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Elliott Pauli, Hemant Joshi, Anvit Vasavada, John Brackett

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Evaluation of an Immediate-Release Formulation of Hydroxychloroquine Sulfate with an Interwoven Pediatric Taste-Masking System

Elliott Pauli[1#]
Hemant Joshi[2]
Anvit Vasavada[2]
John Brackett[3]

[1] *RTI International, 3040 Cornwallis Road, Research Triangle Park, NC 27709*
[2] *Tara Innovations LLC, 46 Deforest Ave, East Hanover, NJ 07936*
[3] *Celsus Group, 6800 West Doolin, Ponca City, OK 74601*

[#]**Corresponding Author:**

Elliott Pauli
RTI International
3040 Cornwallis Road
Research Triangle Park, NC 27709

Tel: (919)-541-6804
E-mail: epauli@rti.org

Running Title: Hydroxychloroquine Sulfate Formulation Evaluation

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ABSTRACT

Hydroxychloroquine sulfate (HCQ) is a quinoline used for the prevention and treatment of uncomplicated malaria, lupus erythematosus, and rheumatoid arthritis. For each indication, HCQ is an option for treatment of pediatric and juvenile patients on a weight basis; however, no pediatric product is available on the market. Preliminary research confirmed that a slightly buffered, ion-pairing system reduces the bitterness of HCQ, suggesting a high likelihood that a pediatric taste-masking system could be interwoven into an adult immediate-release formulation allowing the creation of a palatable suspension with water. Since HCQ is a Biopharmaceutics Classification System (BCS) Class 1 drug, the pharmacokinetics for an adult immediate-release formulation would not be altered by the creation of an embedded taste-masking system. Embedding the taste-masking and suspension agents within the adult tablet formulation would remove the need for aqueous-based vehicles and simplify the creation of a water-based suspension formulation to support improved compliance, dosing accuracy, and health outcomes in pediatric patients that are weight-base dosed with HCQ.

Keywords: formulation vehicle, preformulation, pediatric, drug design, dispersion, oral delivery, solid dosage form, solubility

1.0 INTRODUCTION

Hydroxychloroquine sulfate (HCQ) is used for the treatment of lupus erythematosus and rheumatoid arthritis in pediatrics, juvenile, and adult populations. HCQ can also be used for the prevention or treatment of uncomplicated malaria due to *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum* or *P. vivax*, in regions where chloroquine-containing drugs are still effective.[1] The global burden of these diseases are estimated at an incidence of 212 million cases of malaria and a prevalence of 5 million cases of lupus and 70 million cases of rheumatoid arthritis.[2-4] The available adult daily dosage on the market is either 200 mg or 400 mg to treatment of malaria, lupus, and rheumatoid arthritis.

Children under 5 years of age are particularly susceptible to malaria infection, illness, and death with an estimated 70% of all malaria deaths occurring in this age group. The World Health Organization listed chloroquine-containing drugs in the *Model List of Essential Medicines for Children in 2015* for treatment and prevention of malaria due to *P. vivax* infection.[5] For malaria prophylaxis treatment, pediatric patients are weight-based dosed with HCQ at 6.5 mg/kg/dose (5 mg base/kg/dose; Max: 400 mg/dose or 310 mg base/dose) orally once every 7 days. Dosing begins 2 weeks before entering an area where malaria transmission occurs and continues for 4 weeks after leaving the endemic area. For the treatment of malaria, pediatric patients are weight-base dosed with HCQ at 13 mg/kg/dose (Max: 800 mg/dose or 620 mg base/dose), then 6.5 mg/kg/dose (Max: 400 mg/dose or 310 mg base/dose) at 6, 24, and 48 hours after the initial dose with HCQ.[6]

Many physicians who treat cutaneous lupus and systemic lupus erythematosus (SLE) agree that antimalarial treatments, particularly HCQ, should be used long-term in all lupus patients who can tolerate them.[7] HCQ has beneficial effects on SLE activity by reducing the risk of flares, organ damage, and thrombotic effects, while also exerting beneficial effects on bone metabolism and survival.[8-10] Because of a higher disease severity associated with childhood-onset of SLE, children are prescribed HCQ, unless there are contraindications for its use.[11] HCQ therapy is prescribed to almost all patients with pediatric SLE, but requires ophthalmological screening for HCQ-induced retinopathy.[11] Both pediatric SLE and, similarly,

juvenile rheumatoid arthritis (JRA) are treated at doses of HCQ at 5 to 7 mg/kg/day. For both pediatric SLE and JRA, children are weight-base dosed daily for long periods.[10,12]

