

Air-filled, cross-linked, human serum albumin microcapsules

Air-filled HSA microcapsules

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Chemical name:	Air-filled, cross-linked human serum albumin microcapsules
Abbreviated name:	Air-filled HAS microcapsules
Synonym:	Quantison™
Backbone:	Albumin
Target:	Non-targeted contrast agent, blood pool
Mechanism:	Passive nontargeted filling of cardiac chambers
Method of detection:	Ultrasound (US)
Source of signal/contrast:	Air-filled microbubble
Activation:	No
Studies:	<input checked="" type="checkbox"/> <i>In vitro</i> <input checked="" type="checkbox"/> Humans

Background

[PubMed]

The air-filled, cross-linked, human serum albumin (HSA) microcapsules (air-filled HSA microcapsules) is a stabilized microbubble formulation that is being developed as an ultrasound (US) contrast agent for use in echocardiography to enhance US images (1)

US contrast agents, or echopharmaceuticals, are designed to change the attenuation (absorption, reflection, and refraction) or impedance (resistance to sound propagation) of sound to enhance the differentiation of the signal (echo) of a target organ from that of the surrounding tissue (2-5). Gas-liquid emulsions (i.e., microbubbles or gaseous particles) are highly echogenic *in vivo* because of the nonlinear rarefaction and compression effects that lead to volume pulsations of microbubbles (3, 6, 7). HSA, synthetic polymers, and phospholipids have been used to construct the membranes of these bubbles. Microbubble preparations of various formulations have been developed, and their clinical usefulness depends very much on the size and stability of these bubbles *in vivo*. The current clinical application of these agents is in myocardial contrast echocardiography (MCE) (8).

In addition to acoustic parameters, microbubble preparations must meet two other requirements in order to be useful for MCE applications. Microbubble preparations cannot be trapped significantly by the lung capillaries and they must be able to survive the high intracardiac pressure. Air-filled microbubbles stabilized within a galactose

matrix were the first commercially available echopharmaceutical (9). However, these microbubbles are not stable enough to pass through the pulmonary capillary bed after a peripheral intravenous injection and can be used only to opacify the right heart chamber. Sonicated human serum microspheres (Sonicated HSM) were the first US contrast agent approved in the United States for cardiac applications. HSM consists of air-filled microbubbles stabilized in a thin shell of HSA with a mean diameter of $3.8 \pm 2.5 \mu\text{m}$ (10). Although these air-filled microbubbles are very sensitive to pressure changes with an *in vivo* half-life ($t_{1/2}$) of <1 min, they can pass through the pulmonary capillary bed and reach the left heart chamber. The *in vivo* life-times of air-filled microbubbles can be prolonged by increasing the stiffness of the bubble shell (11). Air-filled HSA microcapsules have stabilized shells that can withstand pressures in excess of 300 mm Hg (1). Other microbubble preparations use perfluorocarbons which dissolve poorly in blood to increase the stability of the microbubbles (12).

Serious cardiopulmonary reactions following the administration of ultrasound microbubble contrast agents have been reported (13). In 2007, the US FDA [<http://www.fda.gov/cder/drug/InfoSheets/HCP/microbubbleHCP.htm>] requested that warnings emphasizing the risk for serious cardiopulmonary reactions be added to the labeling of these agents. The uses of these agents are contraindicated in patients with unstable cardiopulmonary status.

Synthesis

[PubMed]

Air-filled HSA microcapsules are air bubbles encapsulated by a shell of HSA (1, 11). The microbubble shell is formed by spray-drying a solution of HSA. This shell is stabilized by heat fixation and chemical cross-linking. The final preparation is a dry powder that must be resuspended before use. The mean diameter is $3.2 \mu\text{m}$, and less than 0.5% of the preparation had a diameter $>6 \mu\text{m}$. The shell thickness is 200-300 nm and is able to withstand static pressure up to 600 mm Hg without losing the air within the microbubble. The density of the bubbles is approximately 780 kg/m^3 . The particle density in the preparation is about 1.5×10^9 bubbles per ml.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Chatterjee and Sarkar (14) suggested an interfacial rheological model with intrinsic surface rheology for studying the US microbubbles. Frinking and De Jong (11) studied the *in vitro* scatter and attenuation properties of air-filled HSA microcapsules based on an adapted version of the Rayleigh-Plesset equation which treats the microbubbles as a viscoelastic solid. The acoustic transmission and scattering were measured in the frequency band from 1-10 MHz. The effective bulk modulus (elasticity) of air-filled HSA microcapsules was 17.4 MPa and independent of the bubble diameter. In comparison, the effective bulk modulus of sonicated HSM was 1.3 MPa and increased for decreasing bubble diameter. The acoustic efficiency of air-filled HSA microcapsules was relatively low for low acoustic pressures but the measured scattering coefficient abruptly increased above an acoustic pressure of 200 kPa.

