UEA MTH / IFR Study Group Workshop
14–17 September 2010

Problems

Efficacy of multiparticle dosage forms (Richard Faulks)

The efficacy of oral drug administration can be improved by presenting the dosage form so that either:

- the dose frequency is reduced; or,
- a specific section of the gastro-intestinal tract (GIT) is targeted.

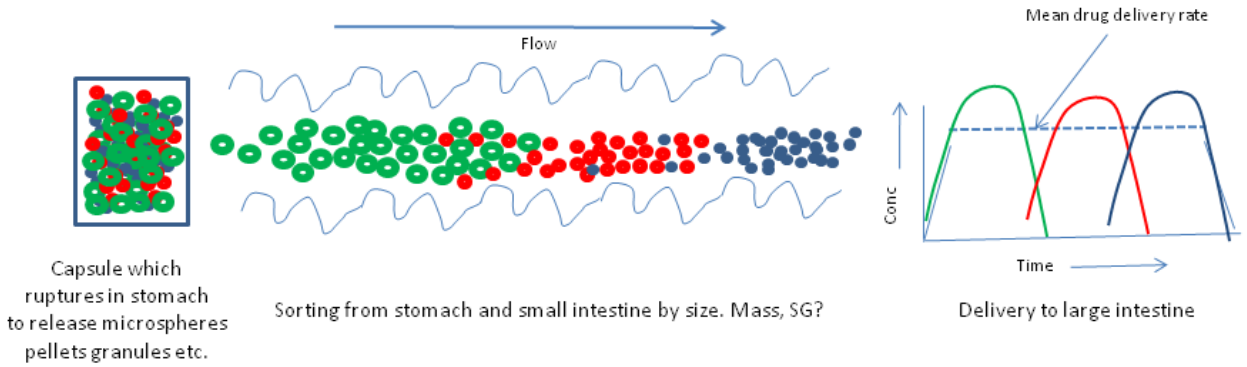
Dosage forms are of two basic types:

1) single dose units (SDU), usually taking the form of a tablet; and,
2) multiple dose units (MDU) comprising smaller particulate systems of pellets or micro-tablets filled into capsules that disintegrate and release their charge when ingested.

Many advantages of MDU have been suggested including:

- easy to coat;
- easy to separate incompatible drugs;
- allows mixing of drugs with different release rates;
- reduced rsik of dose "dumping" and local irritation of the GIT;
- smaller particles are believed to behave like a liquid in terms of gastric emptying;
- distribution of particles over the GIT is generally more uniform and independent of nutrition status (fed/fasted).

Nevertheless, despite considerable scientific effort, the efficacy of MDU forms remains controversial [1]. This raises the question: can a simple mathematical model conclusively establish that the MDU GIT delivery profile can differ in some characteristic way from SDU for some classes of gastric emptying profile?



A capsule ruptures in the stomach to release a population of different sized microspheres $\{\sigma_i\}$ where $i = 1, \ldots, N$ indexs the particle type (component). The microspheres leave the stomach with some degree of sorting prescribed by a family of gastric emptying profiles $\{E_i(t)\}$ (the fraction of type i particles remaining in the stomach at time t after ingestion). On passing through the small intestine (typically over a 12 hour period), the population undergoes further sorting such that each size class emerges into the colon with some temporal distribution $\{A_i(t)\}$

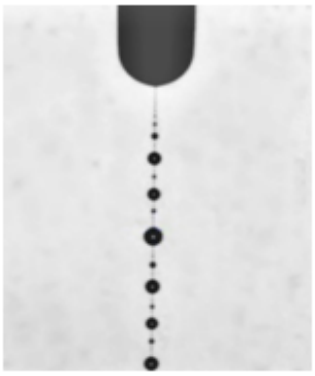
(the "arrival" profile). In the colonic environment, the microspheres are physico-chemically triggered to release their drug content. The goal is to maintain a constant concentration of drug at the colon entrance (the terminal ileum).

