

## THE EFFECT OF FOOD ON THE DISINTEGRATION TIME AND DISSOLUTION PROFILE OF ARTEMETHER-LUMEFANTRINE TABLET

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### Abstract

This study aimed at comparing the release rate of artemether-lumefantrine tablets through artemether release in the presence of simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and food modified simulated gastric fluid (FMSGF) and intestinal fluid (FMSIF). Various quality control parameters including weight uniformity, tablet hardness, disintegration, friability and assay were assessed. SGF and SIF were employed as disintegration and dissolution media and compared with a food (1.3 ml full cream unsweetened evaporated milk, 2.67mg soluble starch) modified SIF and SGF (FMSIF and FMSGF) at  $37 \pm 0.5^\circ\text{C}$ . The product assessed complied with the official specification for uniformity of weight friability and assay. The titrimetric and spectrophotometric assays gave 97.45% and 103.25% of artemether content respectively ( $P < 0.05$ ). No significant differences were observed between the disintegration time for FMSGF and SGF (5.0min and 5.5min) for SIF and FMSIF (7.5min and 6.5min) respectively. There was significant difference in the percentage drug release in FMSGF compared to SGF (35% v 58%) but no significant difference in the release rate for media simulating dosing conditions in the intestine, FMSIF and SIF (28% v 29%) respectively at  $P < 0.05$ . Artemether-lumefantrine is well absorbed in the stomach and in the fasted state dosing condition.

**Keywords:** Artemether- lumefantrine, food effect, simulated fluid

### 1. Introduction

Malaria is by far the world's most important tropical disease which has claimed many lives including pregnant women and newly born children. ACT (artemisinin based combination therapy) is now accepted as the best treatment for uncomplicated falciparum malaria<sup>1</sup>. Drug permeability in the gastrointestinal tracts and drug absorption after oral administration of solid dosage forms (tablets or capsules) depend largely on the release of the drug substance from the drug product after dissolution<sup>2</sup>. Solubilization and the release of drug are critical to drug absorption therefore in vitro drug dissolution is therefore predictive of in vivo performance<sup>3-5</sup>. Drugs are taken with food to limit the gastrointestinal irritations that may ensue hence the study of possible food-drug interaction. Drug interaction with food and beverages are known to occur, exemplified by the well known interaction between monoamine oxidase inhibitor (MAOI) antidepressant and tyramine containing foods<sup>6</sup>. After oral administration of drugs, the drugs rapidly reach the stomach and depending on the state of fill of the stomach (i.e. empty or presence of food), there is rapid or delayed emptying of the content into the duodenum. Food effects are not always

predictable as some food increase the overall absorption while others decrease it<sup>7-9</sup>. Unpredictable food effects on the absorption of antimalarial drugs may be responsible for resistance development and treatment failure. As part of the drive to develop predictive in-vitro models to forecast the in-vivo performance of malaria drug products when taken with food or on empty stomach (lack of appetite), hence food modified simulated intestinal and gastric fluids are proposed<sup>10-12</sup>. The studies of meal digestion have been demonstrated to enhance the solubility of poorly lipophilic drugs<sup>13-15</sup>. This study evaluates the in-vitro predictiveness of the in-vivo dissolution profile of artemether-lumefantrine fixed dose composition in the fed state especially with food composition typified by food consumed in tropical African setting.

### 2. Materials and method

**2.1. Materials:** Hydrochloric acid, sodium hydroxide, ethanol were products of BON Chemicals Limited England and monobasic phosphate products of Kernel Chemicals, UK.

#### *Prepared reagents*

**Simulated intestinal fluid:** 40g of sodium hydroxide and 34g of monobasic potassium were added to 2L of distilled water and the

volume made up to 5L mark in a volumetric flask. The resulting pH was 7.32<sup>16</sup>.

**Simulated gastric fluid:** 43ml of concentrated hydrochloric acid was added to 2L of distilled water in a volumetric flask. This was followed with 500ml of 20% sodium chloride solution and the final volume made up to 5L mark. The resulting pH was 1.13<sup>16</sup>.

**Food modified SGF and SIF (FMSGF and FMSIF):** Food modified SGF and SIF were prepared by adding 100ml of peak milk and 25mg of soluble starch with 500ml of SGF and 300ml of SIF respectively rotating basket.

## 2.2 Method

**Tablet hardness:** Ten tablets were randomly taken from the drug and placed on the edge of the tester and subjected to crushing strength of the tester.

**Friability test:** Twenty tablets were weighed and subjected to abrasion using a Veego tablet friability tester a 25 rev/min.

**Uniformity of weight:** Ten tablets were taken from the A-L brand and weighed individually. The mean and percentage deviation was determined.

**Disintegration time:** Six tablets were placed in the tubes. The end of the tubes were lowered and raised in a bath of SIF and SGF maintained at  $37 \pm 1^\circ\text{C}$ . The time when no drug particle was found on the screen was noted and recorded. This was repeated for the FMSIF and FMSG.

**Calibration curve and extraction:** Stock solution of the pure sample of artemether powder was prepared. 5ml was taken from the stock and serial dilutions made with distilled water. The absorbances of the resulting solutions were read using a UV-VIS spectrophotometer at 245nm.

**Assay:** Twenty tablets of the innovator drug were weighed and powdered. 260g equivalent to 13g of artemether was accurately weighed and transferred into a 100ml volumetric flask. 50ml of 100% ethanol was added and shaken up vigorously for 15 minutes. The solution was filtered and 10ml of the filtrate was accurately measured into a 50ml volumetric flask and made up to mark. The flask was stopped and placed in a water bath at  $55^\circ\text{C}$  for 1 hour. A blank was similarly treated and used to adjust the spectrophotometer to zero calibration. The determination was done in triplicate and the percentage content of the drug calculated.

