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Modeling of microbubble dissolution in aqueous medium

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ABSTRACT

A mathematical model for microbubble dissolution in an aqueous medium containing dissolved gases is presented. None of the models available in the literature take into account the influence of shell elasticity (E_s), variation in surface tension (σ) at the gas–liquid interface and shell resistance (Ω) on the kinetics of microbubble dissolution. Moreover, values of these shell parameters are not known/available and hence arbitrary values for these variables have been assumed in many of the reports for estimation of dissolution kinetics. Therefore, in this work, a mathematical model is developed to describe microbubble dissolution which takes into account the effect of shell elasticity (E_s), shell resistance (Ω), surface tension (σ) and their variation, on the microbubble dissolution. The values of these shell parameters have then been estimated using the proposed model and the experimental data available in literature. The proposed model accurately predicts the experimental microbubble dissolution data using estimated values of shell parameters. Analysis of the results further show that the surface tension and shell resistances change drastically during the microbubble dissolution process and the variation in these parameters during the dissolution process is highly dependent on the shell elasticity which in turn affects the microbubble dissolution times. The methodology developed in this work can be used to estimate shell parameters for any microbubble formulation, to accurately predict in-vitro/in-vivo dissolution of microbubbles, and hence to design a microbubble system with desired characteristics and performance.

1. Introduction

Microbubbles with size of up to 10 μm suspended in an aqueous medium are being used as contrast agents for ultrasonic imaging. These microbubbles are also emerging as carriers for targeted drug delivery. The gaseous core of these microbubbles is generally coated with a thin shell of materials such as proteins, lipids, polymers or surfactants [1]. The shell provides a barrier between gas and surrounding aqueous medium and thus adds resistance to the mass transfer of a gas from the microbubble to the surroundings. The microbubble dissolution dynamics and the time for microbubble dissolution (circulation persistence time) are very important for the viability of microbubbles for biomedical applications. There are several mathematical models available in the literature which try to capture the dynamics of the microbubbles dissolution mathematically. However, each model is based on certain assumptions which limit its application. A model suggested by Epstein and Plesset [2,3] does not take into account the shell resistance. It also assumes surface tension at the gas–liquid interface coated to be a constant throughout the microbubble dissolution process. Subsequently, a model developed by Borden and Longo [4] assumes different values for shell resistance but also assumes shell to be inelastic material and hence the constant value for the surface tension. The models developed by Sarkar et al. [5] and Katiyar et al. [6] take into account shell elasticity but assume constant shell resistance. Further, the model developed by Azmin et al. [7] show that the shell resistance and surface tension changes during the dissolution process. However, it does not take into account the shell elasticity (E_s) in the model. Thus, none of these models have accounted for variation in shell resistance, and variation in surface tension due to elastic shell material during the microbubble dissolution in a single model. Also, arbitrary values to many of the microbubble properties such as shell resistance, shell elasticity and the mass transfer resistance have been assumed in these reports. Therefore, a comprehensive model has been developed in this work which takes into account the effect of shell resistance (Ω), elasticity (E_s), surface tension (σ) and their variation on dissolution kinetics. The values of these unknown shell properties have been estimated by using the proposed model and the experimental dissolution data available in the literature [4,9]. These properties were further used to predict the microbubble dissolution behavior in an aqueous environment containing dissolved gases.

