Description for a problem studied at the UK Mathematics-in-Medicine Study Group Keele 2012
< http://www.maths-in-medicine.org/uk/2012/colon-drug-delivery/ >

Drug delivery – Colon specific sustained release by hydrodynamic sorting: a feasibility study

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Motivation

- ☐ The efficacy of oral drug administration and patient compliance can be improved by presenting the dosage form so that:
  - a specific section of the gastro-intestinal tract (GIT) is targeted; and
  - the dose frequency is reduced.
- ☐ Novel drug delivery systems (NDDS) provide a cheaper and quicker complement to the discovery and development of new drugs by increasing the market value and competitiveness of existing medicinal compounds as well as extending their patent life.
- ☐ We are entering the era of "personalised medicine" that offers customised healthcare, both palliative and preventative, tailored to the needs of individual patients.

Background

The site-targeted delivery of drugs to the terminal ileum and large bowel has implications in a number of therapeutic areas including the topical treatment of colonic disorders such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon and irritable bowel syndrome [1]. The localised presence of specific bacterial populations in the colon and/or the increasing pH gradient along the small intestine provide suitable triggers for controlled drug release. Pharmaceutical 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 microtablets filled into capsules that disintegrate and release their charge when ingested.

Many advantages of MDU have been suggested [2,3] including:

- predictable, reproducible and short gastric residence time;
- less inter- and intra-subject variability;
- improved bioavailability;
- reduced adverse effects and increased patient comfort that supports better compliance;
- flexibility in design, with easy separation of incompatible drugs and mixing of drugs with different composition or release patterns;
- elimination of dose "dumping" and lowered risk of local GIT irritation;
- improved stability.

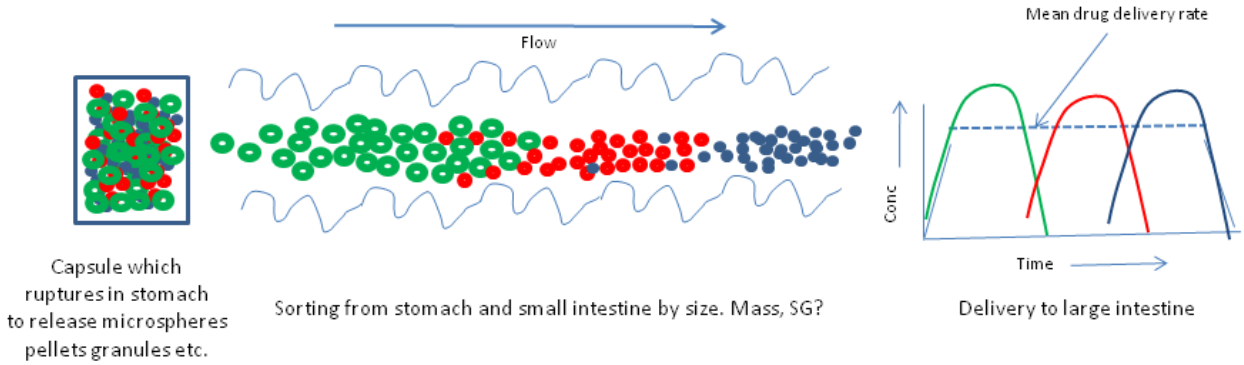
Sustained or pulsatile (impulse discharge after a pre-determined lag time) release patterns are almost invariably engineered by coating drug granules or polymer matrices with functional membranes. To date, diffusion, erosion or osmosis have been the principal physical mechanisms exploited for controlled drug delivery where, the material properties of coating layers determine rates of solvation, swelling or rupture.

The main ("wacky") idea and critical questions

We aim to evaluate the feasibility of an entirely new temporal control mechanism for MDU dosage forms: hydrodynamic sorting based on particle size, shape or mass density. Unlike con-

ventional drug delivery systems, the fundamental physical mechanism hinges on the mechanical *interaction* between the drug carrying object and the GIT fluid flow field.

- ☐ Can *hydrodynamic interactions* provide a tunable mechanism for spatio-temporal of MDU delivery vehicles in the GIT?
- ☐ If yes, then how *sensitive* is the downstream particle distribution to details of the flow field? (E.g., what distinguishes the sorting characteristics of Poiseuille flow and intermittent plug flow, say?)



A capsule ruptures in the stomach to release a population of different sized microspheres $\{\sigma_i\}$ where $i = 1, \ldots, N$ indexes 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 prescribed distribution?

An alternative delivery vehicle has been proposed where the temporal stratification is controlled by microsphere porosity. The dosage form consists of uniformly shaped and monodisperse particles, but the internal diffusion rate of the active ingredient is distributed over the population. Again, the goal is to achieve a prescribed delivery profile at the terminal ileum.

- Can the prescribed delivery profile be "inverted", via the fluid mechanical problem of the GIT flow, to predict the optimal porosity distribution for rationally engineering a dosage form of this type?

It should be emphasised that this idea runs counter to orthodoxy in pharmacy and medical practice. There is also a substantial risk of indifferent success at best and abject failure at worst. For this reason, a (cheap) preliminary mathematical modelling study is highly desirable in order to establish any feasibility in the approach before investing in much more costly experimental development.

Some starting points?

A recent MMSG (Strathclyde, 2010) considered a model of the normal human swallowing process as a precursor to analysing disorders associated with dysphagia. Although concerned with the oral cavity and the upper oesophageus, this is part of the GIT nevertheless and presents some features in common with the lower gut lumen (stomach, small intestine and colon). This earlier model may offer some footholds on the present problem.

As a preliminary attack on this inverse problem, an analysis of the forward problem has been suggested where the unsteady GIT flow is described as a 2D meandering jet. In a reference frame moving with phase speed c, a streamfunction of the following form [2] is prescribed,

$$\Psi(x,\ y) = \Psi_0 \left(1 - \tanh \left(\frac{y - y_c}{\lambda / \cos\alpha} \right) \right) + cy \quad ,$$

where Ψ_0 is a scale factor which, together with the width scale λ, determines the maximum downstream speed. The centre of the streamline is defined by,

$$y_c = y_c(x) = A \sin(kx) \quad ,$$

with wave amplitude A and,

$$\alpha = \arctan\big(Ak\cos(kx)\big) \quad ,$$

is the direction of the current. The first task is to determine the spatio-temporal stratification that arises downstream from a prescribed initial distribution of particles localised upstream. The particle motions will be subject to viscous drag and hydrodynamic interactions. Owing to the ubiquity of multiphase flow processes in industrial units, there is a vast chemical engineering literature on fluid flows through stationary or moving particle beds. For example, Cello et al. [3] have developed a semi-empirical model for the drag force and fluid-particle interaction in polydisperse suspensions that may provide useful data for the forward problem. Greenspan and Nigam [4] have also reported a quantitative study on the substantial particle segregation (radially and axially) that occurs in a bimodal mixture undergoing pipe flow, provided the size disparity is large. Some relevant data from experimental studies of gastric emptying may be found in the references [5]–[9].

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