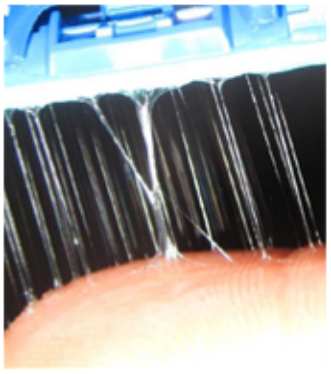
- What is the optimum practical number monodisperse size classes?
- Can the analysis be extended to account for a polydisperse continuum microsphere population with a prescibed distribution?

Formation of "beads-on-a-string" (BOAS) structures in saliva (Pete Wilde)

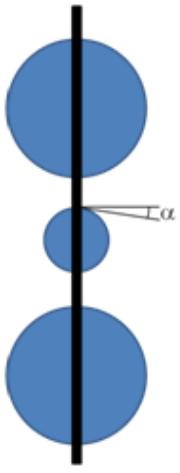
The functions of saliva are primarily to aid digestion and to control oral microflora, both symbiotic and pathological. By moistening food, saliva helps to create the food bolus for effective swallowing. Salivary amylases and lipases also initiate the breakdown of starches and fats in the mouth. Human saliva is % 98 water but also contains electrolytes, proteins, mucus (polysaccharides and glycoproteins) and antibacterial agents including secretory IgA, lactoferrin and peroxidase, as well as whole bacterial cells. This complicated "soup" of biopolymers confers saliva with an unusually resilient viscoelastic rheology, both in bulk and at surfaces.

By numerical simulation, Bhat et al. [2] have recently clarified the formation mechanism of "beads-on-a-string" (BOAS) structures that develop before the breakup of viscoelastic filaments under stress. Filaments of saliva (left and centre) form beads when stretched, but filaments formed from a soap strip (right) do not.

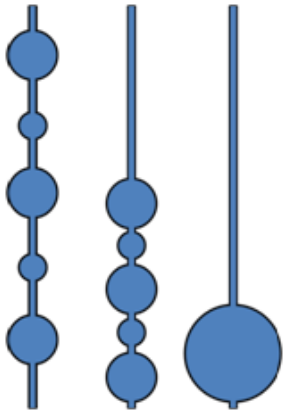




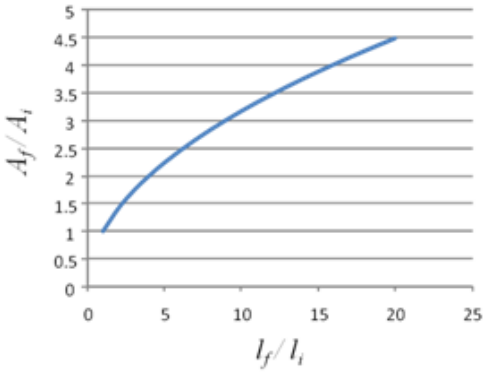
The claim is that viscoelasticity of the fluid alone does not give rise to a small satellite bead between two much larger beads, but that inertia is also required to develop this morphology. The seminal work of Boys [3] demonstrated the formation of BOAS morphology by a viscous Newtonian fluid surrounding a central rigid core driven by capillary action.

This is predominantly due to the degree of wetting governed by the contact angle α that measures the competition between interfacial tension and surface hydrophobicity. If fluids like saliva form beads, and there is no solid core, why don't the beads simply fall down under the action of gravity and coalesce into a single bead? In fact, saliva is a special case, as it forms extremely high surface elasticities, thus forming a rigid shell, rather than a core. This may prevent the droplet from falling, but also may promote the droplet formation in the first place. Our hypothesis is that the surface rigidity of the saliva film promotes the creation of beads, and also immobilises them.



Ignoring gravitational effects, suppose a cylindrical volume V of fluid with diameter d_i, and length l_i is held between two solid supports. When the incompressible fluid is stretched to form a filament, material conservation demands that the diameter shrinks to d_f as the length increases to l_f . A simple calculation shows (if I've got it right) that the surface area will increase dependent on the increase in l_i as shown.

