EFFECT OF EUCALYPTUS OIL ADDED SURFACTANTS ON THE RHEOLOGY OF MUCUS GEL SIMULANTS

R. Banerjee* and R. R. Puniyani

School of Biomedical Engineering, Indian Institute of Technology, Bombay, India
* Present address: University of California, San Francisco, CA 94118-1245, U.S.A.
fax: x1.415.476.3586
e-mail: rban@itsa.ucsf.edu

Received: 18.8.1999, Final Version: 29.11.1999

Abstract

Eucalyptus oil is a commonly used remedy for common colds. For a substance to be effective therapy in obstructive airway diseases, it must reduce the viscosity of respiratory mucus. The present study evaluates the effectiveness of eucalytpus oil added phospholipid mixtures as possible substitute therapies in diseases of altered mucus viscosity by studying their effect on the viscosity of mucus gel simulants in *vitro*. Test formulations of surfactants consisting of phospholipid-eucalyptus oil mixtures in the ratio of 1 part of oil to 9 parts of phospholipid were prepared. The phospholipids used were dipalmitoyl phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylglycerol (PG). The effects of these phospholipid-eucalyptus oil mixtures on the viscosity of Mucus Gel Simulant (MGS – a polymeric gel consisting mainly of gum tragacanth and simulating respiratory mucus) was studied by application of steady shear rates ranging from 0.512 to 51.2 s^{-1} in a concentric cylinder viscometer at 37°C. The change in MGS viscosity, after incubation with surfactants, with application of shear rates was found to have a Non-Newtonian flow and to follow the power law model with R^2 values > 0.8. The addition of eucalyptus oil-phospholipid mixtures caused a decrease in the MGS viscosity when compared with the effect of the phospholipid alone at both low and high shear rates. The combination of PG with eucalyptus oil and of PG with eucalyptus oil and calcium caused ratios of change in MGS viscosity < 1, *i.e.* they caused a decrease in the MGS viscosity. Thus, the addition of eucalyptus oil improved the ability of the phospholipids to alter MGS viscosity. The combinations of PG with eucalyptus oil and PG with eucalyptus oil in the presence of calcium were even capable of lowering mucus gel viscosity and should be further researched as possible substitute therapies for diseases of altered mucus viscosity.

Kurzfassung

Eukaluptusöl wird gewöhnlich als Hilfsmittel für gewöhnliche Erkältungen verwendet. Für eine Substanz zu einer wirksamen Therapie bei chronischen Luftwegerkrankungen muss die Viskosität des Atemwegschleims reduziert werden. Die vorliegende Studie bewertet die Effektivität der mit dem Eukaliptusöl versetzten Phospholipid-Mischung als mögliche Ersatztherapie bei Erkrankungen durch veränderte Viskosität mit der Analyse der Effekte eines Schleimgels an der Viskosität *in vitro*. Testansätze von Reinigungsmitteln, die aus Phospholipid-Eukaliptusöl-Mischungen mit dem Konzentrationsverhältnis 1 Teil Öl zu 9 Teilen Phospholipid bestehen, wurden hergestellt. Die verwendeten Phospholipid-Lösungen waren Dipalmitoyl-Phosphatidylcholyne (PC), Phosphatidylethanolamine (PE) und Phosphatidylglyzerine (PG). Der Effekt dieser Phospholipid-Eukaliptusöl-Mischungen an der Viskosität des Schleimgel-Simulants (MGS, ein polymeres Gel bestehend hauptsächlich aus Gummi-Tragacanth, simuliert die Atemwegschleime) wurde in dem Schergeschwindigkeitsbereich von 0.512 – 51.2 s^{-1} in einem aus konzentrischen Zylindern bestehenden Rotationsrheometer bei T = 37°C untersucht. Die Änderung der MGS-Viskosität, nach der Inkubation mit dem Reinigungsmittel bei der angewendeten Schergeschwindigkeit äußerte sich in nicht-newtonschem Fließverhalten und konnte mit dem Potenzgesetz mit dem Fließexponenten R^2 > 0.8 beschrieben werden. Das Hinzufügen von Eukaliptusöl-Phospholipid Mischungen führte zu einer Abnahme der MGS-Viskosität im Vergleich mit dem Effekt der Phospholipide alleine sowohl bei niedrigen als auch bei hohen Schergeschwindigkeiten. Die Kombination von PG mit Eukaliptusöl und von PG mit Eukaliptusöl und Calcium führte zu Änderungen in der MGS-Viskositätsverhältnis kleiner eins, d.h. sie verursachte eine Abnahme der MGS-Viskosität. Demgemäß verbessert die Zugabe von Eukaliptusöl das Vermögen von Phospholipids die MGS-Viskosität zu ändern. Die Kombination von PG mit Eukaliptusöl im Beisein von Calcium reduzierte die Schleimgelviskosität und sollte als möglich Ersatzheilmittel für Krankheiten durch veränderte Schleimviskosität weiter erforscht werden.

