Taste Masked Artesunate/Amodiaquine Micropellets in the Fight Against Malaria

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Malaria & Treatment Challenges

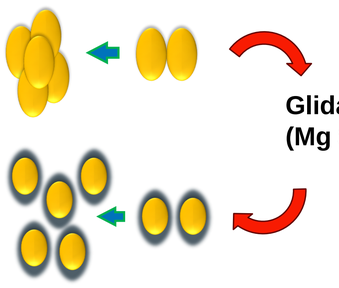
Children aged under 5 years are the worst affected by malaria, causing about 10 % of all children's deaths in regions where malaria is endemic[1]. Fixed dose combination (FDC) of Artesunate (AS) and Amodiaquine (AQ), are recommended by the WHO for malaria treatment. Currently AS/AQ is only available as bilayer tablets which are crushed for paediatric administration causing noncompliance due to the bitter taste of AQ. The aim of this work is to develop a FDC of AS/AQ taste masked micropellets (diameter <250 µm) with improved palatability and mouthfeel for oral administration in young children. The manufacturing of effectively taste masked micropellets is facilitated using the **MicroCoat™** technology.

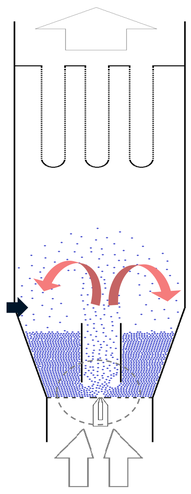
MicroCoat™ Technology

What is MicroCoat™ Technology?

Drug is layered on MCC microspheres (Cellets®,100-200 µm) in a fluidized bed coater where dry powder glidant is added into coating chamber by external feeding port to eliminate agglomeration.

- Reducing inter-particular cohesive forces
- "in-situ" stabilization of coating process
- Reducing agglomeration/aggregation
- Significantly increasing production yield
- Increasing spray rate





AQ

Drug loading

Taste masking coating

AQ layer

Taste Mask Coating

(77.5/22.5 Ethocel/Methocel™ E5)

AS

Drug loading/seal coating

Microcrystalline cellulose

(Cellets 100)

Seal Coating

(PVP K30)

AS layer

AS/AQ Fixed Dose Combination

Application in Lab and Pilot Scales

MiniGlatt

Batch Size:50-100g

GPCG2

Batch Size:1-2 Kg

MiniGlatt Outcome	AS Loading/ seal coating	AQ Loading	AQ TM Coating
Agglomeration Acceptable limit < 5 %	2.3	1.9	0.30
Yield Acceptable limit > 95 %	97.7	98.1	99.70
Average particle size Acceptable limit < 250 µm	179.31±2.48	180 - 250	225.4±1.18

GPCG2 Outcome	AS Loading/ Seal Coating	AQ Loading	AQ TM Coating
Agglomeration Acceptable limit < 5 %	3.86	0.27	0.77
Yield Acceptable limit > 95 %	95.86	88.93	100.15
Average particle size Acceptable limit < 250 µm	200.51±1.07	209.85±0.39	224.30±0.48

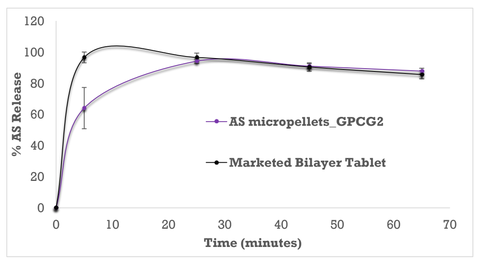
Final Product Evaluation

Drug Release

Sotax Dissolution USP1 Apparatus (#150 baskets), 900 mL acetate buffer pH 5.5, 100 rpm and 37 °C