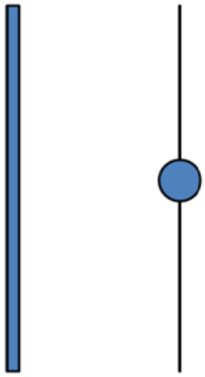


The surface area increases quite markedly. The interfacial rigidity of the saliva will resist the expansion in surface area. This can only be accomplished if the filament becomes as thin as possible. The constant volume constraint leads to the formation of large beads, as a compromise for the loss of volume created by a much thinner filament. For example, the following diagram illustrates the situation at $l_f/l_i = 10$.

No bead

$$\frac{A_f}{A_i} = 3.16$$

$$d_f = 0.316$$



One bead

$$\frac{A_f}{A_i} = 1.47$$

$$d_f = 0.017$$

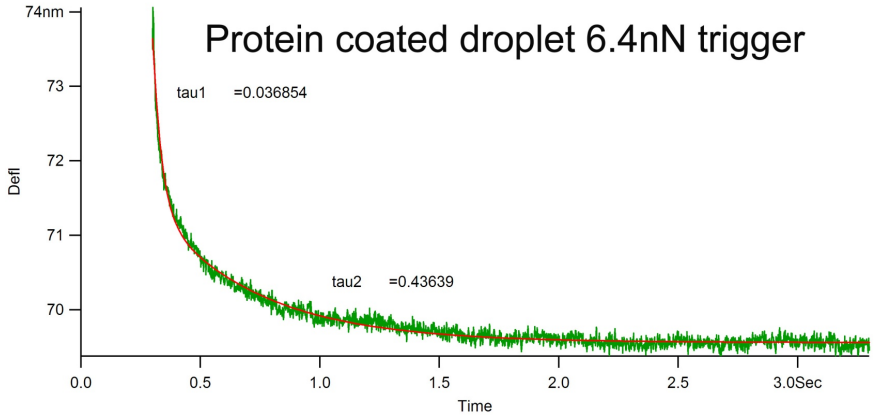
$$d_{\text{bead}} = 1.413$$

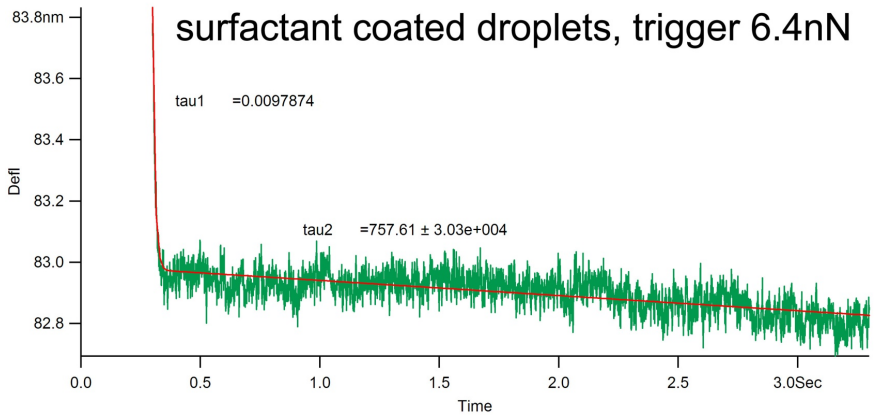
Can we show that a surface elasticity can give rise to the formation of beads. How strong does the surface need to be? Why do both small and large beads form? Can we provide some experimental observations of formation, sizes etc.?

Creep and relaxation of emulsion droplets observed by atomic force microscopy (AFM)
(Pat Gunning)

For some time now, the quantitative micromanipulation facility offered by atomic force microscopy (AFM) has been exploited to study the viscoelastic response and mechanical stress relaxation of individual living cells [4]. By using the same indentation technique at IFR, we have recently observed similar creep phenomena with inanimate oil-in-water emulsion droplets.

