Overview: Development of a Multiparticulate-based Formulation Platform for Delivering Functionalised Capability as an Oral Liquid Dosage Form

Alexandra Bowles[1], Isra Al-Haddad[1], Shivani Manghani[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

Children are not small adults is a commonly quoted adage: nowhere is this more true that in the field of pharmaceutics. When trying to make an "age appropriate" oral dosage form, a number of patient needs must be met including swallowability, dose adaptability and acceptability. Acceptability may be enhanced by many things including reduced dosing frequency or better tasting/non-gritty medicines. It is this this in mind that this project attempts to make functionalised (taste-masked or modified release) microspheres by aqueous spray drying to be administered in a suspension fomulation

AIMS

1. To investigate the influence of particle size characteristics and suspending media viscosity on the suspendability of particles and grittiness/ acceptability of the resulting suspension
2. To make functionalized (e.g. modified release or taste-masked) multiparticulates and suspensions
3. To optimise the method of production by investigating the effect of different operating parameters/excipients on the multiparticulates and hence suspensions
4. To investigate the effect of different drugs (of a variety of physicochemical properties) added to the suspension to try to make a universal suspension

IDEAL PRODUCT SPECIFICATION

Criteria	Minimum	Upside	Downside
Particle Stability	5 days in liquid	1 month + in liquid	Powder for recon
Particle size/shape	Not gritty/spherical	-	Slightly gritty/big
Drug Loading	Polymer:Drug 1:5	Drug>Polymer	Polymer:Drug 10:1
Density	Self suspending	Disperses any media	Redisperses easily
Release	Taste Masking	MR for any drug	Only immediate
Industrial Needs	50% Yield	100%	30% (other specs met)
	No/minimal organic solvents, low cost, reproducible & scaleup-able		

PREVIOUS WORK

SPRAY DRYING

Eudragit ®E PO (a reverse enteric polymer soluble below pH 5 but not in the higher pH of the buccal cavity) was used to try to make taste masked particles containing quinine/quinine hydrochloride dihydrate (QHD) by aqueous spray drying with composition as seen in Table X (all at the minimum levels) and [solids] of 4% w/v (conditions shown below)

Table 2: Conditions/Parameters of Spray Drying Experiments

Condition	Parameters
Initial	Niro SD Micro Dryer with inlet temperature 110°C, atomising air flow (AAF) set at 2.5kg/h (feed rate: 5ml/min), chamber inlet flow (CIF) 25kg/h) with feed homogenised for 30mins at 100rpm
Increased Homogenisation	Same as above but with homogenisation at 1000rpm (with 5s at 3000rpm for surface encompassation)
Increased temp/flow	Same as above with inlet 140°C, AAF 3kg/h, CIF 30kg/h
Buchi B191 Dryer	Different spray dryer with inlet temperature 140°C, aspirator setting 90% and pump setting 20-35%

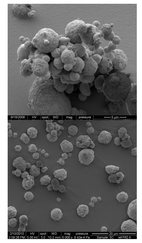


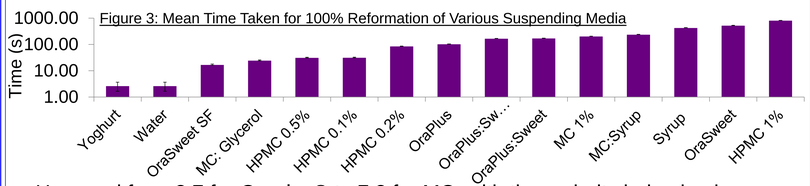
Figure 1: SEM Images of Spray Dried Eudragit® EPO with (top) quinine base made initially and quinine hydrochloride dihydrate made using increased homogenization

It was found the initial conditions produced large aggregates and increasing homogenisation improved this as seen in Figure 1. Smaller particles were formed by increased temp/flow (X90<20µm) and aggregates formed using the Buchi. All microparticles had a very low drug loading and encapsulation efficiency (range: 1.6-2.6% and 10.11-12.3% for drug loading for quinine and the quinine salt particles respectively; 7.1-11.9% and 45.8-55.2% for encapsulation efficiency) while all the drug was released within five minutes in simulated gastric or salivary fluid.

SUSPENDING MEDIA CHARACTERISATION

Rheology (viscosity flow curve, step test with a shear rate of 1 1/s for 60s followed by 1000 1/s for 60s then 20 minutes of recovery time and a yield stress analysis) and pH measurements were carried out on commonly used suspending media (Figure 2).