No pediatric formulation is on the market for HCQ, and it is extremely bitter (249 on a bitter scale compared to caffeine at 46). Given the disproportionately high mortality rate in children for malaria and the required chronic administration of HCQ for childhood lupus and JRA, a cost-effective pediatric dosage form would reduce the cost and improve health outcomes of pediatric patients. Currently, a pediatric suspension formulation derives from the 200-mg tablet after a pharmacist strips the outer film coating, crushes the tablet(s), and then suspends the powder in water and Ora-plus®.[13,14]

Preliminary research summarized in this article suggests an improved HCQ formulation can be created to simplify the pediatric suspension preparation. Since HCQ is a Biopharmaceutics Classification System (BCS) Class 1 compound and an amine-based cation, it will ionize with common anionic excipients to reduce the bitterness. Anionic ion-pairing agents, such as sodium carboxymethyl cellulose (NaCMC) and sodium citrate (Na-citrate), were used in the preliminary research at a pH of 7.5–8.5, and if further coupled with a sweetener and flavor, would complete the taste-masking system for a palatable water-based suspension formulation. Therefore, an ideal, improved HCQ formulation would contain ion-pairing agents, buffer, nonacidic flavor, sweetener, and other standard excipients to create a 200-mg strength for adult administration and have an interwoven taste-masking system to prepare a palatable pediatric water-based suspension.

2.0 MATERIALS AND METHODS

Key steps were taken to maximize the uses of resources. For example, as summarized below, an electronic tongue (e-tongue) was used to quantitate taste-masking capabilities, a more simplistic assay method was developed to support the assessment of dissolution profiles of prototype formulations, and the prototype formulation utilized known HCQ compatible excipients with a capsule.

2.1 Preliminary Taste-Masking System

Since HCQ is a highly water-soluble cation and extremely bitter alone in water, it was considered that ion exchange with an anionic excipient would reduce the bitterness. NaCMC and Na-citrate

were used as the two molecules to test this hypothesis since they are commonly used excipients noted in the Inactive Ingredients Database (IID) for oral administration. To quantitate the taste-masking systems capabilities, an e-tongue analysis was used to assess bitterness reduction using a buffered, ion paring of NaCMC and NA-citrate. The assays were conducted on an Astree e-tongue system equipped with an Alpha MOS sensor Set #2 for pharmaceutical applications composed of sensors with specificity taste attributes of sourness, astringency, bitterness, umami, sweetness, spiciness, metallicness, and saltiness. Acquisition times were fixed at 120 seconds. All data generated on Astree system were treated using multidimensional statistics on AlphaSoft V14.3 software. Using Principal Component Analysis (PCA), the Euclidian distances between the test samples of HCQ formulations were calculated to assess taste proximity between the control samples. The samples were coded to blind the samples for analysis at Alpha MOS.

2.2 Dissolution Method

The dissolution method based upon the USP monograph for HCQ consisted of 0.1 N HCl for 60 minutes at 50 rpm and 20 minutes at 150 rpm. For calculation of percent dissolved values of prototype formulations, it was assumed 100% dissolution at 80 minutes. The dissolution profiles consistent of sampling timepoints at 0, 10, 20, 30, 45, 60, and 80 minutes. The samples were analyzed by the HPLC method described in Table 1.

Table 1 would be here.

2.3 Preliminary Prototype Formulation

Excipients used to create the granules within this project were either used within a commercial product or were known excipients to be compatible with HCQ. Prior to the creation of the granules, the key focus was creation of a suspension formulation and in understanding how to taste-mask HCQ. The taste-masking elements could then be included within the development of a prototype. For the initial prototypes, hydroxypropyl methylcellulose (HPMC) capsules were used from Capsugel called Coni-snap® sprinkle capsule. The capsule design is aimed specifically for standard administration and for ease of opening. Therefore, by filling the Coni-snap® capsules with the novel granules, the capsules could be easily opened for creating a pediatric suspension. The dissolution profile of a commercial product was assessed using the refined assay method and then used to cross-assess the dissolution profile of prototype formulations. Dissolution

timepoints consisted of 0, 10, 20, 30, 45, 60, and 80 minutes (∞). All HCQ experiments were conducted with USP-grade material from Chongqing Kangle Pharmaceutical Co. Ltd., China.

