Journal of Non-Newtonian Fluid Mechanics 222 (2015) 272–287

Contents lists available at ScienceDirect

Journal of Non-Newtonian Fluid Mechanics

journal homepage: http://www.elsevier.com/locate/jnnfm

A CaBER computational–experimental rheological study on human sputum ☆

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ARTICLE INFO

Article history:
Received 19 June 2014
Received in revised form 5 March 2015
Accepted 11 March 2015
Available online 25 March 2015

Keywords:
Chronic Obstructive Pulmonary Disease (COPD)
Capillary Break-up Extensional Rheometer
Modified Bautista-Manero (MBM) model
Single Extended pom–pom (SXPP) model
Hybrid finite element/volume

ABSTRACT

The main focus of this computational modelling study is to determine the extensional rheological response of sputum biofluids to provide a diagnostic tool (biomarker) for experimentally-based pathological analyses and clinical practice. This may be accomplished through advanced rheological parameterisation and characterisation of sputum samples, when considering extensional deformation flow situations that mimic sputum escalator deformation in the lung-airways. Sputum samples have been collected from patients (male and female, over fifty years of age) suffering from Chronic Obstructive Pulmonary Disease (COPD) at two stages of development: uninfected (stable or non-infective) state and infected (suffering exacerbations) state.

Samples have been tested without any pre-treatment such as mechanical homogenisation. Experimental and numerical studies of Capillary Break-up Extensional Rheometer (CaBER) have been performed, from which comparison significant correlations are presented. Typically, the dynamic development of the mid-filament diameter is monitored during the process of necking and filament-failure (break-up). The aim is to link this type of data with that emerging from experimental/clinical trials to provide a biomarker revealing insight on state of disorder and resultant treatment.

The rheology of sputum samples is represented through two rheological fluid modelling approaches: (i) a kinetic Single Extended pom–pom (SXPP) model and (ii) a time-dependent thixotropic Modified Bautista-Manero (MBM) model. These models are sufficiently rich to enable description of both network-structure and rheological properties, exhibiting viscoelastic response (memory), with strain-hardening/softening and shear-thinning properties.

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1. Introduction

Biological materials have been the subjects of many rheological studies due to the relationship between their viscoelastic properties and their physiological function. Typically, the biorheology field covers the investigation of deformation and rheological properties of materials within biological systems. One such situation, in which the viscoelastic properties of a biomaterial is linked to a pathologic state, is via the enhanced elasticity and viscosity of sputum in patients with pulmonary disease conditions – such as, cystic fibrosis (CF), chronic obstructive pulmonary disorder (COPD), and asthma. The increased rigidity of respiratory mucus (sputum) has been proposed to be responsible for the exertion in lung clearance observed in CF patients. As such, some current treatments are directed towards decreasing the stiffness of infected sputum, and rebuilding its viscoelastic features, that are suitable for clearance. Hence, it is important to study the viscoelasticity of sputum, and its rheology in relation to physiological function, so that diagnosis and treatment of respiratory infection can be improved.

1.1. On COPD

To provide some background, chronic obstructive pulmonary disorder (COPD) is the third main disease killer world-wide (fourth highest killer in UK). It is estimated that about three million people in the UK have COPD. Most patients with COPD remain undiagnosed until late in their disease history; yet, early detection can be influential. It is important to capture COPD-sufferers at an initial

☆ Dedicated to Prof Ken Walters FRS on the occasion of his 80th Birthday.

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http://dx.doi.org/10.1016/j.jnnfm.2015.03.005
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stage of infection to prevent possible irreversible lung-damage inflicted by intense COPD. Currently the initial diagnostic of COPD is defined according to breathing tests (such as spirometry), CT scan, electrocardiogram, chest X-ray and blood-tests. Nevertheless, these assessments are often inaccurate and involve professional analysis.

1.2. Rheometry

Conventional rheometry, performed using rotational/oscillatory rheometers, reveals the shear properties of a material sample (in ideal shear flow deformation). However, most actual flows in nature (for instance those which are biologically relevant) and in technology are complex and can include both shear and extensional components. In fact, extensional flows can significantly stretch macromolecules, providing orders of magnitude increase in elastic forces and extensional viscosity. Hence, quantifying the extensional rheology properties of a material in a complex flow condition is crucial in order to fully characterise its rheological behaviour. The rheology of biological complex fluids is necessary for normal vital functions of many processes in the body. Examples of biological flows where extensional mechanism are likely to play a key role comprise blood circulation [1], mucus transport in the airways, tear-fluid flow in the eyes, and saliva-flow in the mouth [2,3]. As a result, understanding the behaviour of healthy and unhealthy bio-fluids under extensional deformation could provide significant insight and medical benefits, in terms of discovering and developing novel treatments, therapies and more accurate/potential diagnostic outcomes.

