An enhanced, rational model to study acoustic vaporization dynamics of a bubble encapsulated within a nonlinearly elastic shell

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Abstract

Acoustic droplet vaporization (ADV) is a new approach to generate vapor bubbles that have potentially broad medical applications. ADV-generated bubbles can be used as contrast agents in acoustic imaging, as drug carriers to deliver drugs to particular targets, and also in embolotherapy, thermal therapy, and histotripsy. However, despite much progress, ADV dynamics have still not been well understood and properly modeled. In this paper, we present a theoretical study of ultrasound-induced evaporation of a droplet encapsulated by a shell. The main emphasis of this theoretical study is on a proper description of the supercritical state occurring after bubble collapse. For this purpose, an isentropic equation of state for a van der Waals gas is used to describe the bubble behavior in the supercritical state. Sensitivity of the vaporization process is investigated for different acoustic and geometrical parameters and mechanical properties of the shell. Results show that the value of the minimum pressure required for direct vaporization (without any oscillatory behavior) depends on shell elasticity and initial size of the droplet, especially at high frequencies (greater than 2 MHz). Moreover, it has been shown that applying an acoustic wave with proper phase such that thermal equilibrium of the bubble temperature with the surrounding liquid is attained, results in direct vaporization at lower acoustic pressure.

Keywords:
Acoustic droplet vaporization
Nonlinear elastic shell
Isentropic process
Mathematical model
Numerical simulation

1. Introduction

Acoustic vaporization of small droplets (in the range of nano and micro scales) has been the focus of attention for many researchers in the field of medicine [1–3]. The small size of submicron droplets and their stability due to their liquid core make them promising agents for diagnostic and therapeutic applications. Droplets can reach different parts of the body in particular cancerous tissue and can be used as ultrasound contrast agents after vaporization into microbubbles [4]. They can also be used as carriers to deliver drugs to specific targets, which is particularly beneficial in the administration of anti-tumor drugs to tumoral tissues [5]. Depending on the application, the drug might be placed inside the particle (within the liquid) or attached to the material encapsulating the droplet [6]. Volumetric expansion of micrometric droplets after vaporization can block feeding blood vessels and eradicate tumor cells through starvation [7]. This process is known as embolotherapy. All these mechanisms are induced by means of focused ultrasound which results in a phase change of the inner liquid [8]. This particular process is known as acoustic droplet vaporization (ADV). With regard to the composition of droplets, perfluorocarbons (PFCs) are good candidates for ADV because of their low boiling point (below human body temperature) and their metastability. Due to the additional Laplace pressure resulting from surface tension of droplets, pressure inside a droplet is larger than the saturating vapor pressure, which makes a droplet metastable. Hence, droplets cannot evaporate spontaneously at body temperature [9]. Exposure to supplementary acoustical energy results in evaporation of such metastable droplets: they grow by rectified heat transfer during the expansion phase when pressure is sufficiently low. The minimum acoustic pressure amplitude required to vaporize a droplet is called the ADV threshold.

Several experimental studies have been conducted to probe the mechanisms underlying the ADV process. These studies are dedicated to investigating the effects of key factors such as temperature, acoustic amplitude and frequency on the ADV threshold in a system containing a droplet in an infinite liquid [10–13]. Besides experimental studies, theoretical investigations have also been carried out to predict the ADV threshold for droplets. For example the authors in [14] used classical nucleation theory to predict the ADV threshold for perfluorohexane (PFH) nanodroplets. Qamar et al. generalized the Rayleigh-Plesset (RP) equation for ADV, accounting for the effect of tube geometry. The RP based model is further extended in [15,16] to consider the effect of heat transfer and temperature on evaporation rate. The same mathematical
modeling strategy is used in [17] to study the effects of acoustic parameters on the ADV threshold. Droplets are usually encapsulated by materials such as an albumin layer, a polymeric shell, or phospholipids [18–21]. Encapsulating the droplets increases their stability, but makes the evaporation process more complicated. Since the mechanical effects of the coating materials on the evaporation process is not negligible [22] (despite the accuracy of the models mentioned above), they must be modified to account for the mechanical effects of the encapsulating shell. An extension of the vapor bubble dynamics model that considers the mechanical effect of the shell is proposed in [23] under the assumption that the shell is composed of a linear elastic material. However, due to the significant shell deformation after the liquid to vapor phase change, a linear elastic model cannot describe the ADV process accurately [24]. This assumption is relaxed in [25] to study the ADV process incorporating nonlinear elasticity in the shell rheology to capture large deformations of the encapsulating shell. Authors in [24,25] studied the vaporization process for an ideal gas without any distinction between sub and supercritical states, i.e. before and after the bubble collapses rapidly), we assume that gas inside the bubble is a VDW gas (rather than an ideal gas) that follows the VDW equation [27]:

