Evaluation of the Rheological & Suspending Properties of Commonly Used Oral Suspending Vehicles

Alexandra Bowles[1],Terry Ernest[2], David Clapham[3] and Catherine Tuleu[1,4]

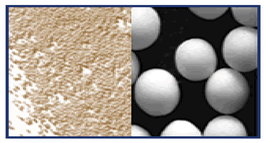
1 Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX
2 GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW
3 GlaxoSmithKline Pharmaceuticals, Park Road, Ware, Hertfordshire, SG12 0DP
4 Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London, BMA House, Tavistock Square, London, WC1H 9JP

INTRODUCTION

Little is documented about the rheology of commonly oral used suspending vehicles (which include everything from water through commercial suspending agents to semi-solid foods such as yoghurt which are often used in the administration of medicines to children). Following on from this, little is known about how larger particles (e.g. micrometre sized pellets which may be useful for modified release or taste-masking properties) suspend in media corresponding to the rheological profiles of these.

AIM

To determine the rheology of commonly used oral suspending vehicles and the suspendability of pellets within media corresponding to these viscosities to aid the development of functionalised multi-particulate suspension formulations for children



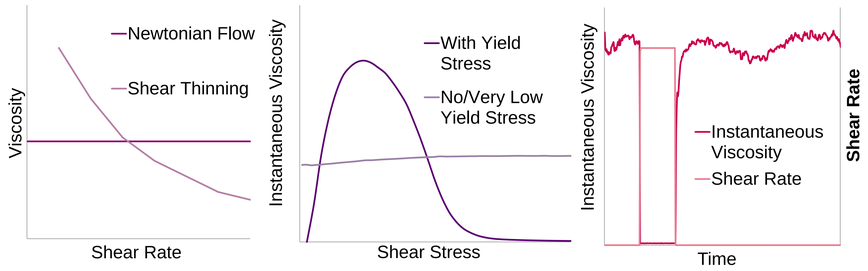
MATERIALS AND METHODS

- Hydroxypropyl methylcellulose (HPMC) 65SH-4000 (ShinEtsu Chemical Co Ltd) & Methylcellulose (MC) 400cP at 2%/25°C (Sigma Aldrich) both at concentrations from 0.1-10% in water by hot method
- OraPlus®, OraSweet® and OraSweet SF® (Paddock Laboratories Inc) along with mixtures of OraPlus® and OraSweet ® or OraSweet SF® (1:1)
- SyrSpend® (Kindly supplied byGallipot Inc)
- Glycerol 99.5% (Sigma Aldrich) and mixtures of glycerol:MC 1% (2:5)
- Syrup BP (William Ranson and Son plc) and mixtures of syrup:MC 1% (1:1)
- Yoghurt (Vanilla müllerlight® from Molkerei Alois Müller GmbH &Co. KG)
- Microcrystalline cellulose pellets (Cellets®) from 100-1000µm (Kindly supplied by Pharmatrans Sanaq)

RHEOLOGY

All samples described above were subjected to three forms of test as described below (all using a Bohlin Gemini HR Nano Rheometer at 25°C with a 2°/55m cone/plate and 70µm gap and all repeated in triplicate):

Viscosity Flow Curve	Yield Stress Determination	Thixotropic Step Test
At shear rates from 0.9-200 1/s	Using a shear ramp of 0.33-38Pa	Time taken to reform to initial viscosity after a shear rate of 1000 1/s for 60s

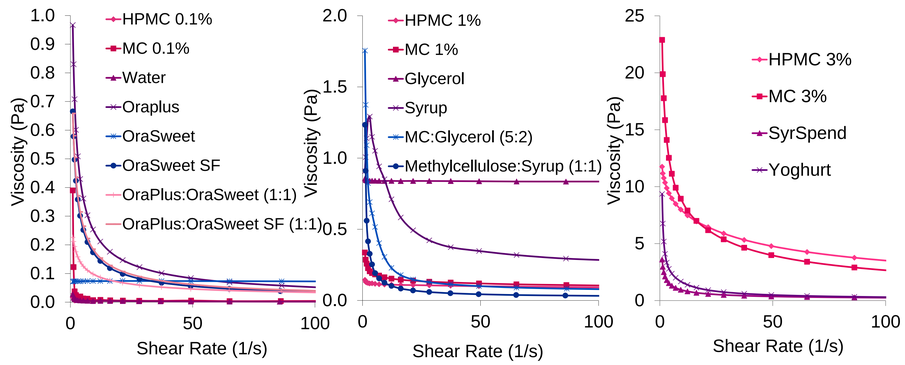


SUSPENDABILITY

- 30ml of suspending agent (MC or HPMC 0.1, 1 or 3%) and 3g of pellets (ranging from 100-1000µm) were mixed using a magnetic stirrer for one minute
- The time taken for all the particles to sediment was determined

