Institution: University College London		
Unit of Assessment: 12- Engineering		
Title of case study: Rheological model for optimized manufacturing of oral healthcare products		
Period when the underpinning research was undertaken: 2000- 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Panagiota Angeli	**Role(s) (e.g. job title):** Professor of Chemical Engineering	**Period(s) employed by submitting HEI:** 1996-date
Luca Mazzei	Associate Professor	2009- date
Period when the claimed impact occurred: 2013- 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

UCL research on properties of complex formulations (in particular rheological changes and flow) has led to the development of a rheological model and computational fluid dynamics (CFD) simulations, implemented by [TEXT REMOVED FOR PUBLICATION] for manufacture of their [TEXT REMOVED FOR PUBLICATION] . The new and improved methodologies devised by UCL and applied by [TEXT REMOVED FOR PUBLICATION] have reduced production time by [TEXT REMOVED FOR PUBLICATION] , reduced technical assessment time for new formulations by [TEXT REMOVED FOR PUBLICATION], and increased confidence in current manufacturing processes. The research has increased manufacturing efficiencies and led to alternative design processes, resulting in an increase in annual turnover for [TEXT REMOVED FOR PUBLICATION] . The research has been applied to assess complex fluids in the petrochemical industry and paved the way for more industrial collaborations, including with global leaders in sustainable technologies such as Johnson Matthey Plc.

2. Underpinning research

Oral care products such as toothpastes and gels (including active ingredients), play an important part in maintaining good oral healthcare and preventing diseases. These products have advanced enormously in the past 20 years in terms of quality, function and effectiveness. This increased level of sophistication, along with the complex rheological behaviour, poses many product formulation and process development challenges to healthcare companies, which aim to deliver high-value products to consumers. The standard process development and optimization work requires extensive and time-consuming product rheological characterisation at lab scale, preliminary feasibility exercises at pilot scale and thorough experimental scale-up work from lab to pilot and from pilot to production scales. Uncertainties in the manufacturing process because of lack of understanding of the effect of process conditions on the formulation properties, means that companies produce based on forecast. This usually entails production of volumes larger than those required.

Recently non-aqueous formulations have been introduced in oral healthcare to protect the stability of water sensitive active ingredients up to the point of application. They are prepared by mixing gels produced at elevated temperature with high viscosity non-aqueous solutions. Non-aqueous formulations have different rheological behaviour compared to their aqueous counterparts, while in general require longer mixing times [TEXT REMOVED FOR PUBLICATION]. The non-aqueous formulations are strongly viscoelastic and thus temperature sensitive. The lack of previous lab and pilot plant data for these formulations necessitates extensive laboratory, feasibility and scale-up studies. To overcome these limitations reliable rheological models are required for new formulations. These models can then be implemented within Computational Fluid Dynamics (CFD) modelling tools to simulate complex real conditions in industrial unit operations. Once validated against experimental data, the rheological models and CFD simulations can predict product quality characteristics in a cost-effective manner, yet building fundamental process knowledge.

In UCL's Department of Chemical Engineering and through a consultancy project, Case and Impact studentships and further industrial and EPSRC funding, a systematic approach has been developed by Professor Angeli and Dr Mazzei to characterise the complex rheology of non-aqueous oral formulations and to improve mixing for current formulations. Professor Angeli and her research group carried out extensive experimental measurements to develop a rheological model of the formulations for a variety of temperatures and compositions (**R1**). The rheological model developed was then implemented in a Computational Fluid Dynamics (CFD) code. As a validation measure for the CFD code, power requirements predicted computationally were compared against those obtained experimentally at the UCL laboratory and very good agreement was found, which confirmed the validity of the approach.

The rheological and CFD models developed in (**R1**) were then used to study the power consumption and the mixing in the industrial scale units equipped with complex impeller blades and holes. The predictions were validated against detailed experimental data in scale down systems in the UCL laboratory (**R2**). The measurements included velocity profiles and flow patterns obtained from advanced laser-based particle image velocimetry (PIV) approaches developed by Professor Angeli's group (**R3**), supported by EPSRC funding. Results indicated that in the current vessel configurations large velocities develop around the blades, however in the majority of the vessel the velocities were low. In addition, the impeller configuration with holes was observed to increase the shear rate locally, which reduces viscosity for shear thinning fluids (**R2**).

At industrial scale, temperature of the formulation usually varies with detrimental effects on product quality. Detailed knowledge of the effect of temperature on gel rheology can reduce the number of failed batches and hence has been used to design novel, more efficient process routes. As a result of previously developed methodologies by Professor Angeli (**R1, R2**), a new intensified continuous approach was then proposed for the initial stages of the production of the oral formulation. In this approach, low viscosity fluids are mixed together and the gelation process takes place subsequently at room temperature (**R4**). As such, the mixing is faster, while the heating and temperature control requirements are significantly reduced.