\[
\begin{cases}
    p_b = \frac{\rho_b R_b}{1 - b p_b} - \alpha p_b^2 \\
    a = \frac{\gamma R_b^2 \rho_b}{b_p}, \quad b = \frac{\gamma R_b}{b_p}
\end{cases}
\]

where \( R_b \) is the gas constant and the subscript \( c \) denotes the critical state. Mass conservation along with the assumption of incompressibility of external liquid and shell and spherical symmetry gives the radial velocity \( u \) outside the bubble as:

\[
u(r,t) = \frac{R_b}{r} U_b(t)
\]

where \( r > R_b \) and \( U_b \) is the liquid velocities at \( r = R_b \). Note that the velocity of inner liquid near the bubble surface is not equal to \( R_b \) because of the non-zero mass flux (J) during condensation and evaporation. The mass flux is defined as

\[
J = \rho_b (R_b - U_b) = \rho_d (R_d - U_d)
\]

where \( \rho_b \) and \( \rho_d \) are densities of bubble and droplet respectively and \( U_b \) is the vapor velocity at \( r = R_b \). Integration of the momentum equations over the droplet and ambient water (external liquid) and using Eq. (2) gives the following equation that describes the radial motion of the bubble:

\[
\begin{aligned}
\frac{R_b^2 U_d}{r^2} + \frac{2 \rho_b R_b U_d}{r^2} - \frac{2 \rho_b U_d^2}{r^2} = \frac{1}{\rho} \frac{\partial p}{\partial r} + \frac{3}{T_w + \rho} + \frac{p}{\rho}
\end{aligned}
\]

In Eq. (4), \( \rho \) is the density, \( p = -\frac{\partial U}{\partial r} \) is the hydrostatic pressure, and \( T_w \) is the radial component of the stress tensor \( T \). \( T \) is composed of two parts: a viscous term \( T_w = 2\eta \frac{\partial}{\partial r} \) is in which \( \eta \) is viscosity and an elastic term \( T_{\text{el}} \). Since liquid in the external and droplet regions are Newtonian fluids with \( T_{\text{el}} = 0 \), only the shell has a nonzero elastic term \( T_{\text{el}} \). Integrating Eq. (4) over the three regions (\( R_b < r < R_1 \), \( R_1 < r < R_2 \), and \( r > R_2 \)) results in the generalized Rayleigh-Plesset equation for the bubble dynamics:

\[
R_b U_d + \left( \frac{2 U_d}{R_b} - \frac{\Gamma}{2 T_1} \left( \frac{U_d}{R_b} \right)^2 \right) \dot{R}_b = \frac{p_b - p_w}{\Gamma_1}
\]

where \( \Gamma_{1,4} \) are coupling coefficients and \( p_b \) is the pressure at the bubble interface defined as

\[
p_b = p_0 - \frac{2\pi + 4\eta U_d}{R} + \phi + \Sigma
\]

In (5), \( p_w = p_0 + p_a = p_0 - A_0 \sin(2\pi ft) \) is the pressure at infinity within the ambient water, \( p_0 \) is the static pressure and \( p_a \) is the acoustic pressure transmitted from a transducer. Since the bubble nucleation occurs during the negative cycle of pressure, \( p_b \) is chosen with minus sign as observed experimentally [25,28]. The effective surface tension coefficient \( \bar{\sigma} \) and effective viscosity \( \bar{\eta} \) in (6) and coupling coefficients \( \Gamma_{1,4} \) in (5) are expressed as

\[
\bar{\sigma} = \sigma + \sigma_0 (R_b / R_1) + \sigma_1 (R_b / R_2)
\]

\[
\bar{\eta} = \eta + (\eta - \eta_a) (R_b / R_1)^4 + (\eta - \eta_a) (R_b / R_2)^4
\]

\[
\Gamma_i = \rho_d + (\rho_a - \rho_i) (R_b / R_1)^4 + (\rho_a - \rho_i) (R_b / R_2)^4, \quad i = 1, 4
\]