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Nomenclature

P_{atm}	atmosphere pressure (Nm^{-2})
k_b	Boltzmann constant ($J K^{-1}$)
D_{AL}	coefficient of diffusivity of gas A in water (ms^{-1})
D_{BL}	coefficient of diffusivity of gas B in water (ms^{-1})
D_{CL}	coefficient of diffusivity of gas C in water (ms^{-1})
D_{DL}	coefficient of diffusivity of gas D in water (ms^{-1})
D_{EL}	coefficient of diffusivity of gas E in water (ms^{-1})
$C_{Al,\infty}$	dissolved gas A concentrated far away from bubble in bulk aqueous medium ($mol\ m^{-3}$)
$C_{Bl,\infty}$	dissolved gas B concentrated far away from bubble in bulk aqueous medium ($mol\ m^{-3}$)
$C_{Cl,\infty}$	dissolved gas C concentrated far away from bubble in bulk aqueous medium ($mol\ m^{-3}$)
$C_{Dl,\infty}$	dissolved gas D concentrated far away from bubble in bulk aqueous medium ($mol\ m^{-3}$)
$C_{El,\infty}$	dissolved gas E concentrated far away from bubble in bulk aqueous medium ($mol\ m^{-3}$)
E_S	elasticity of shell material (Nm^{-1})
H'	Henry's constant (unitless)
R_0	initial radius of microbubble (m)
f	level of saturation (unitless)
k_G	local gas phase mass transfer coefficient (ms^{-1})
k_L	local liquid mass transfer coefficient (ms^{-1})
$\Omega_{s,A}$	mass transfer resistance to gas A through microbubble shell (sm^{-1})
$\Omega_{S,B}$	mass transfer resistance to gas B through microbubble shell (sm^{-1})
$\Omega_{S,C}$	mass transfer resistance to gas C through microbubble shell (sm^{-1})
$\Omega_{S,D}$	mass transfer resistance to gas D through microbubble shell (sm^{-1})
$\Omega_{S,E}$	mass transfer resistance to gas E through microbubble shell (sm^{-1})
$\sigma(R)$	microbubble surface tension at radius R (Nm^{-1})
C_{Ag}	molar concentration of gas A inside the microbubble
C_{Bg}	molar concentration of gas B inside the microbubble
C_{Cg}	molar concentration of gas C inside the microbubble
C_{Dg}	molar concentration of gas D inside the microbubble
C_{Eg}	molar concentration of gas E inside the microbubble
N_A	molar flux across the interface ($mol\ m^{-2}\ s^{-1}$)
N_B	molar flux across the interface ($mol\ m^{-2}\ s^{-1}$)
N_C	molar flux across the interface ($mol\ m^{-2}\ s^{-1}$)
N_D	molar flux across the interface ($mol\ m^{-2}\ s^{-1}$)
N_E	molar flux across the interface ($mol\ m^{-2}\ s^{-1}$)
L_A	ostwald coefficient of gas A (unitless)
L_B	ostwald coefficient of gas B (unitless)
L_C	ostwald coefficient of gas C (unitless)
L_D	ostwald coefficient of gas D (unitless)
L_E	ostwald coefficient of gas E (unitless)
K_L	overall mass transfer coefficient of liquid film (ms^{-1})

The microbubbles are generally stored in an aqueous medium. This medium may contain a dissolved gas which is same as the gas used to make these microbubbles. In such a situation only a one way mass transfer of gas occurs from the core of a microbubble to the bulk of the aqueous medium. On the other hand, when a microbubble is injected in blood, a microbubble faces a multigas environment because of air dissolved in blood along with other gases. In such a case, two way mass transfer occurs where a gas from the microbubble core dissolves in blood and the gas dissolved in blood gets transferred into the microbubble. Therefore, first only a one way mass transfer across the gas–liquid interface was modeled. Subsequently, the model for one way mass transfer was extended to the dissolution of a microbubble in a multi-gas environment. The modified model accounts for the transfer of a gas from a microbubble core to the bulk of the aqueous medium as well as the flux of a gas from the bulk of the aqueous medium to the core of the microbubble.

2. Model formulation

2.1. Model assumptions

The model makes following simplifying assumptions:

1. There exist no convection in the microbubble storage medium or the aqueous medium and hence the mass transfer coefficient for liquid medium is calculated by assuming Sherwood (Sh) number to be 2.
2. Microbubble shell is completely hydrated and hence the gas solubility in the shell can be calculated using Henry's law/Ostwald coefficient.
3. Gas in the microbubble core is an ideal gas.
4. Liquid phase controls the process of microbubble dissolution.

2.2. Model equations

2.2.1. Dissolution of a microbubble in the aqueous media containing a dissolved gas same as the one used to make the microbubble: One way mass transfer

The schematic of a typical microbubble and concentration profiles inside and close vicinity of microbubble is shown in Fig. 1. It is assumed that the microbubble comprises of gas A and the surrounding medium also consists of gas A dissolved in it.

The mole balance over the microbubble for a gas A yields

$$N_A = -\frac{1}{A}\frac{dn_A}{dt} = \frac{-1}{4\pi R^2}\frac{d}{dt}\left(\frac{P_{atm}+\frac{2\sigma(R)}{R}}{BT} * \frac{4}{3}\pi R^3\right) \tag{1}$$

where N_A is molar flux across the interface, R is radius of microbubble, C_{Ag} is molar concentration of gas A inside the microbubble.

Assuming gas inside the microbubble is to be ideal,

$$C_{Ag} = \frac{P_{Ag}}{BT} \tag{2}$$

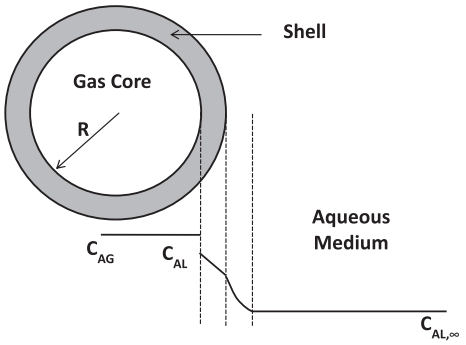

Fig. 1. Schematic of a microbubble dissolving in an aqueous medium.