The rheological studies have since been extended to include solid suspensions, which is the next step in the manufacturing process of oral healthcare products. Implemented in CFD (**R5**), the rheological models of solid suspensions have been used to understand the mixing of the solids in stirred vessels as used by [TEXT REMOVED FOR PUBLICATION]. The CFD modelling and experimental approach have also found applications in other processes that involve dispersions. For example, it has been used to predict the flow and separation characteristics of liquid-liquid emulsions in pipes, as encountered during the transportation of oil multiphase mixtures relevant to the oil and gas production and to the separation for pharmaceutical compounds (**R6**).

3. References to the research

R1. Cortada-Garcia M, Dore V, **Mazzei L**, **Angeli P**. (2017) Experimental and CFD studies of power consumption in the agitation of highly viscous shear thinning fluids. *Chem Eng Res Des*, 119, 171-182. doi: 10.1016/j.cherd.2017.01.018

R2. Cortada-Garcia M, Weheliye WH, Dore V, **Mazzei L**, **Angeli P**. (2018) Computational fluid dynamic studies of mixers for highly viscous shear thinning fluids and PIV validation. *CES*, 179, 133-149. doi: 10.1016/j.ces.2018.01.010.

R3. Voulgaropoulos V, **Angeli, P**. (2017) Optical measurements in evolving dispersed pipe flows. *Experiments in Fluids*, 58 (12), 170. doi: 10.1007/s00348-017-2445-4.
R4. Migliozzi S, **Angeli P**, **Mazzei L**. (2019) Gelation kinetics of non-aqueous carbopol dispersions. *Colloids and Surfaces. Physicochemical and Engineering Aspects*, 577, 84-95. doi: 10.1016/j.colsurfa.2019.05.051.
R5. Jamshidi R, **Angeli P**, **Mazzei L**. (2019) On the closure problem of the effective stress in the Eulerian-Eulerian and mixture modelling approaches for the simulation of liquid-particle suspensions. *Physics of Fluids*, 31, 013302. doi: 10.1063/1.5081677.
R6. Voulgaropoulos V, Rashid J, **Mazzei L**, **Angeli P**. (2019) Experimental and numerical studies on the flow characteristics and separation properties of dispersed liquid-liquid flows. *Physics of Fluids*, 31, 073304. doi: 10.1063/1.5092720.

4. Details of the impact

The rheological model developed at UCL and implemented in CFD simulations (**R1**,**R5,R6**) has significantly enhanced product and process knowledge of the mixing of complex fluids. This rheological model was implemented by [TEXT REMOVED FOR PUBLICATION] (**S1,S2**) and, according to [TEXT REMOVED FOR PUBLICATION] Annual Report 2019: "*recommended most often for sensitivity in 70% of markets"* (**S1**). [TEXT REMOVED FOR PUBLICATION]. Professor Angeli's research contributes to [TEXT REMOVED FOR PUBLICATION] (**S3**). The research also contributes to [TEXT REMOVED FOR PUBLICATION].

Professor Angeli shared progress of her underpinning research (**R1-R6**) with [TEXT REMOVED FOR PUBLICATION] via several routes. These include direct meetings between Professor Angeli and her group and the company, emails, visits, round table discussions and presentations to the company, participation of research students in the [TEXT REMOVED FOR PUBLICATION], PhD annual conference and secondments of PhD students to the company. Within the company the information has been disseminated from R&D into the production sites through points of contact and trials. This has led to optimised production time and processing and personal development for researchers.

UCL's novel modelling approach to optimise production time and manufacturing processes

UCL's viscosity model and supporting CFD studies were used to reduce production time and optimise the process. The viscosity of the gel formulation, which influences mixing, is very sensitive to temperature. Previously the temperature range was used as one control of the gelation. The knowledge of the detailed correlation between temperature and viscosity (**R1**), enabled the operation of the mixing unit over a tighter temperature window that reduced the batch cycle time. Through reduction of batch cycle times, Professor Angeli's work therefore helps respond to consumers' higher demand to address tooth-sensitivity with access to products in the UK and worldwide such as Romania, Saudi Arabia, the USA and South America to name a few (**S4,S5**).