Résumé

L'huile d'eucalyptus est un remède couramment utilisé pour lutter contre les rhumes. Pour qu'une substance soit une thérapie efficace contre les maladies liées à l'obstruction des voies respiratoires, elle doit réduire la viscosité du mucus respiratoire. L'étude présentée ici vise à évaluer l'efficacité de mélanges d'huile d'eucalyptus et de phospholipides comme thérapies de substitution possibles pour les maladies où la viscosité du mucus est altérée. Pour ce faire, l'effet de ces mélanges sur la viscosité de gels de mucus simulés est étudié. Des formules tests de surfactants composés de mélanges d'huile d'eucalyptus et de phospholipides à des ratios de 1 pour 9 respectivement ont été préparées. Les phospholipides utilisés sont le dipalmitoyl phosphatidylcholine (PC), le phosphatidylethanolamine (PE) et le phosphatidylglycerol (PG). Les effets de ces mélanges sur la viscosité du gel de

© Appl. Rheol. 9, 6, 254-261 (1999)

This is an extract of the complete reprint-pdf, available at the Applied Rheology website
http://www.appliedrheology.org

explained by the presence of semi-rigid rod like structures as have been described in dilute suspensions of xanthan gum [19]. The increase in the viscosity of the MGS on addition of phospholipids is in accordance with the finding of Vallejo et al [20] that the addition of lecithin to surfactant systems causes an increase in the micellar volume resulting in an increase in the viscosity.

The addition of eucalyptus oil caused a significant decrease in the ratio of change in MGS viscosity at both low and high shear rates when compared with that of the phospholipids without any additive. No studies have been conducted regarding the effect of eucalyptus oil on the viscosity of polymeric gums. However, it is postulated that the oils cause a conformational change of the rigid rod like particles facilitating a shear thinning and a decreased viscosity of the gel-oil mixture. It is also possible that the oil interacts with the phospholipid leading to the formation of smaller micelles which prevent the increase in viscosity caused due to the lipids alone. The spatial dependence of the droplet size distribution on addition of oils to a polymeric mixture can be studied by a combination of pulsed-field-gradient spin-echo (PGSE) nuclear-magnetic-resonance (NMR) restricted diffusion analysis and NMR imaging as suggested in a recent study by McDonald et al [21] to better elucidate the structure-rheology effects of oil-polymer suspensions.

On comparing the surfactants at shear rates of relevance to large, medium and small bronchi namely 0.9, 0.7, and 0.25 s^{-1} respectively; the combination of PG in the presence of eucalyptus oil (PGEO) was found to perform better than Survanta, ALEC and Exosurf. The combination of PG in the presence of eucalyptus and calcium (PGEOCA) was equivalent to Exosurf at all three levels of the airway tested. For a surfactant to be effective in chronic obstructive airway diseases, it should lower the increased mucus viscosity observed in these conditions. Thus, PG in the presence of eucalyptus oil formed a favourable surfactant formulation as it caused a decrease in the MGS viscosity at high shear rates (with a ratio of change in MGS viscosity < 1) and obtained lower values of ratios of change in MGS viscosity than the commercial surfactants at all the shear rates considered. PG in the presence of eucalyptus oil and calcium was also a favourable surfactant and performed equivalent to Exosurf at all the shear rates of physiologic relevance

6 CONCLUSION

In the present study, PGEO and PGEOCA were found to decrease the viscosity of mucus gel simulants at a high shear rate of 51.2 s^{-1}. The ratio of change in mucus gel viscosity due to these surfactants was significantly lower than that of the commercial surfactants and of the phospholipids alone at all shear rates (n = 5, p < 0.05, Mann-Whitney U test). The addition of eucalyptus oil caused a significant lowering in the ratio of change in MGS viscosity as compared with that of the phospholipid alone. Thus, eucalyptus oil appears to improve the effect of phospholipids on the viscosity of mucus gel simulants. This could prove as a basis for future research into eucalyptus oil-phospholipid mixtures as possible substitutes of bronchial surfactants in airway diseases characterised by an altered mucus viscosity. Of course it is to be remembered that the present study is conducted *in vitro* and cannot be directly extrapolated to *in vivo* conditions. Also the study of viscoelasticity instead of pure viscosity and the use of actual mucus samples instead of polymeric gums in the form of mucus gel simulants would be more informative from an application viewpoint. Nevertheless, the present study shows that phospholipid-eucalyptus oil mixtures, as substitute artificial surfactants, are capable of reducing the viscosity of mucus gel simulants and do so far better than the commercial surfactants. Thus, these formulations should be further researched using actual mucus samples and should be evaluated as possible substitutes for bronchial surfactants in obstructive airway diseases.

