Ultrasound in Med. & Biol., Vol. 37, No. 2, pp. 301–311, 2011

0301-5629/$ - see front matter

ELSEVIER

doi:10.1016/j.ultrasmedbio.2010.11.006

● *Original Contribution*

ACOUSTIC RADIATION FORCE ON A SPHERICAL CONTRAST AGENT SHELL NEAR A VESSEL POROUS WALL – THEORY

Amir K. Miri* and Farid G. Mitri†

*Biomechanics Laboratory, Mechanical Engineering Department, McGill University, Montreal, Canada; and †Los Alamos National Laboratory, Sensors & Electrochemical Devices, Acoustics & Sensors Technology Team, Los Alamos, NM

(*Received* 22 *September* 2009; *revised* 28 *October* 2010; *in final form* 8 *November* 2010)

Abstract—Contrast agent microshells (CAMSs) are under intensive investigation for their wide applications in biomedical imaging and drug delivery. In drug delivery applications, CAMSs are guided to the targeted site before fragmentation by high-intensity ultrasound waves leading to the drug release. Prediction of the acoustic radiation force used to nondestructively guide a CAMS to the suspected site is becoming increasingly important and gaining attention particularly because it increases the system efficiency. The goal of this work is to present a theoretical model for the time-averaged (static) acoustic radiation force experienced by a CAMS near a blood vessel wall. An exact solution for the scattering of normal incident plane acoustic waves on an air-filled elastic spherical shell immersed in a nonviscous fluid near a porous and nonrigid boundary is employed to evaluate the radiation force function (which is the radiation force per unit energy density per unit cross-sectional surface). A particular example is chosen to illustrate the behavior of the time-averaged (static) radiation force on an elastic polyethylene spherical shell near a porous wall, with particular emphasis on the relative thickness of the shell and the distance from its center to the wall. This proposed model allows obtaining *a priori* information on the static radiation force that may be used to advantage in related as drug delivery and contrast agent imaging. This study should assist in the development of improved models for the evaluation of the time-averaged acoustic radiation force on a cluster of CAMSs in viscous and heat-conducting fluids. (E-mail: mitri@lanl.gov) © 2011 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasonic contrast agents, Drug delivery, Vessel wall interaction, Impedance boundary, Time-averaged radiation force function, Spherical shell.**

INTRODUCTION

The diagnostic and therapeutic applications of ultrasound contrast agents have been increasing rapidly since the first agents were introduced in the 1970s (Quaia 2005). Microbubbles with diameters ranging from 1 to 10 μm, known as *the key agent*, are commonly filled with air or a higher molecular weight gas that can be stabilized by a surfactant or by a lipid or polymeric shell ranging in thickness between 10 to 200 nm (Sboros 2008; Stride and Edirisinghe 2008). The microbubbles are injected into the bloodstream circulation, and, because of their superior acoustic impedance relative to the neighboring tissues, they provide effective imaging (Wei and Kaul 1997). Regarding recent developments in improving biofunctionality of the shell material, microbubbles now play an important role in modern drug delivery systems. The ultrasound–mediated microbubble mechanism is very effective while being nonimmunogenic and eliminating the possibility of under- or overdosing. Furthermore, microbubbles can be utilized for other purposes like metabolic gas delivery (Kheir et al. 2007).

The structure of contrast agent microshells (CAMSs), their incident ultrasound wave field and their mutual interactions control the performance of the contrast agents, especially when conjugated to a drug. In recent years, many investigations have utilized microbubbles/CAMSs for drug and gene delivery. For a review on this subject, the following works are recommended: Postema and Gilja (2007), Ferrara et al. (2007), Ferrara (2008), Wu and Nyborg (2008), Sboros (2008) and Frenkel (2008).

The effect of the acoustic radiation force on microbubble-based imaging and drug-delivery systems has also been experimentally studied. The radiation force of high-amplitude ultrasound waves is primarily used to suppress the buoyancy force, particularly near the bubble resonance frequency (Dayton et al. 1997). Then, the

Address correspondence to: Farid G. Mitri, Los Alamos National Laboratory, MPA-11, Sensors & Electrochemical Devices, Acoustics & Sensors Technology Team, MS D429, Los Alamos, NM 87545. E-mail: mitri@lanl.gov

displacement of microbubbles toward the vessel wall is established (Dayton et al. 1999; Dayton et al. 2002). In an *in vivo* mouse cremaster preparation, localization of contrast agents has been observed along the wall of a 50-μm diameter arteriole (May et al. 2002; Klibanov et al. 1998). Using the model introduced by Dayton et al. (1999), it has been shown that a resonant contrast microbubble can be displaced on the order of millimeters during a short time (Zhao et al. 2004).

