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Proposing Biowaver as a Prompt Tool for the New Pharmaceutical Products Approval in Management of Coronavirus Outbreaks

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Abstract

Coronavirus disease (COVID-19) is a pandemic disease appeared in China in December 2019 and has since spread throughout the world. The recent outbreak of acute respiratory infection is caused by a new type of coronavirus, named as (SARS-CoV-2). At the moment, there are no specific medications or vaccines to treat COVID-19. Recently, a combination of the antimalarial hydroxychloroquine (HCQ) and azithromycin (AZM) antibiotic is used effectively in treatment of COVID-19. The present article discusses the possibility of the development of a new cost-effective pharmaceutical product combing HCQ and AZM in management of coronavirus infections. Such an approach would involve waiving of the *in-vivo* bioavailability and bioequivalence studies of the conventional oral dosage forms for emergency approval from regulatory affair authorities.

Keywords: Hydroxychloroquine, Azithromycin, COVID-19, Coronavirus, SARS-CoV-2, Antimalarial, Biowaver, BCS, Cost effective

INTRODUCTION

Coronaviruses (CoVs) are a broad family of zoonotic viruses that are typically associated with respiratory and gastrointestinal infections (i.e., can be transmitted from animals to humans). CoVs which affect human health belong to the Coronaviridae family, particularly the Coronovirinae subfamily. Only Alpha coronavirus and Betacoronavirus are of concern to human and clinical virologists among the four genera listed in this subfamily(1–3). Table 1 epitomizes the classification and source of human-affected Coronaviruses until 2019-nCoV emerges (2). In late December 2019, a novel strain of Betacoronavirus (namely SARS-CoV-2) was identified in Wuhan city, Hubei province of China causing an outbreak of a highly transmittable and pathogenic viral infection known as (COVID-19).The roots of the outbreak was linked to Huanan Seafood Wholesale Market (4). This novel coronavirus disease has since spread to over 140 countries, resulting in the current COVID-19 pandemic, and was declared by the World Health Organization (WHO) to be a Public Health Emergency of International Concern (5,6). To this day, about 1 476 819 confirmed cases of COVID-19 have been reported, including 87 816 deaths mostly from Italy, United states, Spain, France, and United Kingdom, among others (7). Fig. 1 represents schematic labelled diagram of Coronavirus (SARS-CoV), reproduced from Peiris *et al.*, 2003 (8). No vaccines or drugs are currently available to treat these viruses. Human-to-human transmission of SARS-CoV-2 has been described with incubation times between 2-14 days, facilitating its spread via droplets produced by the infected persons 'respiratory system, contaminated hands or surfaces. Clinical manifestations seen in patients with SARS-CoV-2 infection ranged from mild, moderate, to severe and rapidly progressive and fulminant disease(1,4). In most cases, onset of symptoms was mild and nonspecific, presenting by fever, dry cough and shortness of breath. Very few COVID-19 patients had early notable upper respiratory tract symptoms (9). As regards the viral load profile, SARS-CoV-2 is similar to influenza, which peaks at around the time of onset of symptoms, but contrasts with SARS-CoV, which peaks at about 10 days after onset of symptoms, and MERS-CoV, which peaks at second week after onset of symptoms (10).

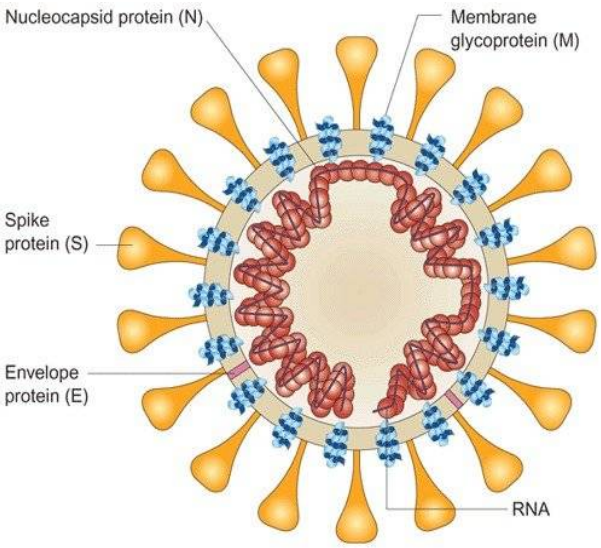

Fig. 1: Schematic labelled diagram of Coronavirus (SARS-CoV) (adopted from reference 8).