- MC/HPMC 0.1, 1 and 3% solutions covered the range of viscosities of commonly used suspending vehicles so were used for suspendability/grittiness tests
- Most suspending media (except glycerol) exhibited shear thinning behaviour
- Most commercial yield strengths are low (shown by Figure 2) & time to reformation ranged from a few seconds (shown in Figure 3) to > 20minutes for HPMC/MC > 3%



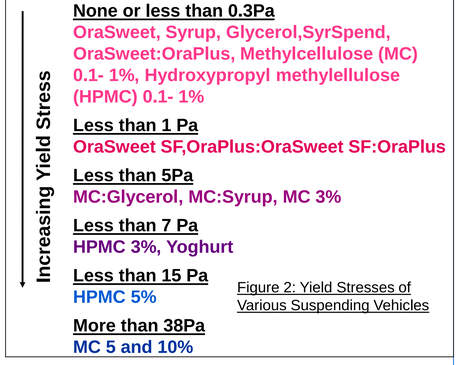


Figure 2: Yield Stresses of Various Suspending Vehicles

- pH ranged from 3.7 for Oraplus® to 7.3 for MC, with the majority being basic
- When microcrystalline cellulose pellets (Cellets® 100-100µm) were suspended in MC/HPMC 0.5-3% solutions, smaller particles/more viscous suspending media caused slower sedimentation as expected but dispersibility was difficult

GRITTINESS AND ACCEPTABILITY

10 males and 10 females (18-24yo) each orally rinsed 10ml of 27 samples (plus +/-ve controls)
Each sample had one of three levels of: viscosity (unflavoured HPMC 0.1, 1 or 3%), Cellets® sizes (100, 200 or 500 µm) & particle concentrations (5, 100 or 500mg/5ml)
Grittiness scores were marked on a bipolar scale/2 most acceptable formulations recorded

- Increasing particle size or concentration significantly increased grittiness scores (Figure 4)
- No correlation was found between grittiness scores and acceptability (Table 3/Figure 4)
- Viscosity was not found to have a clear effect on grittiness and the thicker vehicle was not well tolerated despite reducing grittiness scores.

Table 3:Five "Most Pleasant" Formulations with their Composition/ Grittiness

Rank	Frequency (/20)	[HPMC] (%)	Size (µm)	[Particles] (mg/5ml)	Grittiness (Mean±SD)
1	14	1	500	5	36.5±35.8
2	13	1	100	5	12.2±11.5
3	11	0.1	100	5	12.6±11.1
4	6	1	200	5	21.6±19.4
5	5	0.1	500	5	11.1±10.6

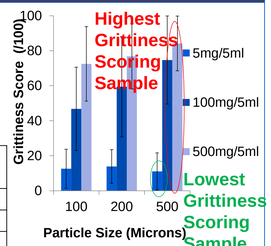


Figure 4: Mean Grittiness Scores (±SD) for all Different Particle sizes/ concentrations in HPMC 0.1%

CURRENT WORK

SPRAY DRYING

Different levels of excipients were investigated in an attempt to improve the low encapsulation efficiencies (EE)/release retardation at pH 6.8 using a central composite face centred design of 16 experiments with 3 midpoints to screen for the effect of the different levels as shown in Table 1.

Following initial scoping work on spray drying parameters using the middle formulation (shown in yellow in Table 1), it was found the maximum solids concentration and feed rate which could be achieved were 5%w/v and 5ml/min respectively at inlet temperature of 140°C on a Buchi B191.

The effect of the excipients on yield, encapsulation efficiency, drug release at pH 1.2/6.8, particle size and density is in the process of being identified with a view to optimising EE and minimising drug release at pH 6.8

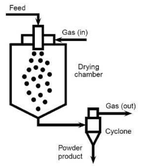


Table 1: Table showing the order/composition of spray drying suspensions (with red, yellow and green showing maximum, middle and minimum levels respectively)

Run	Eudragit® E PO	Sodium dodecyl sulphate	Stearic acid	Aerosil® 200 (Colloidal Silica)	Polyethylene glycol 400
	(x QHD)	(% Polymer)	(% Polymer)	(% Polymer)	(% Polymer)
1	3.75	30	32.5	75	30
2	3.75	30	32.5	75	30
3	5	10	50	100	20
4	2	10	50	100	10
5	2	50	50	100	10
6	2	10	50	100	50
7	2	50	15	100	50
8	2	10	15	50	10
9	5	50	50	50	50
10	5	50	50	100	50
11	2	50	15	50	50
12	5	50	15	100	50
13	2	10	50	50	10
14	5	10	15	100	10
15	5	10	50	50	10
16	2	50	50	50	50
17	5	50	15	50	50
18	5	10	15	50	10
19	3.75	30	32.5	75	30

SUSPENDING MEDIA CHARACTERISATION

- Osmolarity
- Surface Tension
- More Rheology
  - Time to reformation at a range of shear rates (10-100s^{-1})
  - Oscillation

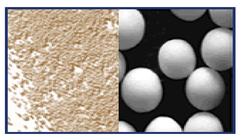
GRITTINESS AND ACCEPTABILITY

Similar to previous trial with the following amendments to reduce the variables to make them more like in use suspensions, improve acceptability and to reduce the Std Dev :

- Particle size range narrowed (90, 127, 263µm)
- [Particle] range narrowed (15mg, 250mg, 500mg/5ml)
- [HPMC] range narrowed (0.5, 1, 2%)
- Sucralose & Permaseal Orange Juice Flavour added
- Sample size increased to 30 subjects

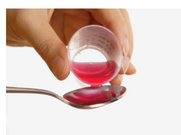
FUTURE WORK

Different Taste Masking Polymers



pH sensitive/Release controlling Polymers

Different Drugs



Particles intro Suspending Media