A priori knowledge on the magnitude of the time-averaged (static) radiation force applied to the bioactive-encapsulated CAMSs is critical to safely guide them with progressive waves toward the desired targeted region. Although extensive studies have been performed to investigate the static radiation force exerted on a particle surrounded by an unbounded liquid (King 1934; Hasegawa and Yosioka 1969; Hasegawa 1979; Lofstedt and Putterman 1991; Brandt 2001; Doinikov 2003; Wei et al. 2004; Mitri 2005a; Mitri 2005b; Mitri 2006; Mitri 2008; Mitri 2009a; Mitri 2009b; Mitri 2009c), there is, in some cases, a boundary or interface that affects the force experienced by the CAMSs. Proper estimation of the force is required to avoid fragmentation of the shell at an inappropriate region close to the vessel wall.

The aim of this study is to analyze the effect of a boundary on the acoustic radiation force experienced by a single CAMS; such an investigation, to our knowledge, has yet to be explored. The development of this theoretical model is timely, because it may be used advantageously in related biomedical ultrasound applications with contrast agent shells. To this end, and to solve the problem with a reasonable amount of mathematics, the theoretical model developed in this paper treats the acoustic radiation force on a single spherical shell of finite thickness, close to a porous flat boundary, thus simulating the presence of a permeable blood vessel wall. Investigating the effect of the acoustic radiation force on a single spherical contrast agent shell is appropriate, because it serves as a necessary interim step before generalizing the study for a cluster of shells (Fig. 1).

However, studies in the literature demonstrate that other types of force (Konig 1891; Weiser et al. 1984; Doinikov 2001), resulting from the interactions between particles in a host fluid, produce a reversible attraction and aggregation of microspheres forming particle grapes (Doinikov and Zavtrak 1996). This type of force, known as the *secondary Bjerknes force* (Bjerknes 1906), does not exist for a single particle in a sound field, but it will be the subject of prospective investigations dealing with a cluster of soft CAMSs.

In the most common imaging applications, the dimensionless frequency ka (where k is the wave number and a is the outer radius of the shell) is not generally greater than unity. In this limit, the formulation for the

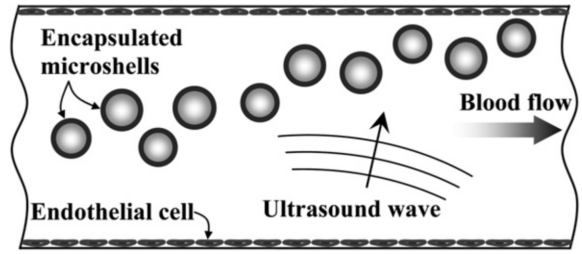

Fig. 1. Drug-loaded ultrasound contrast agents are flowing in a blood vessel that is subjected to low-pressure ultrasound pulses.

acoustic scattering of a spherical target inside a cylinder (vessel) may be reduced to the study of the scattering by the spherical target near a half-space (Doinikov et al. 2009). This assumption is used here to solve the linear acoustic scattering problem based on a modal series expansion (Huang and Gaunaurd 1997), in which the plane waves incident upon a spherical shell placed near a porous plane wall are supposed to propagate perpendicularly to the wall's axis (*i.e.*, normal incidence). The total (incident + scattered) acoustic field, evaluated using the *method of mirror image* (described in Fig. 2; Gaunaurd and Huang 1996) by assuming that the spherical shell and its image are equal in size, pulsating in phase and the wall is halfway between them, allows the attainment of a closed-form solution for the *axial* acoustic radiation force (*i.e.*, the force acting *along the axis* of wave propagation).

For purposes of this study, it is also assumed that both the amplitude of pressure and the particle velocity are sufficiently small and that the peak Mach number is much smaller than unity, so that nonlinear wave propagation effects (generation of harmonics) are neglected. This assumption has been used previously by various authors (Wei et al. 2004; Mitri and Fellah 2007). The surrounding fluid is assumed to be an ideal (*i.e.*, nonviscous) compressible medium that does not support shear wave propagation; thus, the effect of surface tension is not considered. Instead, the force is evaluated in terms of the radiation force function, which is the radiation force per unit energy density and unit cross-sectional surface of the spherical shell.

METHODS

Mathematical formulation

Consider an elastic spherical shell of outer radius a and inner radius b positioned at a distance d from a plane boundary (Fig. 2). The origin O of a spherical coordinate system (r, θ) is placed at the center of the shell. An infinite plane ultrasound wave is incident upon a spherical shell perpendicular to a flat boundary (Fig. 2) (*i.e.*, normal incidence). Due to the composition of the vessel wall (especially the endothelial cells), it is appropriately