RHEOLOGY RESULTS AND DISCUSSION

MC and HPMC 0.1, 1 and 3% solutions covered the full range of viscosities (Fig 1-3) of commonly used suspending vehicles and hence were used for suspendability tests
The majority of suspending media (with the exception of glycerol) exhibited shear thinning behaviour (Fig 1-3) which is desirable for ease of pouring



Figures 1-3: Mean Viscosities of Suspending Media against Shear Rate

Time to reformation was used to measure the thixotropic nature of the media (Fig 4) to assess how long before the suspension reforms completely (important for keeping particles especially longer ones suspended)
- Times ranged from seconds to over twenty minutes for HPMC/MC solutions > 3%

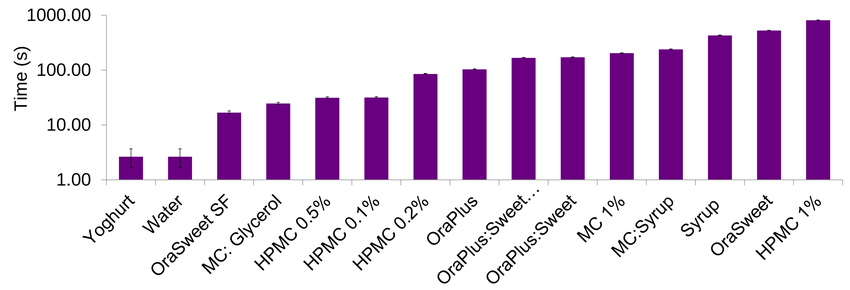


Figure 4: Mean Time Taken for 100% Reformation of Various Suspending Media

Yield stress was used as the maximum stress below which no flow as higher yield stresses would be thought to suspend larger particles better as they require a minimum stress to be applied to allow flow to occur (Fig 5)
- It can be seen the commercial suspending media have lower yield stresses

Increasing Yield Stress

None or less than 0.3Pa/
OraSweet, Syrup, Glycerol, SyrSpend, OraSweet:OraPlus, MC 0.1 - 1%, HPMC 0.1 - 1%

Less than 1 Pa
OraSweet SF, OraPlus OraSweet SF:OraPlus

Less than 5Pa
MC:Glycerol, MC:Syrup, MC 3%

Less than 7 Pa
HPMC 3%, Yoghurt

Less than 15 Pa
HPMC 5%

More than 38Pa
MC 5 and 10%

Figure 5: Yield Stresses of Various Suspending Vehicles

SUSPENDABILITY RESULTS AND DISCUSSION

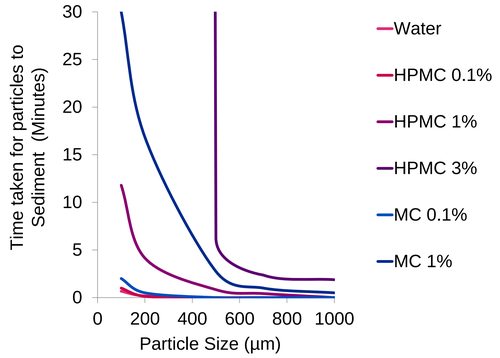
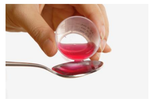


Figure 6: Time taken for Particles of Different Sizes to Settle in Different Concentrations of HPMC and MC Solutions

- Pellet sized particles were able to be suspended (in the case of MC3% for many hours)
- Smaller particles and more viscous suspending media caused the particles to take longer to sediment as per Stoke's Law
- However, smaller particles did not disperse well (especially the smaller particles n the thicker suspending media) so unable to quantify sedimentation by height and so the time taken for all particles to sediment was used

CONCLUSIONS

Most suspending vehicles were found to be shear thinning with relatively low yield stresses and varying times to 100% reformation/thixotropic nature



Pellets can be successfully suspended in media comparable to commonly used suspending vehicles (as determined by rheological measurements) but dispersability (and hence potential dose uniformity) of the smaller pellets in the thickest solutions was difficult.

Further work is needed to improve this dispersability by the addition of "child-friendly" excipients and to find a better method of quantifying suspendabiility