A single droplet attached to the AFM cantilever is driven towards another stationary droplet at a controlled constant "impact" speed. Deflection of the cantilever (a Hookean spring of known force constant) is measured to determine the inter-droplet force. At a prescribed force threshold, the cantilever position is held fixed and the stress relaxation is recorded. The raw creep data are fitted well by a double exponential function with time constants differing by at least one order of magnitude. A process involving two distinct relaxation mechanisms is indicated. In the first experiment the droplets are stabilised against coalescence by the interfacial adsorption of protein. Partial unfolding of the protein polymers, with consequent aggregation and network formation, leads to a relatively rigid and immobile structure that resists momentum transport and confers the interface with considerable elastic character. By in-situ displacement of the adsorbed protein network with much more surface active small molecule detergents, the interface can be"melted" into a mobile viscous state that propagates external flows to the droplet interior. A second creep experiment then observes a very substantial change in the stress relaxation response of the same droplets.





We conclude that the dissipation mechanisms are highly sensitive to details of the interfacial rheology. Moreover, by increasing the impact speed of the experiment the stress relaxation profile becomes oscillatory and suggest a "ringing" vibration of the droplet interface.

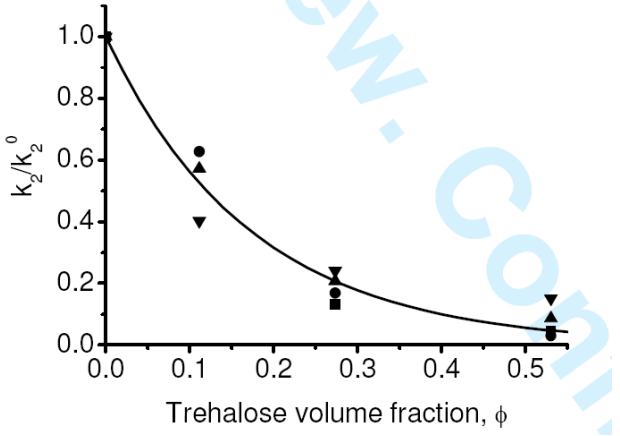
We seek a mathematical model that:

- will elucidate the mechanisms of droplet creep;
- explain the significance of interfacial rheology;
- establish the relevant relaxation time-scales with respect to the impact speed of the AFM experiment;
- clarify the role of hydrodynamic drag and adhesion effects.

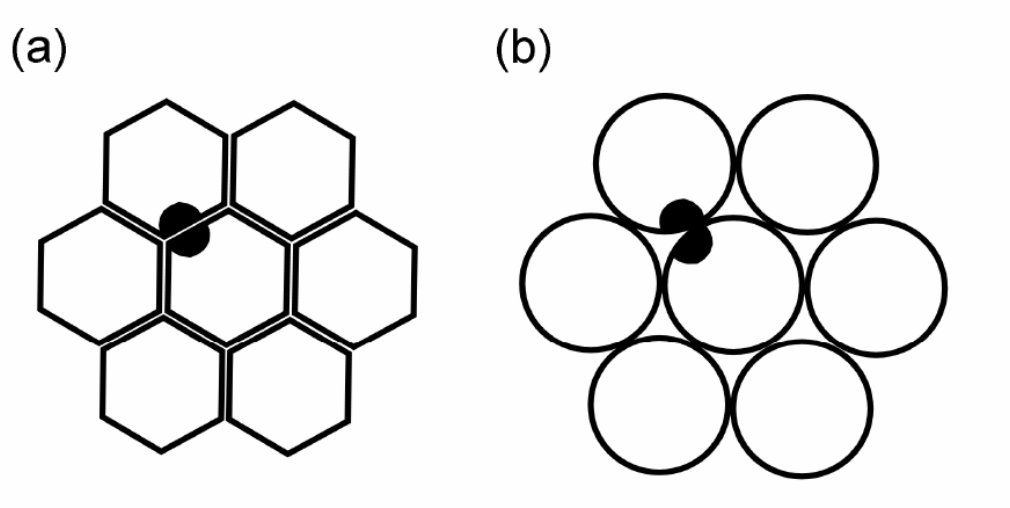
Rate dependence of glassy state aggregation on diluent concentration (Roger Parker)

At low water content, protein solutions typically solidify into glassy states. Examples include seeds, pollens, spray dried milk powders and biopharmaceutical formulations. Despite the slowing of kinetic processes in the dehydrated solid state, physical or chemical instabilities persist in the glass or near the glass transition so that thermally driven specific aggregation phenomena can continue. Moreover, on forming a solid solution with carbohydrates, the rate of protein aggregation can be modulated by the concentration of diluent and the "water substitution hypothesis" [5] can be brought under test.

