

## FORMULATION AND EVALUATION OF A COMBINED CHLOROQUINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE PRODUCT

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### ABSTRACT

Chloroquine phosphate granules (B1) and chlorpheniramine maleate granules (B2) were separately formulated with maize starch and lactose with polyvinylpyrrolidone (10% w/v) as binder. B1 was coated with 5% w/v ethylcellulose to varying degrees by increasing the spray time of the coating solution by 2 minutes between successive batches to produce B1A, B1B, B1C, B1D, B1E, B1F, B1G, B1H and B1I of increasing coat thickness. B2 was not coated. The release profiles of the coated and uncoated granules were studied using the US Pharmacopoeia XXIV (2000) dissolution apparatus II. The release profiles showed a significant and progressive retardation of the release of chloroquine phosphate from B1A to B1I as the coating time was increased. Batch B1I which gave the most desired release profile was selected and combined with the chlorpheniramine maleate granules, encapsulated and the release profiles studied. Each capsule contained granules equivalent to 4mg chlorpheniramine maleate (uncoated) and 250mg chloroquine phosphate (coated). Almost all the chlorpheniramine (97.4%) in the combined product (capsule) was released in 35 min while only about a quarter (24.4%) of the chloroquine component was released in the same period. The combined formulation appears to possess the ability to protect susceptible patients from chloroquine-induced itching by releasing a greater amount of the antihistamine before the chloroquine is released.

**Keywords:** Chloroquine phosphate; Chlorpheniramine maleate; Wet granulation method; Coated granules; Drug release profiles

### INTRODUCTION

Even though Artemisinin-based Combination Therapy is currently the drug combination of choice for the treatment of malaria (Purcell,

2004), chloroquine continues to enjoy a high patronage for the prophylaxis and treatment of uncomplicated malaria in Ghana and other African countries (Erah *et al.*, 2003; WHO, 2005). The dominance of chloroquine stems from the fact that it remains the cheapest drug in terms of treatment cost and has relatively fewer side effects.

The use of chloroquine in the global fight against malaria is however diminishing as a result of the emergence of resistant strains of *Plasmodium falciparum* (Mohamva et al., 1996; Mharakurwa et al., 1998; Mockenhaupt et al., 2000). Allergic reactions to chloroquine such as itching or pruritus contribute to poor compliance or treatment defaulting (Mayinka and Kihamia, 1991; Bussaratid et al., 2000; Sowunmi et al., 2000), which can give rise to the development of drug resistance. A high proportion of patients develop itching within 24 hours of ingestion of chloroquine (Bussaratid et al., 2000; Davis et al., 2004; Fehintola et al., 2004) and the defaulting rate attributable to chloroquine-induced pruritus is very high (Ajayi et al., 1998; Ademowo and Sodeinde, 2002; Fehintola et al., 2002, 2004).

Antihistamines are commonly used to prevent or resolve allergic disorders. This approach requires the initial administration of the antihistamine to allow the drug molecules to occupy the histaminic receptors before chloroquine is administered. However, the low level of literacy and lack of adequate education to patients makes compliance with this dosage regimen difficult. While some patients take the two drugs concurrently others take chloroquine before the antihistamine thereby predisposing susceptible individuals to chloroquine-induced itching.

One possible approach at resolving the problem of chloroquine-induced itching is to develop an appropriate dosage form which would contain both chloroquine and an antihistaminic agent and would possess the requisite drug release profiles. This study aims at the development of an encapsulated dosage form containing chloroquine and chlorpheniramine, a common antihistamine, which would allow the release of a sufficient amount of the antihistamine to occur in a suitable time period before the chloroquine component is fully released. Such a dosage form will improve patient compliance and enhance therapeutic success, especially in susceptible patients.

## MATERIALS AND METHODS

### Materials

Chloroquine phosphate BP powder, chlorpheniramine maleate BP powder and polyvinylpyrrolidone (PVP) were supplied by UK chemicals Ltd. (Kumasi, Ghana). Ethylcellulose Ph. Eur. was produced by Pacegrove Medical and Pharmaceutical Chemical (England) and was used as received. All other chemicals used were of analytical reagent grade.

### Formation of granules

Granules of chloroquine phosphate (380g) and chlorpheniramine maleate (100g) were individually formulated using the wet granulation method (Summers, 1995). Chloroquine phosphate granules consisted of chloroquine phosphate (67.4% w/w), maize starch (5.5% w/w) and lactose (27.1% w/w) while chlorpheniramine maleate granules consisted of chlorpheniramine maleate (4.7% w/w), maize starch (5.7% w/w) and lactose (89.6% w/w). The powders for the two formulations were separately massed with 10% w/v PVP in a porcelain mortar and mixed. The wet mass of the formulations were screened using a 1.18 mm sieve and dried at 60°C for 1 hour in a hot air oven. The dry granules were again screened through sieve size 1.18 mm. The dry screened granules of the chloroquine phosphate formulation were re-screened using sieve size 850µm.