Moran et al. (15) used an *in vitro* tissue-mimicking phantom to study the scatter phenomenon of air-filled HSA microcapsules. A 3.5-5.0 MHz probe was used. At high concentrations (no dilution), no significant change in mean integrated backscatter was observed during continuous sonication. For medium (1:25 dilution) and low (1:50 dilution) concentrations, mean integrated backscatter values reached their maximum values and then decreased.

In various experiments, Sboros et al. studied the *in vitro* properties of US contrast agents (16-20). Using dilute suspensions of microbubbles, air-filled HSA microcapsules appeared to produce an increasing number of scattering events per unit volume with increasing acoustic pressure. However, the behavior across the acoustic

pressure range was not uniform. Free bubbles appeared at the high acoustic pressure of 0.83 MPa peak negative pressure. Postema et al. (21) investigated the phenomenon of sonic cracking. They used high-speed photography to observe the high-mechanical index US-induced air released from air-filled HSA microcapsules. For air-filled HSA microcapsules, sonic cracking was observed more often at driving frequency closer to the resonance frequency (1.7 MHz). Most of the released air bubbles had smaller equilibrium diameters (between 1.25 and 1.75 μm).

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Perkins et al. (1) used ^{123}I -labeled, air-filled HSA microcapsules and gamma imaging to study the biodistribution of air-filled HSA microcapsules in 12 normal healthy male subjects. The chloramines-T method was used to perform radiolabeling. The radiolabeling efficiency was 15%. The preparation was washed four times so that 100% of the radioactivity was bound to the microcapsules. Each subject received a dose of 50 MBq (1.35 mCi) with a total of 50 million microcapsules/kg. All subjects also received 100 mg potassium iodide three times to reduce thyroid uptake of [^{123}I]iodide. Gamma planar imaging showed immediate radioactivity uptake in the myocardium. There was evidence of myocardial perfusion at 3 min. The myocardial radioactivity which displayed a doughnut pattern, appeared to be more intense than that in the blood of the left ventricle. The washout of the agent from the myocardium was observed as no radioactivity was detected after 3 h. There was also rapid uptake of radioactivity by the liver and spleen. Posterior images showed some bone marrow uptake. Within the first hour, the liver had the highest radioactivity level of $41.8 \pm 10.4\%$ injected dose (ID). Transient lung activity of $4.0 \pm 3.4\%$ ID was observed. The maximum heart radioactivity level was $0.7 \pm 0.4\%$ ID at 0.06 hr. The spleen and kidneys had maximum radioactivity levels of $11.0 \pm 6.2\%$ ID at 1 hr and $1.6 \pm 1.0\%$ ID at 5 min, respectively. There was a rapid initial elimination of radioactivity from the blood with 15% ID at 5 min. About 63% ID radioactivity was excreted into the urine over 58 h and $<0.5\%$ in the feces over 36 h.

In a dose-finding study, van der Wouw et al. (22) conducted echocardiographic imaging (two-dimensional and color Doppler) in 12 healthy male volunteers. Each volunteer received two i.v. doses. The first dose was 25, 50, 100 or 150×10^6 microcapsules/kg, and the second dose was 300×10^6 microcapsules/kg. Air-filled HSA microcapsules required higher US output for visualization but the US contrast was visible in the left ventricular cavity for up to 30 min in two-dimensional and up to 60 min in color Doppler imaging.

NIH Support

NIH P50 CA103130-01.

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