	11.2	36%	27.7	29%	20.5
Stage 1	25%	16.7	31%	19.9	17%	12.7	15%	10.3
Stage 2	4%	2.6	5%	3.4	5%	4.1	5%	3.4
Stage 3	17%	11.1	18%	11.6	11%	8.4	14%	9.5
Stage 4	34%	23	24%	15.6	25%	19.1	31%	21.6
Filter	5%	3.2	4%	2.5	5%	3.9	6%	4.2
Dose ex-device	100%	66.8	100%	64.2	100%	75.9	100%	69.5

The mean mass of material with an APSD of below 3.1µm was calculated by the summation of stages 3, 4 and filter. This was found to be 33mg (30-37mg) which equates to a fine particle dose of 49% (41-56%).

Discussion

Despite using a crude delivery device, the mean fine particle dose achieved, using a definition of fine particle dose as particles with an aerodynamic particle size of sub 3.1µm, was 33mg (49% of the dose delivered into the MSLI). This was achieved without the use of a carrier particle and demonstrates that excellent *in-vitro* performance can be achieved by using neat spray dried material.

The spray drying technique employed produced fine micro-particles with a volume mean diameter (VMD) of 2.9µm. This compares well with other size reduction technologies, such as micronisation. However, by using spray drying, the micro-particles were largely uniform and circular, as observed in the scanning electron micrograph. This allowed for a strong correlation to be shown between data generated by laser particle sizing and the APSD.

Conclusion

The use of spray drying to produce a dry powder formulation of the MRI contrast agent Gadovist ® has been demonstrated. The micro-particles produced were spherical and uniform with an *in-vitro* aerodynamic particle size that suggested that *in-vivo* deep lung deposition would be achieved.

The micro-particle formulation was used in an *in-vivo* study. Due to confidentiality reasons, we cannot share the output from that study at this stage but we have been informed by our client that following the dosing of our formulation, the MRI imaging of the lung was improved due to the contrast agent being deployed into the deep lung.

References

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