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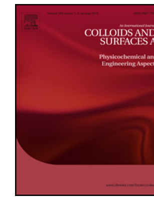

Estimation of Storage Stability of Aqueous Microbubble Suspensions

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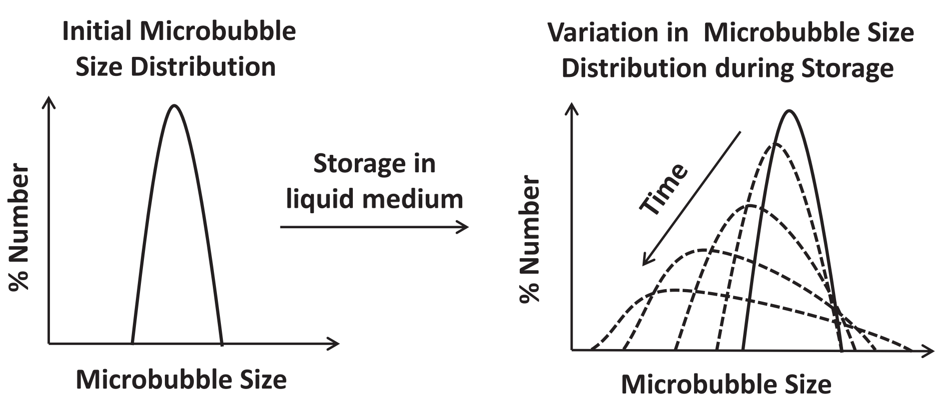
HIGHLIGHTS

- A simple model is proposed to estimate storage stability of microbubble suspensions.
- Shell resistance influenced the microbubble storage stability the most.
- Higher total resistance to mass transfer increases the storage stability.
- Higher viscosity of storage solution enhances the storage stability.
- Larger microbubbles were found to have higher storage stability.

GRAPHICAL ABSTRACT



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ABSTRACT

The aqueous suspensions of gaseous microbubbles are currently being used as contrast enhancing agents for ultrasonic imaging and as potential vehicles for targeted drug delivery. The storage stability of microbubble suspensions is very important as for any possible application of microbubbles, a stable microbubble suspension is needed. A stable microbubble suspension is a suspension for which there is no drastic change in concentration (number of microbubbles/mL of storage solution) and microbubble size distribution during the period of storage. To characterize storage stability, half-life of the microbubble suspensions, which is the time required for the microbubble concentration (#/mL) to decrease by 50% during storage, was estimated using a simple model. The proposed model estimates the storage stability of aqueous microbubble suspensions and effect of material properties on their storage stability. It takes into account an inter-bubble mass transfer and combines it with a population balance equation to account for a change in concentration (#/mL) as well as size and size distribution of microbubbles in the aqueous suspensions. The calculations have been performed for microbubbles made of three gases, namely oxygen (O_2), sulphur hexafluoride (SF_6) and perfluorobutane (PFB). The variation in storage stability of microbubble suspensions was examined by varying microbubble shell properties such as shell elasticity, surface tension and shell resistance as well as the other parameters such as viscosity of the storage medium and the initial size distribution of the microbubbles. The analysis of the results show that, among the shell properties studied, the shell resistance influenced the suspension stability the most and shell elasticity influenced the stability the least. Similarly, a gas with the lower liquid phase diffusivity and lower Ostwald coefficient results in a stable microbubble suspension. Also, higher viscosity of storage solution and microbubbles with larger sizes tend to increase the storage stability. Overall, the increase in the total resistance (combination of shell resistance and resistance in the storage solution) to mass transfer of a gas increases the storage stability of the microbubble suspensions.

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Nomenclature

P_{atm}	Atmosphere pressure (Nm^{-2})
k_b	Boltzmann constant (JK^{-1})
D_{AL}	Coefficient of diffusivity of gas A in water ($m^2 s^{-1}$)
E_s	Elasticity of shell material (Nm^{-1})
H_A	Henry's constant (-)
R_0	Initial radius of microbubble (m)
f	Level of saturation (-)
k_G	Local gas phase mass transfer coefficient ($mol\, m^{-2} s^{-1} Pa^{-1}$)
k_L	Local liquid mass transfer coefficient (ms^{-1})
Ω	Overall mass transfer resistance (sm^{-1})
$\Omega_{s,A}$	Mass transfer resistance to gas A through microbubble shell (sm^{-1})
$\Omega_{L,A}$	Liquid phase mass transfer resistance to gas A (sm^{-1})
Ω_n	pre-exponential factor in the equation for mass transfer resistance (sm^{-1})
$\sigma(R)$	Microbubble surface tension at radius R (Nm^{-1})
C_{Ag}	Molar concentration of gas A inside the microbubble ($mol\, m^{-3}$)
N_A	Molar flux across the interface ($mol\, m^{-2} s^{-1}$)
L_A	Ostwald coefficient of gas A (-)
K_L	Overall mass transfer coefficient of liquid film (ms^{-1})