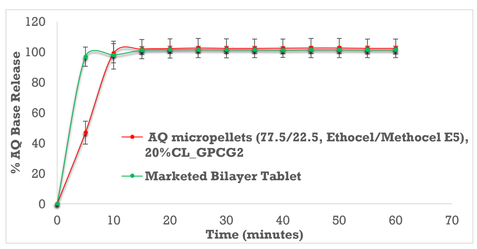
AS

HPLC analysis



AQ

UV analysis

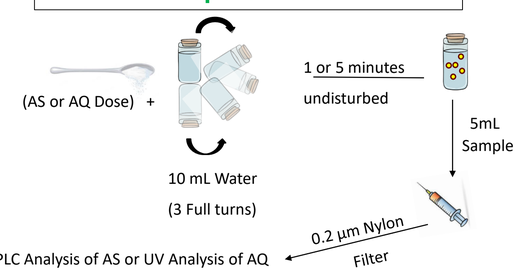


Release profiles of AS micropellets and AQ micropellets from GPCG2 in comparison to marketed AS/AQ bi-layer tablets.

Taste Assessment

In Vitro

Dispersal test



AQ and AS micropellets (GPCG2) *in vitro* dispersal results vs *in vivo* bitterness threshold

Time (min)	Concentration (mg/mL)	
	AQ Micropellets	AS Micropellets
1	0.0005±0.000	0.117±0.010
5	0.088±0.033	0.148±0.001
Bitterness Threshold	0.0069	0.15

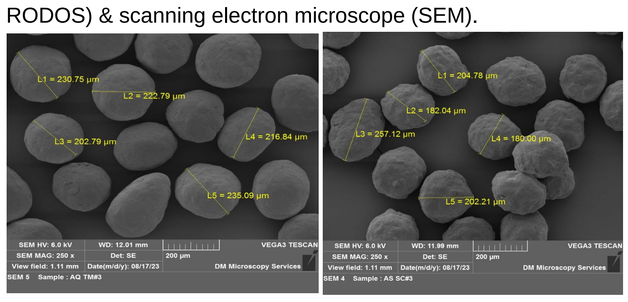
In Vivo

Taste Assessment

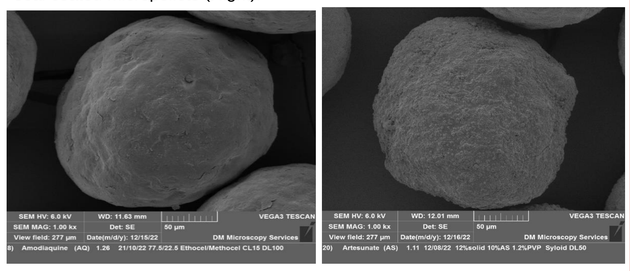
Taste aversiveness and bitterness taste detection thresholds for AS and AQ were established using a human adult panel (n=29 &15 respectively) and swirl and spit method [2,3] after ethics approval (UCL REC (4612/030) & WHO ERC (ERC.0003733).

Particle size and Morphology

Particle size was measured using laser diffraction (HELOS-RODOS) & scanning electron microscope (SEM).



SEM images of GPCG2 manufactured pellets: AQTM micropellets (Left) and AS seal coated micropellets (Right).



SEM images of MiniGlatt manufactured pellets: AQTM micropellets (Left) and AS seal coated micropellets (Right).

Excipient Safety Evaluation

Total excipients intake was calculated at two dose strengths: 25 mg/67.5 mg and 50 mg/135 mg (AS/AQ) for use in children 4.5 kg to <18 kg, corresponding to (2 months-5 years). Excipients safety profiles were evaluated against the "Generally Regarded as Safe" (GRAS), "Safety and Toxicity of Excipients for Paediatrics" (STEP) and "FDA Inactive Ingredient" databases. No excipient safety concerns were raised following the evaluation process to be used in the target population.

Conclusions

An effective taste masked coating was successfully applied on drug loaded micropellets using MicroCoat™ technology on both laboratory and pilot scale giving an acceptable paediatric ASAQ FDC product which can improve adherence of anti-malarial treatments in children under 5 years. The final formulation will be further assessed by acceptability and biorelevant dissolution studies.

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