2. Mathematical model

To model the dynamics of a vapor bubble nucleated in the center of a droplet encapsulated by a shell, we consider a four-phase computational domain: vapor + liquid + shell + surrounding environment, c.f. Fig. 1. A vapor bubble of radius \( R_b(t) \) is nucleated at the center of a liquid droplet with which it forms a two-phase metastable vapor–liquid mixture. The droplet is encapsulated within a spherical incompressible viscoelastic shell with inner and outer radii \( R_1(t) \) and \( R_2(t) \) respectively and this three-phase system is immersed in an infinite liquid medium (external liquid). For the sake of simplicity, it is assumed that the system is symmetric and that droplet and shell preserve their spherical shape during the simulation. Moreover, due to the timescale separation between evaporation and mass diffusion [26], we assume that mass exchange does not occur at the shell interfaces \( R_1(t) \) and \( R_2(t) \). For more accurate consideration of the supercritical process (which occurs when the bubble collapses rapidly), we assume that gas inside the bubble is a VDW gas (rather than an ideal gas) that follows the VDW equation [27]:
For simplicity, we assume $\sigma_1$ and $\sigma_2$ (surface tensions of internal and external interfaces of the shell) are negligible which simplifies $\eta$ as $\eta \propto \sigma$. Moreover, for a thin shell, it is reasonable to assume that the coupling coefficients $\Gamma_i$ depend only on the density of liquids within the droplet and outside the shell [25], i.e.

$$\Gamma_i = \rho_i + (\rho_j - \rho_i)(R_b/R_i)^i \quad i = 1, 4 \quad (8)$$

The third term in Eq. (6) is $\phi$ that describes the contribution of mass flux due to the evaporation process and is given by

$$\phi = f \left( \frac{1}{\rho} - \frac{1}{\rho_j} \right) \quad (9)$$

To calculate the mass flux $J = \frac{d \rho}{dt} \frac{\partial \rho}{\partial \xi} |_{\xi = R_b}$, a spatio-temporal heat equation must be solved. Introducing the moving coordinate $\xi = \rho - R_b$, the heat equation in the liquid regions is given by [4]:

$$\left( \rho c \right) \frac{dT}{dt} + v \frac{\partial T}{\partial \xi} = \frac{1}{r^2} \left( \rho \frac{\partial}{\partial r} \left( r^2 \lambda \frac{\partial T}{\partial r} \right) \right) + \frac{2 \eta_1}{\rho b^2} \quad (10)$$

where $v_1 = \left( \frac{2 \rho^2}{\rho b^2} \right) U_0 - \rho_b$ is the convection velocity and subscript $l$ refers to liquid inside the droplet or external environment. Together with the boundary condition $T(t) = T_{b1}(t)$ at the moving bubble surface, this equation can be solved with the same procedure as $C$. The last term in Eq. (6) is the elastic response $\delta$. Accounting for Mooney-Rivlin behavior of the shell, which allows capture of the large deformation resulting from the bubble growth, $\delta$ is obtained as

$$\delta = \left( 1 + \frac{\beta}{\gamma} \right) \frac{R_{10}}{R_i} \frac{R_1}{R_i} \frac{R_{10}^3}{4R_1} \frac{R_{10}^{3/2}}{4R_i} \left( \frac{R_b}{R_i} \right)^2 \left( \frac{R_1}{R_i} \right)^2 \quad (11)$$

where $\beta$ is a nonlinear coefficient, $\delta$ is the linear shear modulus and $R_2(t) = \sqrt[3]{R_{10}^3 + R_1(t)^3 - R_{10}^3}$ (because of incompressibility of shell). The reference is referred to [25] for a detailed description of the derivation procedure for $\delta$. To solve Eq. (5), $R_b(t)$ and $R_1(t)$ should be determined. Coupling Eq. (3) with the following differential Eqs. (12) (for the bubble and droplet mass conservation) allows us to solve for $\rho_b(t), R_b(t)$ and $R_1(t)$

$$\frac{d \rho_b}{d t} = \frac{3}{R_b} \left( G - \rho_b \dot{R_b} \right) \quad (12)$$

To determine $p_b$, we can use the VDW equation together with a differential equation that gives the solution for $T_b(t)$. Combining the differential equation for the pressure in the bubble with the Clausius-Clapeyron law (assuming pressure within the bubble is uniform and that the bubble is in an adiabatic state) gives the following differential equation to calculate the temperature at the bubble interface ($T_b$) [18,23]:

$$\frac{d \rho_b}{d t} = \frac{3}{R_b} \left( G - \rho_b \dot{R_b} \right) \quad (13)$$

The vapor bubble nucleated in the droplet grows upon interaction with an acoustic wave and collapse may occur depending on the acoustic parameters. Although this process is very fast, it may still cause the pressure and temperature of the bubble to exceed the critical values ($p_c, T_c$) and the bubble may enter a supercritical state that must be treated}

### Table 1: Nomenclature

| Symbol | Description | Unit |
|--------|-------------|------|
| $A_0$  | pressure amplitude of acoustic pulse |       |
| $f_a$  | frequency of acoustic pulse |       |
| $c$    | specific heat |       |
| $\rho$ | density |       |
| $J$    | phase-change mass flux |       |
| $\rho_b$ | density |       |
| $\lambda$ | thermal conductivity |       |
| $\eta$ | viscosity |       |
| $U$    | velocity |       |
| $T$    | temperature |       |
| $p$    | pressure |       |
| $t$    | time |       |