Specifically, the optimised temperature range for core gel premix led to a reduction of the batch cycle time of [TEXT REMOVED FOR PUBLICATION] . UCL's technique therefore [TEXT REMOVED FOR PUBLICATION] (**S2**). As a result of better operation and optimal process control following Professor Angeli's and Dr Mazzei's CFD studies contributing to [TEXT REMOVED FOR PUBLICATION] was able to meet consumers demand through over the counter products and [TEXT REMOVED FOR PUBLICATION]

UCL's rheology model was also used as a fast-technical assessment tool for new non-aqueous formulations. It enabled risk quantification when working in near critical conditions, thus reducing the need of costly pilot scale trials. This has led to timing reduction of [TEXT REMOVED FOR PUBLICATION] (**S2**). The detailed rheological studies from UCL and the effect of temperature have revealed the kinetics and times involved in the gelation process and led to alternative processing routes where mixing of low viscosity materials at room temperature precedes the gelation (**R4**).

This novel approach ensures faster processing times, better mixing and reduced heat requirements; in turn [TEXT REMOVED FOR PUBLICATION] (**S2**). A recent survey conducted by the UK government in 2020 showed that the number of users for the [TEXT REMOVED FOR PUBLICATION] range increased by 9% in the UK (from 2018 to 2019) (**S6**); this shows that Professor Angeli's modelling continues to facilitate ease of toothpaste productivity and meeting consumers increased demand to address their oral health. The ability to meet consumers demand through innovation is no surprise in oral healthcare, since "*Customers seek innovative, multifunctional oral care products that can deliver results and help maintain oral hygiene*" (**S7**).

[TEXT REMOVED FOR PUBLICATION]

Panagiota's work on complex fluids has supported market growth for [TEXT REMOVED FOR PUBLICATION] . Her work has contributed to a brand worth GBP270,000,000 in book value and contributing to the 7% growth of oral health sales (**S1**). Professor Angeli's work also initiates energy savings, in alignment with [TEXT REMOVED FOR PUBLICATION] current commitment of "t*ackling climate change…reducing its carbon footprint in line with the Paris Agreement*" (**S1**).

Substantial training and personal development for researchers

The UCL research team have contributed to training company stakeholders and also the next generation of scientists. Through the [TEXT REMOVED FOR PUBLICATION] -UCL collaboration, PhD students received industrial preparedness through [TEXT REMOVED FOR PUBLICATION] leadership and experts in the field (**S2**). They spent time working on the company site, where they received training on safety and industrial practice. A former PhD student seconded to [TEXT REMOVED FOR PUBLICATION] for 6 months as a Product Development Engineer, is currently employed as a Product Development Engineer at Repsol, Spain supporting development of motorcycle engine oils, working with complex viscous fluids and using "*all skilled acquired (…) at UCL and at* [TEXT REMOVED FOR PUBLICATION] " (**S8**) . As both lubricants and toothpastes are complex viscous fluids, the Product Development Engineer at Repsol, is currently implenting skills gained through the UCL-[TEXT REMOVED FOR PUBLICATION] collaboration solving motorcycle engine oil problems.

Similarly, one post-doctoral research assistant (PDRA) has now progressed to an academic post focusing on CFD research and teaching, while another PDRA has moved onto data analytics. The UCL-[TEXT REMOVED FOR PUBLICATION] partnership is therefore, promoting transferrable technical skills (such as communicating technical information to versatile audience and senior company leads) in industry within a short timeframe.

Application of mathematical modelling in industry

The methodological approach developed which combines the detailed characterisation of complex mixtures and the subsequent development of models (**R6**), have attracted further collaborations. As an example, Johnson Matthey Plc (JM), a global leader in sustainable technologies, is currently collaborating with Professor Angeli looking at continuous processes involving complex multiphase mixtures for separations in the pharmaceuticals industry. A Principal Scientist for Separation Technologies and Process Chemistry at JM , states that '*JM was very attracted to working with Professor P. Angeli at UCL for her expertise in fundamental chemical engineering science. In particular, her on-going in-depth work on complex multiphase flows, advanced experimental capabilities, mathematical modelling, and the characterisation of mixture properties'* (**S9**). In January 2020, this led to JM funding an EPSRC industrial CASE PhD award of GBP39,132 over four years. As of

December 2020, the UCL-JM collaboration has already provided new understanding on novel design and optimisation for extraction flow systems for JM, which they continue to pursue.

5. Sources to corroborate the impact

S1. Company annual report 2019
S2. Testimonial from collaborator
S3. Brushing up on the facts. Shelf Life: Ireland's Retail Authority
S4. Case studies
S5. Global Sensitive Toothpaste Market 2019-2023
S6. Vendor Analysis in UK and US
S7. Global Sensitive Toothpaste Market
S8. Testimonial former PhD student
S9. Johnson Matthey's Testimonial