1. Introduction

The gaseous microbubbles with an encapsulating shell of various materials such as lipids or proteins are currently being used as contrast enhancing agents for ultrasonic imaging [1–8] and as potential vehicles for targeted drug delivery [1–8]. The aqueous suspensions of microbubbles are prepared using different techniques such as the sonication of the gas-liquid interface [1,2], high shear emulsification [3], electro-hydrodynamic atomization [3,4–6] and by using microfluidic devices [3,7,8]. About 1–2 mL of such microbubble suspensions containing 10^9 microbubbles/mL is stored in small vials before their use for specific applications such as ultrasonic contrast imaging or targeted drug delivery. The microbubble suspensions, however have poor shelf (storage) stability and may undergo a change in size distribution as well as in concentration, i.e. number of microbubbles per unit volume of aqueous suspension (#/mL) during their storage. This happens due to inter-bubble mass transfer process that occurs during the storage. The gas diffuses out of smaller microbubbles into the surrounding solution owing to the increased solubility due to the Gibbs-Thompson effect. The dissolution of gas molecules then results in an increase in the concentration of gas molecules in the solution. This increased concentration of gas molecules may cause diffusion of gas molecules to the larger microbubbles from the storage solution (as explained in Section 2). As the process continues, some microbubbles shrink or dissolve completely and a few larger microbubbles grow at the expense of dissolving microbubbles. This results in a change in the size distribution of microbubbles as well as the concentration of microbubbles and hence affects their stability. Such a phenomenon has been observed experimentally as well for the microbubble suspensions [9–11].

The storage stability of microbubble suspensions is very important as for any possible application of microbubbles; a shelf-stable microbubble suspension is needed. Hence, any changes in microbubble size, size distribution and concentration during storage should be minimized. It is therefore essential to estimate the storage stability and to identify the parameters which affect the storage stability of microbubble suspensions. The type (and hence the properties) of shell material used to make microbubbles [2,5,7,8,12], the type of storage solution [6] and even the process of microbubble production [2,6–8] may affect the storage stability of microbubbles.

In order to estimate the storage stability of microbubble suspensions, the change in microbubble size distribution over a period of storage, was calculated by adapting the model developed by Lemlich [13]. However, the Lemlich model assumed microbubble shell to be inelastic with constant shell resistance and constant surface tension. It did not take into account the effect of shell elasticity, the change in shell resistance with time and the effect of storage medium on the microbubbles stability. Therefore, it was necessary to modify the Lemlich model to take into account the effect of shell properties as well as the properties of storage medium on the microbubble stability. There are a few reports [14–16] available in the literature which use Lemlich model for the similar purpose. However, in these reports the Lemlich model is either applied to foams [14,15] with liquid volume fraction being the main parameter under consideration to study the stability of foams or has been used without any modification to study the stability of microbubbles in viscous solutions [16].

Therefore, the model proposed in this work, has been developed to take into account the effect of elasticity of shell material, variation in shell resistance and in surface tension with time and the properties of storage solution such as solution viscosity on the stability of microbubble suspensions. In this model, the mathematical equation depicting the rate of change of microbubble size with time has been coupled with the population balance to predict the change in the number of microbubbles over the period of storage. The variation in storage stability of microbubble suspensions has been studied for the microbubbles made of three gases namely, oxygen, sulphur hexafluoride (SF_6) and perfluorobutane (PFB). These three gases are being used in the calculations mainly because the microbubbles are generally made using these gases for the use as the contrast agents [17,18]. To characterize storage stability, half-life of the microbubble suspensions, which is the time required for the microbubbles concentration (#/mL) to decrease by 50% during storage was estimated by varying different parameters such as shell resistance, surface tension, shell elasticity, viscosity of storage medium and the initial size distribution of microbubbles.

1.1. Mathematical formulation

The model assumes that the process of mass transfer of gas molecules from one microbubble to another microbubble can be considered to be a two-step process. A schematic of this process is presented in Fig. 1. First the gas molecules from a microbubble dissolve in the surrounding solution and then mass transfer from the solution to the surface of another microbubble takes place. Dissolution of a gas in the surrounding solution increases the dissolved concentration of gas in the solution. This dissolved concentration of gas can be assumed to be equivalent of a pressure (P_c) inside a fictitious microbubble with radius, R_c. The microbubbles with size less than R_c will dissolve since for such microbubbles, the pressure inside the microbubbles is greater than the pressure of the dissolved gas in the surrounding solution ($P_{bubble} > P_c$). On the other hand, the microbubbles with size greater than R_c will continue to grow since for such microbubbles P_c is higher than the pressure inside microbubble ($P_c > P_{bubble}$). Such a behavior has been observed for microbubble suspensions experimentally as well [9–11]. The model assumptions and detailed model equations are given in the sections below.