### Table 2: Nondimensionalized variables

| Symbol | Description | Unit |
|--------|-------------|------|
| $\bar{t} = \frac{t}{t_a}$ | reduced time |       |
| $\bar{\tau} = \frac{\tau}{\tau_a}$ | reduced relaxation time |       |
| $\bar{R}_1 = \frac{R_1}{R_1}$ | reduced bubble radius |       |
| $\bar{\rho}_b = \frac{\rho_b}{\rho_b}$ | reduced bubble density |       |
| $\bar{U}_b = \frac{U_b}{U_b}$ | reduced bubble velocity |       |
| $\bar{J} = \frac{J}{J_a}$ | reduced phase-change mass flux |       |
| $\bar{\rho}_b = \frac{\rho_b}{\rho_b}$ | reduced bubble density |       |
| $\bar{\lambda} = \frac{\lambda}{\lambda_0}$ | reduced thermal conductivity |       |
| $\bar{\eta} = \frac{\eta}{\eta_0}$ | reduced viscosity |       |
| $\bar{U}_b = \frac{U_b}{U_b}$ | reduced bubble velocity |       |

**Description of the parameters and subscripts used in the above Eqs. (1)-(13) are presented in Table 1.**

The vapor bubble nucleated in the droplet grows upon interaction with an acoustic wave and collapse may occur depending on the acoustic parameters. Although this process is very fast, it may still cause the pressure and temperature of the bubble to exceed the critical values ($p_c, T_c$) and the bubble may enter a supercritical state that must be treated.
To simulate the bubble dynamics, we assume the content of droplet and vapor is perfluoropentane (PFPE) C₅F₁₂ and the vapor-droplet mixture is immersed in water at temperature 37°C and atmospheric pressure. Initial radius of the bubble is fixed at \( R₀ = 80 \text{[nm]} \), and initial radius of the droplet (inner radius of the shell) and shell thickness are set to \( Rₜ₀ = 1 \text{[µm]} \) and \( Rₜ = Rₘₙₜ = 10 \text{[nm]} \) respectively. Values of parameters used in the numerical simulations are summarized in Table (3). To be consistent with experimental studies in [28], we assume the parameters used in the numerical simulations are summarized in Table (3).

The simulation is terminated when \( Rₜ = Rₙₜ \), or radius of the bubble is zero (\( Rₜ = 0 \text{[nm]} \)), or droplet is totally converted into vapor, i.e. \( \text{mass} = \text{mass}_{\text{sat}} + \text{mass}_{\text{d}} \) or \( \rhoₜ Rₜ² = \rhoₜ (Rₜ₀² - Rₘₙₜ²) + \rhoₜ₀ Rₘₙₜ² \), or shell thickness becomes zero (typically \( 10^{-14} \text{[nm]} \) at machine precision), or when a specific final time is reached.

Internally all numerical calculations are based on the dimensionless formulation, but we will describe our input parameters based on the dimensional values for easier physical interpretation.

4. Results

4.1. The effect of acoustic amplitude (\( Aₕ \)) on ADV process

Dynamics of the bubble radius for different values of acoustic amplitude (\( Aₕ = 1.5, 2.5, 3, 4 \text{[MPa]} \)) is depicted in Fig. 2. Frequency of the acoustic wave and shear modulus are set to \( fₚ = 3 \text{[MHz]} \) and \( G = 20 \text{[MPa]} \) respectively. It is observed that for both values of the nonlinear coefficient \( \beta \) the bubble either evaporates directly or shows oscillatory behaviour depending on the value of \( Aₕ \). For \( \beta = 1 \), direct vaporization occurs at all amplitudes however for \( Aₕ = 1.5 \text{[MPa]} \) it happens after a short intermediate behavior (after one rebound). Increasing the stiffness of Mooney-Rivlin material used for the shell, i.e. changing \( \beta \) from 1 to \(-1 \) slightly affects the bubble radius at the highest amplitude (\( Aₕ = 5 \text{[MPa]} \)), but has a strong influence on the intermediate behavior. The results in Fig. 2B indicate that for \( \beta = -1 \) evaporation is inhibited at low pressures (\( Aₕ = 1.5, 2.5 \text{[MPa]} \)) and occurs after one rebound at \( Aₕ = 3 \text{[MPa]} \). This can be attributed to the role of \( \beta \) as a stiffness measurement which is related to material nonlinearities. Furthermore, one can notice that (depending on the acoustic amplitude) direct vaporization occurs at different times and the final bubble radius is not constant, contrary to what is assumed in [25].