3.0 RESULTS

3.1 Electronic Tongue Analysis

To quantitate the effects of ion pairing and pH increase, the Astree e-tongue system was used to assess the taste differences of six coded samples (F1–F6) at a 1:1 ratio of HCQ to NaCMC or NA-citrate with the use of 0.01 N sodium hydroxide (NaOH) as the buffer. The repeatability of the measurements was determined for each sample on three replicates. The six samples analyzed were defined as follows:

- F1—HCQ 4 mg/mL without NaCMC, pH 7
- F2—HCQ 4 mg/mL with NaCMC, pH 7
- F3—HCQ 4 mg/mL without NaCMC, pH 8
- F4—HCQ 4 mg/mL with NaCMC, pH 8
- F5—HCQ 6.5 mg/mL with NaCMC, pH 8
- F6—HCQ 6.5 mg/mL with NA-citrate, pH 8

Using PCA, the Euclidian distances between the HCQ formulations were calculated to assess taste proximity between the samples (***Figure 1***). The lower the distance, the closer the samples will be in taste. As expected, F1 is the most bitter sample, and it was confirmed that slightly buffered ion-pairing significantly modified the taste as seen with F4, F5, and F6. Surprisingly, however, F5 was slightly further away than F4, wherein F6 was the furthest away from F1. This suggests the buffered ion-pairing system can be challenged by increasing the HCQ concentration, decreasing the amount of an ion-pairing agent, or minimally increasing pH to 7.5. Furthermore, this PCA did not include a sweetener or flavor, as it was solely seeking confirmation of the effective taste difference by using a buffered ion-pairing system.

Figure 1 would be here.

3.2 Preliminary Prototype Formulation

Upon confirming the buffered-NaCMC ion exchange resulted in supportive taste-masking, several formulations were assessed for a suitable dissolution profile using Design of Experiments (DOE) methods. A Size 0 Capsugel Coni-Snap Sprinkle Capsule of hydroxypropyl methylcellulose

(***Figure 2***) was used to assess the effects on dissolution for prototype formulations with the preliminary taste-masking system embedded.

Figure 2 would be here.

Although not an optimal formulation, "Formulation #15" (F15) proved to have a suitable dissolution profile (n = 3) with 17.5% of NaCMC with a comparable dissolution profile to a formulation ("Formulation #16" [F16]) without NaCMC. ***Table 2*** shows the quantitative composition of F15 and F16 and ***Figure 3*** show the dissolution profiles of F15 and F16. The dissolution profile within Figure 3 is also comparable to that of a commercially available tablet used to develop the new assay method described in Section 2.2.

Table 2 and Figure 3 would be here.

4.0 DISCUSSION

The proof of concept in this research shows that an improved, inexpensive single strength immediate-release capsule or tablet HCQ formulation can be created to support adult and pediatric administration for the treatment of uncomplicated malaria, lupus, and rheumatoid arthritis. Three activities would need to be conducted to conclude the research for a proposed commercial prototype. First, perform a comprehensive excipient compatibility study with the inclusion of ion-pairing agents (e.g., NaCMC, Na-citrate, triNA-citrate, trisodium phosphate, tripotassium phosphate), sweeteners (e.g., saccharin, sucralose, neotame, advantame), nonacidic flavors (e.g., cherry, strawberry, grape), and supportive alkalizing agents (e.g., potassium bicarbonate). Then, select amounts of compatible excipients to be used in conjunction to create the taste-masking system (ion-pairing agent[s], sweetener[s], alkalizing agent[s], and flavor[s]) to standardize the highest concentration of HCQ in water. In looking at Figure 1, the goal would be to maintain a significant distance from "F1," and moreover, remain within Quadrant 1. Ion-pairing agents alone and in combination, with and without buffers, flavors, and sweeteners, would be assessed in solution at different pH ranges to confirm identification of an optimal taste-masking system. The stability of the best taste-masked solutions with the highest HCQ concentration would then need to be challenged to ensure the solution remained stable for at least 30 days. Finally, upon confirming the optimal amounts of excipients and the stability of the solution of the taste-masking system in water, a commercial prototype formulation could be

created to meet an equivalent quality target product profile (QTPP) as commercially available HCQ tablets. Since HCQ is a BCS Class 1 drug, the granules and formulation could easily be created to maintain pharmacokinetic performance.