### Dissolution of uncoated granules

Dissolution studies on the dry, uncoated granules of chloroquine phosphate and chlorpheniramine maleate were carried out with the use of the US Pharmacopoeia XXIV (2000) dissolution apparatus II (paddle method). Granules of chlorpheniramine maleate and chloroquine phosphate equivalent to 4mg chlorpheniramine and 250mg chloroquine respectively, were used.

The experimental conditions used were as follows:

**Medium:**

- 900ml distilled water for chloroquine phosphate granules
- 500ml distilled water for chlorpheniramine maleate granules

**Paddle speed:**

- 100 rpm for chloroquine phosphate granules
- 50 rpm for chlorpheniramine maleate granules

**Sampling times:**

5, 20, 35, 50, 65, 85 and 125 min

**Temperature:**

37 ± 0.5°C

**Wavelength of absorption:**

- 343nm for chloroquine phosphate granules
- 245nm for chlorpheniramine maleate granules

At the specified time intervals, 10 ml samples of the dissolution media were taken and replaced with fresh media. The collected samples were filtered and the amount of the respective drugs in the dissolution medium determined spectroscopically (Spectronic 21D single beam spectrophotometer, Milton Roy, UK) at the specified wavelengths with the use of regression data obtained from calibration plots of chloroquine phosphate ( $R^2 = 0.9997$ ) and chlorpheniramine maleate ( $R^2 = 0.9992$ ) in distilled water. From the data obtained, plots of the percentage of the drugs released from the granules (mean ± SD.,  $n = 6$ ) versus time were made.

**Coating of granules and capsule formation**

Chloroquine phosphate granules (100g) were weighed and introduced into the pan of a Manesty tablet coater fitted with a sprayer (Manesty Ltd., England) rotating at a speed of 30 revs/min. The exhaust for dry air was turned on and the temperature of the set up was allowed to reach 60 °C. The nozzle of the pumping device was directed at the centre of the rotating disc and a 5% w/v ethylcellulose coating solution was applied onto the granules continuously

over a period of 1 minute. The granules were stirred while drying continued to prevent gross agglomeration. The process was repeated after 5 minutes drying period to complete one cycle. The coated granules were weighed and sifted through sieve size 1700µm to remove larger particles, and sifted through sieve size 850µm to remove finer particles. This procedure was used for all the batches produced i.e., B1A, B1B, B1C, B1D, B1E, B1F, B1G, B1H, and B1I by increasing the spray time by 2 minutes between successive formulations (Table 1). Other process parameters used to coat the granules were: spray rate of pump (15 ± 2 ml/min); temperature of drying air (60 °C); spray time (2 min/complete cycle).

Granules of chlorpheniramine maleate (uncoated) and chloroquine phosphate (coated) equivalent to 4mg chlorpheniramine and 250mg chloroquine respectively, were weighed, mixed and packed into gelatine capsule size 00 and sealed.

**Dissolution of coated and encapsulated granules**

Studies on the dissolution of the coated chloroquine phosphate granules as well as the encapsulated combined formulation were carried out with the use of the US Pharmacopoeia XXIV (2000) dissolution apparatus II (paddle method). Experimental conditions used were: 900 ml distilled water; 100 rpm paddle speed; and temperature of 37 ± 0.5°C.

**Statistical analysis**

Statistical analysis (ANOVA) was carried out on the data obtained using GraphPad Prism version 4.03 for Windows (GraphPad Software, San Diego California, USA). P-values of <0.05 were considered to be significant.

**RESULTS AND DISCUSSION**

The use of antihistamines such as chlorpheniramine maleate, mepyramine maleate and promethazine hydrochloride in the management

of chloroquine-induced pruritis is well documented in the literature (Okor, 1990; Davis *et al.*, 2004; Fehintola *et al.*, 2004); even though their effectiveness have also been questioned (Adebayo *et al.*, 1997). Chlorpheniramine maleate was selected as antihistamine of choice for the current study as it is commonly used to reduce or prevent chloroquine-induced pruritis (Fehintola *et al.*, 2004). Also, it has similar absorption profiles as chloroquine phosphate.

Figures 1 and 2 show the drug release profiles for the uncoated chloroquine phosphate and chlorpheniramine maleate granules, respectively.