4.2. Influence of shell elasticity on bubble behavior

The objective in this section is to study the effect of shell rheology on the ADV process. For this purpose, we fix the pressure amplitude and frequency at \( Aₕ = 4 \text{[MPa]} \) and \( fₚ = 3 \text{[MHz]} \) and compute the bubble radius for various values of \( G \). As the numerical results in Fig. 3 show, the bubble dynamics is sensitive to the shell elasticity such that evaporation is inhibited at higher values of \( G \). For \( \beta = 1 \), the bubble vanishes at \( G = 320 \text{[MPa]} \) and oscillates during the whole simulation time at \( G = 220 \text{[MPa]} \). Whereas it evaporates after a bounce at \( G = 120 \text{[MPa]} \) and directly at the lowest shear modulus \( G = 20 \text{[MPa]} \), c.f. 3A. Results in Fig. 3B reveals that changing \( \beta \) to \(-1 \), (i.e. making the shell stiffer) delays the direct evaporation. In fact, for the considered values of \( G \), direct vaporization does not occur. Evaporation occurs after a rebound for the lowest value of \( G \) and more time is required to complete the vaporization process. Thus, if the droplet is encapsulated by a stiff shell, the acoustic amplitude must be increased to achieve direct vaporization, which can be problematic. Moreover, based on the numerical results shown in Figs. 3A,B, there is an optimum value for shell elasticity above which the bubble either collapses (which is better avoided in applications of ADV because of its association with high temperatures) or oscillates during exposure to acoustic waves without achieving direct vaporization.

Figs. 4A, B represent the temporal behavior of the bubble temperature, pressure, and density for different values of shear modulus (\( G = 20, 120, 220, 320 \text{[MPa]} \)) and \( \beta = 1, -1 \). The acoustic amplitude and frequency are set to \( Aₕ = 4 \text{[MPa]} \) and \( fₚ = 3 \text{[MHz]} \) respectively. Numerical results in the first row show that the bubble temperature is slightly below the ambient temperature \( (Tₐ) \) during direct vaporization. This indicates that, contrary to the assumption in [25], the bubble is not at the equilibrium temperature with the surrounding liquid after complete vaporization. Moreover, we observe that when the bubble collapses its temperature increases and exceeds the critical temperature \( (\sim 1.4 \text{ after nondimensionalization}) \). Time course of the bubble pressure and density are depicted in the second and third rows of Fig. 4A, B. As the bubble grows, its pressure decreases and its temperature becomes smaller than \( Tₐ \). While the bubble density increases due to evaporation. During the shrinkage phase of the bubble, its pressure increases and the temperature reaches some values greater than \( Tₐ \) and the bubble density decreases as a result of the condensation. If increase in the bubble pressure is large enough to overcome all pressures applied from the surrounding environment including acoustic pressure and surface tension, the bubble rebounds otherwise it vanishes. When the bubble collapse occurs i.e. at the supercritical stage, since \( J = 0 \) and consequently the bubble mass constant, the bubble density increases. These explain the oscillatory behavior of \( Tₜ, \rhoₜ, \) and \( \rhoₚ \) observed in Fig. 4. Moreover, numerical results in Fig. 4 indicate that the supercritical state that occurs after the bubble collapse is captured properly without resulting in any inaccurate solution for \( Tₜ, \rhoₜ, \) and \( \rhoₚ \) (physically and mathematically).
4.3. Direct vaporization threshold

Results obtained in Sections 4.1-4.2 show that the fate of the vapor bubble when interacting with acoustic waves depends on $G$ and $\beta$. However, as discussed in [33], the bubble growth is optimized if the shell material behaves as the softest Mooney-Rivlin material with $\beta = 1$. Hence, we fix $\beta$ at 1 and investigate the effects of some key factors on the Direct Vaporization Threshold (D.V.T) in the following sections. D.V.T is the minimum acoustic amplitude required for vaporization without any rebound.

4.3.1. Influence of shear modulus on direct vaporization threshold

To study the effect of the shear modulus $G$ on the threshold of direct vaporization, we calculate the D.V.T at three different values of $G$: 20, 60 and the limiting case ($G \to 0$) where the shell does not exhibit any elasticity at different frequencies. The numerical results presented in Fig. 3 show that in the range of low frequencies (below 2–2.5 [MHz]) depending on the value of $G$, $G$ does not have any effect on the D.V.T and it decreases by increasing the frequency up to a specific value in all three cases. Whereas for high frequency, increasing $f_a$ increases the D.V.T for all cases. One can observe that there is an optimum pressure and frequency for direct vaporization (minimum of the curves in Fig. 5) that depends on the mechanical property of the shell. Making the shell stiffer makes the optimum frequency smaller and pressure larger. Moreover, it makes the difference between graphs obtained for different $G$ more significant. Thus, to achieve direct vaporization at lower pressure we can either select a softer shell or modify the frequency to be in a specific range depending on the elasticity of the shell. However, if $G$ is very large (even at low frequencies) the D.V.T is high.