**Dissolution test:** 5ml of the dissolution medium was sampled at 0, 5, 10, 20, 30, 60, 90, and 120 min with replacement of 5ml of fresh dissolution medium for every withdrawal.

## 3. Result

The details of the drug used in the study are expressed in Table 1. The physicochemical analysis of the artemether-lumefantrine brand is presented in Table 2. The regression equation for the calibration curve plotted was  $y=3.67x+0.0982$ ;  $R^2=0.9915$

The comparative percentage release of the drug in the different simulated media is outlined in Fig 1. Disintegration and dissolution profile of the drug are presented in Table 3.

**Table 1: The details of the drug used in the study.**

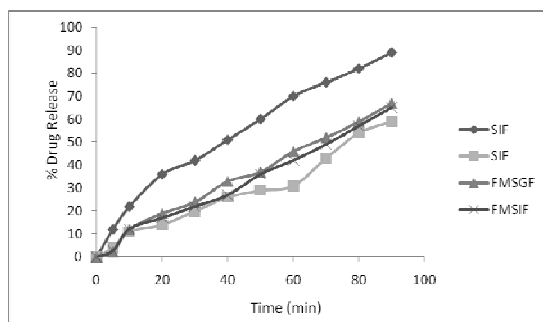
Brand name	Coartem
Manufacturer's name	Novartis
Country of origin	China
Batch number	F1861
Registration number	04-3275
Manufacturing date	02-2010
Expiry date	01-2012

**Table 2: Physicochemical analysis of the tablet**

Physicochemical parameters of the drug				
Friability (%)	Crushing Strength (Kg/cm <sup>2</sup> )	Weight Uniformity (g)	Chemical content determination (%w/w)	
0.083± 0.001	5.28 ± 0.02	0.259± 0.002	Back titration	Spectrophotometry
			97.45 ±0.03	103.25 ±0.05

**Table 3: Disintegration time and Dissolution indices of chlorpromazine hydrochloride tablet in the various media**

Disintegration time and dissolution C <sub>45</sub> in the media							
Disintegration time (min)				C <sub>45</sub> values (%) from dissolution profile			
SGF	SIF	FMSGF	FMSIF	SGF	SIF	FMSGF	FMSIF
5.0±0.1	7.5±0.2	5.5 ±1.5	6.5±0.2	58	28	35	29



**Fig 1: The dissolution profile of the tablet in the various dissolution media**

#### 4. Discussion

The selected brand complied with compendia specification for the physicochemical parameters assessed in the study<sup>17</sup>. The conformity status of the chosen brand is an indication that all about the performance of the drug is dependent on some variables other than the pharmaceutical or manufacturing factors. An important area worthy of note is the dosing condition of drugs. For the successful prediction of in-vivo drug behaviour, the dissolution media and its composition is important<sup>18</sup>. The SIF and SGF were therefore used to predict the fasting dosing condition for the tablet administration. In the fed state, starch and milk were introduced into the SIF and SGF to mimic the typical composition of an average African diet. The volume of 300 and 500ml were used for fluid volume in the fasted and fed states respectively. The higher volume for fed state reasonably pictures the fluid volume of the ingested meal and the fluid intake after meal. Milk (low protein and moderate fat) has been considered for medium design because of its ratio of carbohydrate-protein-fat similar to that observed in the stomach after meals<sup>18</sup>. The physicochemical properties of the tablet agreed with the pharmacopoeia specifications hence the basis for the reliability of the disintegration time and dissolution outcome. The chemical content determination of artemether content using the titrimetric and spectrophotometric methods gave values that had positive linear relationship. The likelihood of interference by the presence of the food particles may however give misleading results with titrimetry, if this method was used to evaluate the drug release<sup>19</sup>. The analysis might be cumbersome if blanks containing the food particles were designed to correct for errors due to food particle interference and to standardize the determinations. Therefore, the spectrophotometric method was used to evaluate the drug release. The drug release observed in

the SGF and FMSGF were observed to be higher than in SIF and FMSIF. Artemether-lumefantrine drug combination is lipophilic and the artemether release may not significantly differ from what can be obtained for lumefantrine if the release rate were followed using lumefantrine. The fixed dose antimalaria is presented with artemether and lumefantrine occurring in ratio 1:4. Ionizable drugs dissolves faster in aqueous medium and present a higher dissolution profile than oily drugs which occurs in molecular form and require an oily medium for substantial dissolution, which the type of food taken can determine<sup>20</sup>. African diet is essentially high in oil and carbohydrate content hence the simulated media featured evaporated milk which contains fat and oil in emulsified state. The rate of dissolution of the tablet was expected to be higher in the SIF than SGF and similarly the FMSIF than FMSGF due to the larger volume available for solubilization. This was expected in the in-vivo condition where the bile acids were present as solubilizing agents. The experimental design however did not include the addition of bile acids<sup>21</sup>. In this work, the release rate of artemether in the fasting and fed dosing conditions was lower than the pharmacopoeia standard indicating not less than 70% in 45 minutes. This therefore predicts the performance of the drug in the light of the war against malaria parasite where an appreciable amount of the drug is required to achieve a clinical or radical cure. Malaria recrudescence or resistance thus can be traceable to inadequate drug release characteristics.

#### Conclusion

The determination of the drug release rate with respect to the dosing conditions for all the antimalaria drug formulations in clinical use is expedient towards the actualization of global victory over established erythrocytic and exo-erythrocytic stages of *Plasmodium* spp.

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