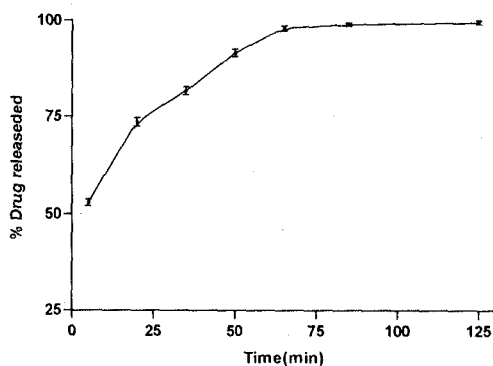


Fig. 1: Release of Chloroquine from uncoated Chloroquine phosphate granules (mean  $\pm$  S.D., n = 6)

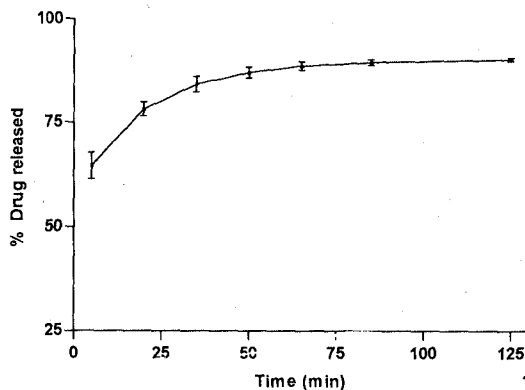


Fig. 2: Release of Chlorpheniramine from uncoated Chlorpheniramine maleate granules (mean  $\pm$  S.D., n = 6)

The dissolution profiles of the two formulations were similar and this appears to support the fact that the two drugs have similar absorption profiles. The release profiles showed rapid release of the drugs from the uncoated granules. At 5 minutes, there was a 53.0% and 63.2% release of chloroquine and chlorpheniramine respectively, while at 35 min the amount of drug released was 81.7% and 88.4% of chloroquine and chlorpheniramine respectively. The rapid rate of release is particularly important for chlorpheniramine which is expected to release the antihistaminic agent ahead of the chloroquine component when combined into a single dosage form. The rapid release of the chloroquine component could, however, enhance its side effects. There is therefore the need to modify the release of chloroquine by coating the granules with an appropriate polymeric material. Ethylcellulose, a safe, versatile polymer that is normally used to control the rate of release of drugs and for coating solid dosage forms, was selected as the coating material. A 5% w/v aqueous ethylcellulose possessed the requisite wetting and rheological properties required to achieve optimal coating of the granules. It is expected that the coated granules would release the drug as rapidly as possible once the coating becomes penetrated or ruptured (Bidah *et al.*, 1991) in order not to delay further the absorption and onset of action of the drug.

Figure 3 shows the release profiles of the coated chloroquine phosphate granules. Nine batches of coated chloroquine phosphate granules (BIA to BII) were produced by increasing the spray time by 2 min between successive batches. Generally, there was a reduction in the percentage of drug released as the spray time was increased (Table 1). An increase in spray time leads to an increase in coat thickness and the thicker the coating, the lower the rate of drug release. A thick coating will increase the diffusion path length and result in a decrease in drug release. Drug release from the coated granules is likely to include drug diffusion through the ruptured or eroded coating or

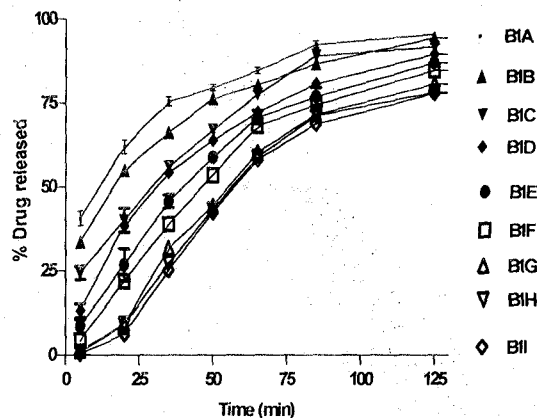


Fig. 3: Comparison of the release profiles of coated Chloroquine phosphate granules prepared by varying the spray time of the coating solution (mean  $\pm$  S.D.,  $n=6$ )

through aqueous channels created in the coating material. In controlled release technology it is not always possible to obtain a zero release before the designated time. However it is pertinent to ensure that the amount of drug released is not significant to cause detectable pharmacological effects. There was a 25.2% release of chloroquine from BII at 35 minutes while 88.4% of chlorpheniramine was released at the same time. Since both chloroquine and chlorpheniramine

maleate have similar rapid absorption between 30 to 60 minutes (AHFS, 1996), it is expected that at 35 minutes when about 25% of the dose of chloroquine would have dissolved, the chlorpheniramine component would have been absorbed and distributed to the receptor sites. By the time the chloroquine reaches therapeutic level in the blood, the patient would have received adequate amount of chlorpheniramine for protection against chloroquine-induced pruritus. The amount of chloroquine released from BII was significantly lower than that of BIH at 35 min. Product BII was therefore selected as the final formulation of coated chloroquine phosphate granules to be combined with chlorpheniramine maleate granules.