4.3.2. Effect of bubble nucleation time on direct vaporization threshold

In all the numerical simulations in the previous sections, we assumed that the bubble nucleation and acoustic pulsing occur simultaneously at $t = 0$ (to be consistent with previous studies [25]). This is an accurate assumption if we are interested in studying the ADV process at a specific location. In the present work, since we are not studying the evaporation process and outcome of the bubble at a particular position, and also to have thermal equilibrium at the bubble interface (as discussed in [4] for the case without encapsulation) we introduce a new parameter called the nucleation time ($t_n$) which is not necessarily zero and changes depending on the acoustic amplitude. Considering the Laplace pressure caused by the surface tensions at the bubble surface, the bubble pressure at the nucleation time can be obtained as [4]:

$$ p_n = \frac{2\sigma}{R_b} + p_0 - A_a \sin\left(2\pi f_a t_n\right) $$

(16)

To preserve the temperature continuity at $r = R_b$, we assume that $T_b = T_i$, which gives $p_n = 0.131$ [MPa] using the Clausius Clapeyron equation. Knowing the pressure amplitude ($A_a$) and $p_n$, Eq. (16) gives the nucleation time which is the initial time in numerical simulations.
Results obtained by assuming that acoustic pulsing and nucleation occur at \( t_n \) are in better agreement with experimental observations compared to the results obtained by assuming acoustic pulsing and nucleation occur at \( t = 0 \) nevertheless without encapsulation \([4, 28]\). Moreover, as we also show later, if an acoustic wave with appropriate initial phase \( (2\pi f_a t_n) \) is applied, minimum pressure is required for nucleation. To investigate how changing the phase of the transmitted acoustic wave, i.e., starting the acoustic pulsing at \( t = t_n \) affects the D.V.T at various frequencies, we repeat the simulation in Fig. 5 assuming that acoustic pulsing starts at the nucleation time \( t_n \) obtained from Eq. (16).

Results in Fig. 6 show that if the applied acoustic wave and nucleation occur simultaneously at \( t_n \) the droplet threshold for direct vaporization increases by increasing the frequency and there is not optimum value for frequency and pressure. One can notice that the D.V.T is higher for a stiff shell and the difference between pressure-frequency diagrams is reduced by decreasing the shear modulus. Comparing the results represented in Figs. 5 and 6 shows that at low frequencies the D.V.T is lower if pulsing starts at \( t_n \) however they are similar at high frequencies. At low frequencies, \( t_n \) is far from zero and higher pressure is required to overcome the stability of the bubble-droplet mixture and forces the bubble to grow. Hence, the results are different at low frequencies. At high frequencies, since \( t_n \) is close to zero, setting the nucleation time to zero or \( t_n \) does not result in a significant difference in the value of the D.V.T, c.f. Figs. 5 and 6 at high frequencies.

Besides studying the influence of bubble nucleation time on D.V.T, it is interesting to investigate its effect on the bubble dynamics and explore how starting the acoustic pulse at \( t_n \) changes the temporal behavior of the bubble. For this purpose, we calculate the bubble radius at four different acoustic amplitudes \( A_a = 0.3, 0.4, 0.5, 0.6 \text{ MPa} \) with \( G = 20 \text{ MPa} \) and \( \beta = 1 \) with nucleation time at \( t_n \). Results are given in Fig. 7.
We observe that by starting the acoustic pulse at \( t_n \), all three vaporization regimes occur: collapse after some rebounds at \( A_0 = 0.3 \) [MPa], vaporization after some oscillations at \( A_0 = 0.4 \) [MPa], and direct vaporization at \( A_0 = 0.6 \) [MPa]. Noteworthy here is that, compared to the results shown in Fig. 2, direct vaporization occurs at lower acoustic pressure which is beneficial in medical applications.

4.3.3. Effect of initial radius of droplet on direct vaporization threshold

To address the question of whether the initial radius of the droplet can change the threshold of direct vaporization is our objective in this section. For this purpose we set the shear modulus \( G \) and \( \beta \) at 20 [MPa] and 1 respectively and compute the value of D.V.T at \( R_{10} = 0.5, 1, 1.5 \) [µm]. Moreover, we assume bubble nucleation and acoustic pulsing occur at \( t = 0 \). As the results in Fig. 8 show, we still have a low- and high-frequency variation. In the range of low frequencies, the droplet size is not a key factor in determining the value of D.V.T, but it becomes crucial beyond an optimum frequency (that depends on the value of \( R_{10} \)). One can observe that below the optimum frequency the value of D.V.T decreases by increasing the frequency for all three sizes and above that, the D.V.T and frequency are directly proportional to each other. Nevertheless, differences between the pressure-frequency diagrams become significant by making the droplet bigger. By increasing the droplet size more time is required to complete the vaporization of the whole inner liquid. Since acoustic excitation is fast at high frequencies i.e. the exposure time is small, high pressure must be applied to obtain direct vaporization.