From the results of a particular experiment, the figure shows the relative initial rate of aggregation as a function of diluent concentration. The effect depends on the changes in mixture structure as the carbohydrate is added.



In a two-dimensional schematic picture, we imagine the pure protein glass can be represented by a space filling structure as indicated where a single pair of localised reactive patches on two adjacent molecules is also shown. When diluent is added, the structure expands so that interstices appear between the proteins, the reactive patches are displaced and the likelihood of aggregation decreases.



With these ideas in mind, we seek a quantitative model describing a plausible mechanism that reproduces the observed trend in concentration dependence.

Boussinesq-Scriven constitutive law for Newtonian interfaces (Rob Penfold)

According to Edwards, Brenner and Wasan [6], transport processes at an interface often bear close anology to volumetric transport phenomena within bulk fluid phases. A fluid interface is not a truly two-dimensional material entity, but the experimental length scale is typically large compared with the microscopic transition zone. Therefore, a convenient idealization considers a two-dimensional singular "surface" possessing a macroscopically defined location, configuration and orientation between a pair of contiguous three-dimensinoal immiscible bulk fluid phases. At this level, phenomenological transport laws are developed to govern the response of the fluid interface and provide boundary conditions imposed upon comparabale volumetric field variables at the interface. Conventionally, the analysis proceeds simply by analogy with existing conservation and constitutive transport laws for 3D fluid continua, but making due allowance for the generally non-Euclidean "metric" nature of curved 2D domains. In this way, the linear Boussinesq constitutive expression appropriate for Newtonian interfaces directly relates the surface excess stress tensor to the surface rate of deformation tensor. The jump in the bulk phase stress vector across the interface becomes

$$-[\mathbf{s}] = \mathbf{F}^s + 2H\sigma\mathbf{n} + \nabla_s\sigma + \big(\kappa^s+\mu^s\big)\nabla_s\nabla_s\cdot\mathbf{v}^0 + 2\mu^s\mathbf{n}(\mathbf{b}-2H\mathbf{I}_s){:}\nabla_s\mathbf{v}^0 + 2H\mathbf{n}\big(\kappa^s+\mu^s\big)\nabla_s\cdot\mathbf{v}^0 + \mu^s\Big(\mathbf{n}\times\nabla_s\big((\nabla_s\times\mathbf{v}^0)\cdot\mathbf{n}\big) - 2(\mathbf{b}-2H\mathbf{I}_s)\cdot(\nabla_s\mathbf{v}^0)\cdot\mathbf{n}\Big) \quad ,$$

where we have,

$\mathbf{F}^s$	surface excess body force density vector
$\mathbf{n}$	surface normal vector
$\mathbf{v}^0$	mass averaged velocity vector at the material interface
$\bar{\sigma}$	thermodynamic interfacial tension
κ^s	interfacial dilatational viscosity
μ^s	interfacial shear viscosity
$\mathbf{I}_s = \mathbf{I} - \mathbf{nn}$	dyadic surface idemfactor
$\nabla_s = \mathbf{I}_s\cdot\mathbf{I}$	surface gradient operator
$\mathbf{b} = -\nabla_s\mathbf{n}$	surface curvature dyadic
$\sigma = \bar{\sigma} - \kappa^s\nabla_s\cdot\mathbf{v}^0$	mean interfacial tension
$H = -\frac{1}{2}\nabla_s\cdot\mathbf{n}$	mean surface curvature

Can this fearsome tensor expression be rendered in terms of undergraduate vector calculus?

References

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[6] D. A. Edwards, H. Brenner and D. T. Wasan, (1991) *Interfacial Transport Processes and Rheology*, Butterworth-Heinemann.