This is an extract of the complete reprint-pdf, available at the Applied Rheology website
http://www.appliedrheology.org

REFERENCES

[1] Billups NF, Billups SM: American Drug Index. J. B. Lippincott Co., Philadelphia. (1979) 363.

[2] Siurin SA: Effects of essential oil on lipid peroxidation and lipid metabolism in patients with chronic bronchitis. Article in Russian Klin. Med. (Mosk) 75 (1997) 43-45.

[3] Davis SS and Dipp JE: The Rheological Properties of Sputum. Biorheology 6 (1969) 11-21.

[4] Morgenroth, K: Morphology of the Bronchial Lining Layer and Its Alteration in IRDS, ARDS and COLD. Eur. J. Respir. Dis. 67 (1985) 7-18.

[5] Widdicombe JG: Introduction to Endobronchial Surface Active Phospholipids: Morphology, Biochemistry, Function and Therapeutic Aspects Eur. J. Respir. Dis. 67 (1985) 1-5.

[6] Gil, J and Weibel ER: Extracellular Lining of Bronchioles after Perfusion-fixation of Rat Lungs for Electron Microscopy Anat. Rec. 169 (1971) 185-200.

[7] Brown LD and Pattishell NE: Other uses of surfactant. Clin. Perinat. 20 (1993) 761-789.

[8] Anzueto A, Jubran A, Ohar JA, Piquette CA, Rennard SI, Colice G, Pattishall EN, Barrett J, Engle M, Perret KA and Rubin BK: Effects of aerosolised surfactant in patients with stable chronic bronchitis: a prospective randomized controlled trial. JAMA. 278 (1997) 1426-1431.

[9] Motta C, Touillon AM, Simon G and Dastugue B: Active Lipid: a Potential Fluidiser of Cystic Fibrosis Mucus Lawson, D. (ed.) Cystic fibrosis: horizons. Chichester: Wiley (1984) 337.

[10] Agarwal M, King M and Shukla JB: Mucus gel transport in a simulated cough machine: effects of longitudinal grooves representing spacings between arrays of cilia. Biorheology 31 (1994) 11-19.

[11] King M, Zahm JM, Pierrot D, Vanquez-Girod S and Puchelle E: The role of mucus gel viscosity, spinnability and adhesive properties in clearance by simulated cough. Biorheology 26 (1989) 737-745.

[12] Tibballs J: Clinical effects and management of eucalyptus oil ingestion in infants and young children. Med. J. Aust. 163 (1995) 177-180.

[13] Day LM, Ozanne-Smith J, Parsons BJ, Dobbin M and Tibballs J: Eucalyptus oil poisoning among young children: mechanisms of access and the potential for prevention. Aust. N. Z. J. Public Health 21 (1997) 297-302.

[14] Webb NJ and Pitt WR: Eucalyptus oil poisoning in childhood: 41 cases in southeast Queensland. J. Paediatr. Child Health. 29 (1993) 368-371.

[15] Banerjee R, Bellare JR and Puniyani RR: Effectiveness of various surfactant formulations at various shear rates experienced in the tracheobronchial tree. Communicated. Biophysical J.

[16] Gijsen FJH, Allanic E, van de Vosse FN, and Janssen JD: The influence of the non-Newtonian properties of blood on the flow in large arteries: unsteady flow in a 90 degrees curved tube. J. Biomechanics 32 (1999) 705-713.

[17] Gibbs SJ, James KL, Hall LD, Haycock DE, Frith WJ, Ablett S: Rheometry and detection of apparent wall slip for Poiseuille flow of polymer solutions and particulate dispersions by nuclear magnetic resonance velocimetry. J. Rheology 40 (1996) 425-440.

[18] Tam KC, and Tiu, C: Steady and dynamic shear properties of aqueous polymer solutions. J. Rheology, 33 (1989) 257-280.

[19] Zirnsak MA, Boger DV, Tirtaatmadja V: Steady shear and dynamic rheological properties of xanthan gum solutions in viscous solvents. J. Rheology 43 (1999) 627-650.

[20] Vallejo AG, Minchero RM and Torres MAL. Anionic surfactant-water systems: influence of lecithin addition on the rheological behaviour. J. Rheology 34 (1990) 1121-1132.

[21] McDonald PJ, Ciampi E, Keddie JL, Heidenreich M, and Kimmich R: Magnetic-resonance determination of the spatial dependence of the droplet size distribution in the cream layer of oil-in-water emulsions: Evidence for the effects of depletion flocculation. Physical Review E 59 (1999) 874-884.