4.4. Initial thickness of shell

To be consistent with previous studies of ADV process accounting for mechanical properties of the encapsulating shell [18,23,25], we defined the one stop criterion to be the time at which the shell thickness (h) is zero (\( \simeq 10^{-14} \) [nm]). This approximation is accurate mathematically, but not achievable practically. We can show that defining a proper size for shell thickness at the time of vaporization (from the physical point of view) inhibits the complete vaporization if the initial thickness of the shell (\( h_0 \)) is not chosen appropriately. Without an appropriate choice of \( h_0 \), the shell thickness forces the simulation to be stopped while complete vaporization does not occur. For example if the minimum achievable shell thickness is 0.5 [nm] the results in Fig. 9A, B show that total vaporization (when \( \frac{\text{mass}_{\text{initial}}}{\text{mass}_{\text{final}}} = 1 \)) occurs only for \( h_0 = 20 \) [nm]. While for \( h_0 = 10.15 \) [nm] the simulation is terminated because minimum shell thickness is reached and the simulation is terminated without completing the vaporization process. Moreover, numerical results in Fig. 9A, B show that if shell thickness is initially large, the determining stop criterion is total vaporization and the shell thickness does not reach its minimum value. Thus, depending on the objective of ADV and whether total vaporization or final size of the shell is of primary importance, we can select an optimum initial shell thickness.
The dynamic behavior of bubbles and droplets has been studied since the 19th century, but their potential in medical applications was first reported by Gramiak et al. [34]. Exposing droplets (that are stable at body temperature and atmospheric pressure) to acoustic waves disturbs their stability and results in a phase change from liquid to gas. This process is known as acoustic droplet vaporization (ADV). ADV-generated bubbles can be used as ultrasonic contrast agents (at moderate pressure) and as therapeutic payloads (at high pressure) [35]. Furthermore, ADV is used in embolotherapy, thermal therapy, and histotripsy [36–38].

The relevance of ADV for medical applications, makes it crucial to study the process in detail and investigate how the process can be optimized under different conditions. In addition to experimental studies, theoretical approaches are effective tools to predict results numerically and achieve this goal.