1.3. Sputum – properties and measurement

To understand the flow mechanism of mucus in the lungs by coughing, there have been many simulated experimental investigations (using a simulated cough machine) [4–9]. These researchers have brought several issues into focus, on the subject of the role played by rheological properties of mucus (as a viscoelastic biomaterial) [10–12]. Most of the published data on the rheology of sputum focused in studies relating to the application of steady and oscillatory shear, considering sputum as a non-Newtonian viscoelastic material exhibiting shear-thinning and thixotropic properties [14].

However, for scientific reasons, many of the early rheological tests performed on sputa have been conducted under relatively large deformation and forces. The increased stiffness of infected sputum prevents its proper airway clearance. As such, therapeutic methods are often directed to reducing sputum-viscoelasticity to their normal (healthy) levels. Design of catalysts capable of altering the increased rigidity of CF sputum is a main target for treatment of this ailment, and rheological studies of these materials can shed light on the structures responsible for the shifted viscoelasticity within the diseased condition. Consequently, much of the rheological data on rheology has focused on the viscosity of the material after the primary disruption of its elastic component.

To investigate the possibility of damaging the network structures in the sputum during the shear viscosity measurements, Nielsen et al. [15] used a combination of oscillatory, creep-recovery and steady shear techniques. Their results suggest that measurements of elastic moduli reflects the mechanical properties of sputum in situ rather than viscosities, and those methods used to measure viscosities, may destroy part of the biopolymer structures responsible for the abnormal rheology of CF sputum. In contrast, measurements of shear elastic moduli at low strain rates appear to protect more of the original structure of the sputum and may establish superior techniques to evaluate the effects of potential mucolytic agents.

1.4. Filament stretching

The filament stretching rheometer has emerged as an approved apparatus for measuring the extensional properties of moderately viscous (mobile) non-Newtonian fluids [16–22]. Under continuous stretching, the filament-stretching rheometer is operated in *FiSER*-mode; alternatively, under step-strain (*CaBER*) mode, operation is under capillary-break-up (short initial stretch) conditions [17,18,22]. In continuous stretching operation, a vertical cylindrical liquid bridge of the sample (vary in length and loading) formed between two circular end-plates is subjected to a prescribed extensional deformation. Subsequent necking leads to significant thinning and reduction of the middle-section of the filament, whilst the rigid end-plates result in considerable shearing within the filament-foot region. In *CaBER* trials, a rapid axial step-strain of fixed magnitude is imposed on the sample, which is subsequently allowed to respond to that local conformational change, before proceeding towards break-up under the action of capillary forces (fluid self-selecting time-scale).

An extensive survey of filament stretching technology is provided by McKinley and Sridhar [16], covering the dynamical response of non-Newtonian fluids within filament-stretching rheometers. In the present study, it is anticipated that sputum samples demonstrate strain-hardening, requiring various representative constitutive equations to accommodate such response. An extensive experimental and numerical review on break-up for Newtonian fluid filaments and jets has been provided by Eggers [17]. Regarding the step-strain mode, Anna and McKinley [18] studied the dependency in the transient of the diameter-profile of the filament, and the time to break-up as a function of the sample molecular weight. This work included comparison against simple theory for breakup of slender viscoelastic filaments.

Typically, in either mode, the transient evolution of the mid-filament diameter profile is monitored during the process of necking and failure, from which the appropriate rheological calculations are performed. Ambitions are to link this type of data (as a rheological bio-marker), with that emerging from experimental/clinical trials to assist diagnosis and treatment-selection in the early stages of COPD advance.

1.5. Predictive CFD study

The focused challenge of the present computational study relates to the advanced prediction of biofluid flows within the respiratory system. Here and under filament-stretching, the focus is principally on the analysis and influence of material parameters on the temporal-evolution of the cylindrical filament shape (R_{mid} profile). The sputum samples are collected from three COPD-suffering patients, without stimulation. These patients have donated sputum-samples that correspond to two distinct stages of disease development: uninfected (stable or non-infective) state and infected (suffering exacerbations) state. In the present context, sputum rheology may be modelled through a number of approaches, from kinetic-molecular theory (non- thixotropic pom–pom SXPP models [23–25]) and from thixotropic micellar network theory (worm-like micelles-MBM model [26–29]). Here, pom–pom parametric variation is conducted over structural network description to explore a wide variety of topologies (entanglement, branching – molecular architecture), rheological properties (tension-hardening or softening, shear-thinning), relaxation mechanisms (backbone stretch, multiple time-scales). Under dynamic thixotropic micellar network models, parametric variation covers temporal network construction and destruction parameters.

To address the simulation and to solve the discretised system of partial differential equations involved, the basis of the present numerical strategies employed follows those implemented in our

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