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6.0 REFERENCES

1. Center for Disease Control and Prevention (CDC). Medicines for the prevention of malaria while traveling. Hydroxychloroquine (Plaquenil™). Lasted accessed on 02 July 2019; https://www.cdc.gov/malaria/resources/pdf/fsp/drugs/hydroxychloroquine.pdf.

2. Smith, Howard and Diamond, Herbert. Medscape. Rheumatorid Arthritis. Lasted accessed on 02 July 2019; https://emedicine.medscape.com/article/331715-overview#a5.

3. The National Resource Center on Lupus. Lupus facts and statistics. Lasted accessed on 02 July 2019; http://www.resources.lupus.org/entry/facts-and-statistics.

4. World Health Organization (WHO). Malaria Fact Sheet. Geneva: WHO. Updated on 27 March 2019. Lasted accessed on 02 July 2019; http://www.who.int/mediacentre/factsheets/fs094/en/.

5. 19th WHO Model List of Essential Medicines: April (2015). Last accessed on 02 July 2019; https://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf

6. Sanofi-aventis US. Plaquenil® hydroxychloroquine sulfate, USP. Last accessed on 02 July 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/009768s041lbl.pdf.

7. Merrill JT. Why are treatments that were developed for malaria now widely used for lupus? (2013); Last accessed on 02 July 2019; https://www.lupus.org/resources/why-are-treatments-that-were-developed-for-malaria-now-used-for-lupus

8. Pooneh S. Akhavan, Jiandong Su, Wendy Lou, Dafna D. Gladman, Murray B. Urowitz, Paul R. Fortin. The Early Protective Effect of Hydroxychloroquine on the Risk of Cumulative Damage in Patients with Systemic Lupus Erythematosus. The Journal of Rheumatology April 2013, jrheum.120572; 40(6) 831-841; DOI: https://doi.org/10.3899/jrheum.120572

9. Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus. *Expert Opinion on Drug Safety.* 2017; 16(3) 411-419; DOI: https://www.tandfonline.com/doi/full/10.1080/14740338.2017.1269168

10. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Annals Rheumatic Disease.* 2010; 69(1) DOI: https://ard.bmj.com/content/69/01/20

11. Thakral A, Klein-Gitelman MS. An Update on Treatment and Management of Pediatric Systemic Lupus Erythematosus. *Rheumatology Therapy.* 2016; 3(2) 209-219. DOI: https://dx.doi.org/10.1007%2Fs40744-016-0044-0

12. Laaksonen AL, Koskiahde V, Juva K. Dosage of antimalarial drugs for children with juvenile rheumatoid arthritis and systemic lupus erythematosus. A clinical study with determination of serum concentrations of chloroquine and hydroxychloroquine. *Scand J Rheumatol* 1974; 3(2) 103-108; DOI: http://www.tandfonline.com/doi/abs/10.3109/03009747409115809.

13. Michigan Collaborative Standardization of Compounded Oral Liquids. Reviewed on Apirl 2013. Last accessesed on 02 July 2019; http://www.mipedscompounds.org/sites/default/files/standard-formulations/Hydroxychloroquine.pdf.

14. Nationwide Children's Pharmacy. Hydroxychloroquine. Reveiwed 23 March 2019. Lasted accessed on 02 July 2019; https://www.nationwidechildrens.org/-/media/nch/specialties/pharmacy/compounding-formulas/hydroxychloroquine-oral.ashx

Table 1. Details of HPLC conditions

Mobile Phase A:	1000ml Water + 500mg Sodium pentane sulfonate + Phosphoric Acid (1N) pH 2.5
Mobile Phase B:	Acetonitrile
Flow Rate:	1.0 mL/minute
Column:	Kinetex 4 μm XBC-18 100A, 250x 4.6 mm
Column Temperature:	Ambient
Injection Volume:	10 μL
Detector Wavelength:	254 nm
Retention Time:	3.919 min
Isocratic Method	%A = 80%, %B = 20%

Table 2. Composition of HCQ "Formulation Nos. 15 and 16"

Ingredient	Formulation 15		16	
	Percent	Actual	Percent	Actual
HCQ	28.84	2.599g	36.05	2.569g
Sorbitol powder	40.84	3.680g	49.33	3.516g
Aspartame	1.8	163.1mg	2.32	165.4mg
Sodium CMC	17.5	1.579g	N/A	N/A
Magnesium Stearate	1.6	145.2mg	2.0	147.6mg
Sodium Starch Glycolate	9.3	842.3mg	10.22	728.5mg
Water for granulation	Q.S.	15-20 drops	Q.S	8-12 drops