Figure 4 depicts the release profile of chloroquine phosphate and chlorpheniramine maleate from the encapsulated combined product. There was a fast release of chlorpheniramine and a delayed and controlled release of chloroquine from the combined product. While most of the chlorpheniramine component (97.4%) was released in 35min, only about a quarter of the chloroquine component (24.4%) was released in the same period. The combined formulation thus appears to have the requisite release profiles to

Table 1: Spray and drug release parameters of different batches of coated chloroquine phosphate granules

Batch	Spray time (min)	Amount of drug released (%) (mean $\pm$ S.D., $n=6$ )	
		5 min	125 min
BIA	2	40.7 $\pm$ 2.6	95.5 $\pm$ 4.9
BIB	4	33.7 $\pm$ 2.2	94.4 $\pm$ 5.4
BIC	6	24.5 $\pm$ 1.7	91.8 $\pm$ 4.2
BID	8	13.3 $\pm$ 1.6	89.6 $\pm$ 3.6
BIE	10	8.6 $\pm$ 1.2	87.1 $\pm$ 4.2
BIF	12	4.4 $\pm$ 0.5	84.8 $\pm$ 4.5
BIG	14	1.3 $\pm$ 0.3	80.7 $\pm$ 3.8
BIH	16	1.0 $\pm$ 0.1	78.3 $\pm$ 2.9
BII	18	0.5 $\pm$ 0.1	77.9 $\pm$ 3.6

S.D = Standard deviation

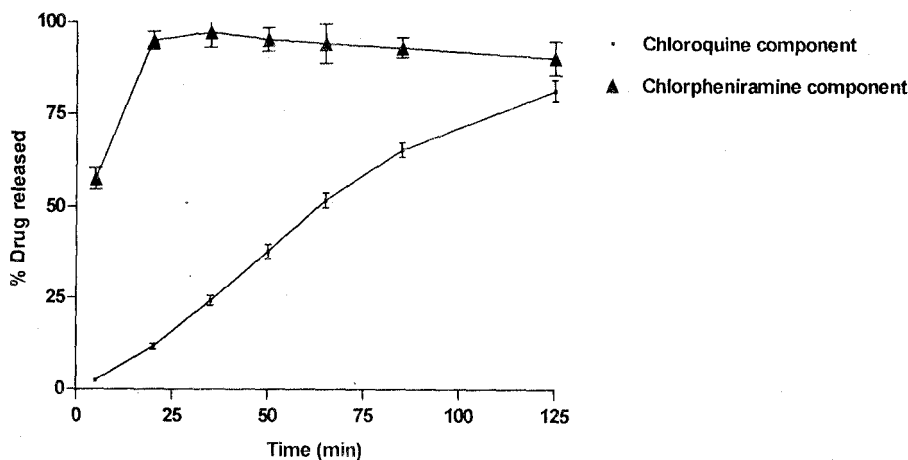


Fig. 4: Release profile of an encapsulated combined Chloroquine phosphate (coated) and Chlorpheniramine maleate (uncoated) granules (mean  $\pm$  S.D., n = 6)

protect susceptible patients from chloroquine-induced itching.

The release profile of the combined formulation showed a pattern of release which is similar though not exactly the same as that established for the individual components. The slight discrepancy may be due to some amount of interference or interaction of one component with the other. For instance, even though chlorpheniramine was uncoated, 63.3% and 88.4% was released at 5 and 35 min respectively, but in the combined encapsulated product, the amount of chlorpheniramine released was 57.6% and 97.4% within the same time frame. Also, the amount of chloroquine released from the coated granules at 5 and 35 min was 0.5% and 25.2% while the amount released from the encapsulated product was 2.4% and 24.4%, respectively. Though the chlorpheniramine maleate component did not show significant absorption at 343nm (maximum for chloroquine) its effect on the chloroquine absorbance at that wavelength is unknown.

## CONCLUSION

The study has shown that it is possible to formulate an encapsulated solid dosage form to contain both chloroquine phosphate and chlorpheniramine maleate for use in preventing or reducing chloroquine-induced itching in susceptible individuals. The release profiles of the combined product exhibited rapid release of chlorpheniramine and controlled release of the chloroquine phosphate component. There appeared to be some level of interaction between chloroquine and chlorpheniramine in the combined product. The release rate of chloroquine from formulated granules can be controlled by manipulating the coating thickness of the granules using a suitable polymer.

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