Cavitation dynamics modeling studies are fundamentally rooted in the van der Waals (VDW) equation and phase-change induced mass flux principles and had their genesis in publications such as [39,40]. In [39], Storey and Szeri throw light on the important role water vapour plays in the physics of strongly collapsing bubbles. Parameters are varied to explore some interesting consequences when water vapour and reactions are taken into account. In earlier work [40], Yasui presented a model of single bubble sonoluminescence. The paper incorporates the kinetic energy of gases and suggests that sonoluminescence originates in thermal radiation from the whole bubble rather than heating of a single point heated by a converging spherical shock wave (as had been suggested by previous theories). Since then, nanodroplets have emerged as a new type of agent for facilitating acoustic cavitation, but their behavior has still to be appropriately modeled. Our contention is that, while van der Waals equation and phase-change induced mass flux principles are likely involved in modeling the dynamics of nanodroplets, the incorporation of these principles into nanodroplet dynamics modeling is not a straightforward task as factors like shell properties need to be taken into account. Various mathematical models have been proposed so far to understand the mechanisms involved and determine key factors influencing ADV. The first mathematical model to study the ADV process was introduced by Gumerov [41]. This basic model has since been improved to take into account different mechanisms and properties of surrounding environments such as the droplet itself and the heat transfer process [16,42]. Further modifications have taken into account the mechanical properties of coating materials that encapsulate the droplet [23,25]. Because ADV is being investigated for potential applications in fields related to human health, it is of paramount importance to model the process properly to obtain reliable results. One challenge in modeling ADV is capturing the supercritical state occurring after bubble collapse. Since, the bubble collapse causes a significant increase in the temperature and pressure of the bubble, the supercritical state requires an accurate description. Park & Son used the van der Waals equation for a proper description of the isentropic process [4]; however the isentropic state equation is for an ideal gas. Moreover, they did not consider the mechanical effects of the shell. We have improved the equation for an isentropic process in [4] to make it suitable for a VDW gas in order to capture the supercritical state more accurately. Although, due to lack of experimental data, we are not able to verify the numerical results, nevertheless the results in Fig. 4 indicate that the supercritical state has been captured properly and bubble pressure, temperature, and density remain in an acceptable range. It has been shown in the present paper and in [23,25] that mechanical properties of the encapsulating shell are important factors that affect the bubble fate. As suggested in [25], we have used the Mooney-Rivlin model (which is suitable for soft incompressible materials) to account for the mechanical effects of the shell. It has been shown in Fig. 3 that increasing the shear modulus either inhibits or delays direct vaporization. For stiff shells, higher pressure is required to complete the vaporization process which can cause damage in the surrounding environment and must be avoided in medical applications. Moreover, our numerical results in Fig. 2 suggest that vaporization occurs earlier at higher pressure amplitude (as shown in the previous studies (4,17,25)) and the final value of $R_b$ is not constant. This finding indicates that the assumption made in [25] is not always true even for an ideal gas (results are not shown). Furthermore, we have shown in Fig. 8 that direct vaporization is very sensitive to the initial thickness of the droplet especially at high frequencies. The obtained results in Figs. 3 and 8 are qualitatively similar to the results in [25], but quantitatively different because of the use of the VDW equation and the treatment of the super and subcritical states separately. Besides studying the effects of acoustic and geometrical parameters and the mechanical properties of the shell on ADV, we have shown that starting acoustic pulsing at an appropriate time, (i.e. applying an acoustic wave with proper phase that guarantees thermal equilibrium of the bubble temperature with the surrounding liquid) decreases the threshold of direct vaporization, see Fig. 6. It has also been shown in [4] that numerical results obtained using this assumption are in better agreement with experimental data, nevertheless the authors in [4] assumed that the effect of the encapsulating shell is negligible. In this work, we have used an adaptive Runge–Kutta method in time to solve the mathematical model. One criterion to stop the numerical algorithm (as defined in [25]) is when the thickness of the shell becomes zero. From the mathematical perspective, zero can be defined in the range of...
Acoustic droplet vaporization (ADV) is an emerging strategy to produce bubbles which can be utilized in various ways in clinical medicine, ranging from contrast agents in ultrasound imaging to carrying drug cargos in delivering drugs to specific targets. To understand the mechanisms underlying the ADV process and to determine key factors involved in the vaporization process, we developed a Rayleigh-Plesset based mathematical model to describe the dynamics of a vapor bubble nucleated in an encapsulated perfluorocarbon droplet. To treat large deformations of the encapsulating shell resulting from the liquid to vapor phase transition properly, nonlinear elasticity must be considered. For this purpose, we used the strain softening Mooney-Rivlin model which is able to describe large deformations of soft, nearly incompressible materials coating the shell. The emphasis in the current study is primarily on a proper treatment of the supercritical state occurring after bubble collapse. This is done by employing van der Waals equation if the gas is below the critical state and defining a proper equation for a van der Waals gas if it is above the critical state and varies in an isentropic manner. We also studied the effects of acoustic and geometrical parameters and the mechanical properties of the shell, on the vaporization process. The main findings are:

- Mechanical properties of the encapsulating shell has a strong effect on ADV. Increasing the shear modulus can inhibit or delay direct vaporization. If a droplet is coated with not sufficiently soft material, a higher acoustic amplitude is required to induce direct vaporization.
- Using an appropriate equation to describe the isentropic process occurring after the bubble collapse, gives accurate solutions, $\rho_b$, $T_b$, $p_b$ (physically and mathematically) in terms of being smooth and in an acceptable range.
- The minimum pressure required for direct vaporization is sensitive to mechanical properties of the shell and initial radius of the droplet. However, the sensitivity is notable at higher frequencies. The obtained numerical results show that depending on the elasticity of the shell and initial radius of the droplet, there exist an optimum pressure and frequency to achieve direct vaporization without any rebound.
- Nucleation time and the starting time of acoustic pulsing are important factors in determining the pressure and frequency of direct vaporization. Assuming the bubble is initially in thermal equilibrium with the surrounding liquid gives the nucleation time which varies for different acoustic amplitudes. The starting time of acoustic pulsing, changes the dependency between droplet vaporization threshold and frequency. Numerical results obtained using this assumption indicate that there is no increasing–decreasing behavior in the pressure-frequency diagram. The threshold for direct vaporization increases with increasing frequency. Moreover, a lower pressure is required for direct vaporization.
- Liquid to vapor phase change decreases the shell thickness, but it cannot be infinitesimally small. We showed that defining a proper size for the final shell thickness (at the time of vaporization) which is meaningful physically needs a proper choice of its initial thickness. Otherwise, the vaporization process cannot be completed.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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