Table I: Classification and Source of Human-Affected Coronaviruses Until the Emergence of the 2019-nCoV (2)

Genus	Virus	Natural host	Intermediate host	Disease	Receptor
Alpha-coronavirus	HCoV-NL63	Bats	Unknown	Mild respiratory tract infections	Angiotensin converting enzyme 2
	HCoV-229E	Bats	Camelids	Mild respiratory tract infections	Human aminopeptidase N
Beta-coronavirus	HCoV-OC43	Rodents	Bovine	Mild respiratory tract infections	9-O-acetylsialic acids
	HCoV-HKU1	Rodents	Unknown	Mild respiratory tract infections and pneumonia	9-O-acetylsialic acids
	SARS-CoV	Bats	Masked palmes civetes	Severe acute respiratory syndrome	Angiotensin converting enzyme 2
	MERS-CoV	Bats	Camelids	Severe acute respiratory syndrome	Dipeptidyl peptidase-4
	2019-nCoV	Bats	Unknown	Severe acute respiratory syndrome	Angiotensin converting enzyme 2

Table II: Conventional Dosage Forms Available for HCQ and AZM in Current Pharma Market (30,31)

Brand Name	Dosage Form	Route	Strength
Plaquenil®	Tablet, film coated	Oral	200mg
Quineprox®	Tablet	Oral	200mg
Apo-hydroxyquine®	Tablet	Oral	200mg
Azithromycin®	Tablet	Oral	250, 600mg
	Tablet, film coated	Oral	600mg
	Injection	Intravenous	2.5g/23mL, 500mg/4.8mL
Zithromax®	Tablet	Oral	250, 500mg
	Tablet, film coated	Oral	250, 500, 600mg
	Powder, for suspension	Oral	100 mg/5mL, 200 mg/5mL
	Injection, powder, lyophilized, for solution	Intravenous	500 mg/5mL
	Capsule	Oral	250mg
Zmax®	Powder, for suspension	Oral	2 g/60mL
AzaSITE®	Solution / drops	Ophthalmic	10mg/mL (1%)

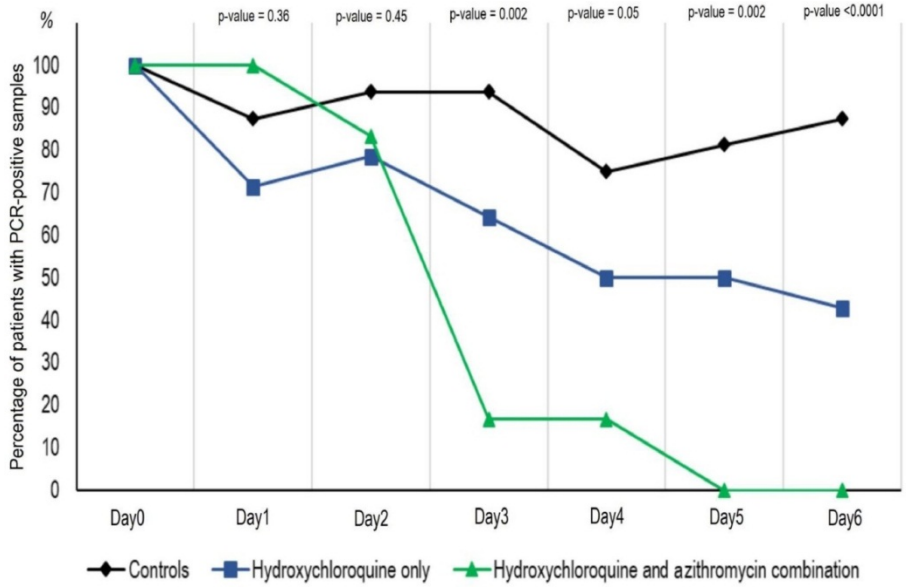

Fig. 2: Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day 6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithomycin combination, and in COVID-19 control patients (adopted from reference 15).

At the moment, the therapeutic strategies to deal with the SARS-CoV-2 infection are only supportive (11) and scientists are endeavoring to find treatments specific to the virus. Research thus far has revealed over 30 agents including Western medicines, natural products, and traditional Chinese medicines that could have potential efficacy against COVID-19. Some of these agents were tested rapidly in clinical studies and demonstrated tentative efficacy against COVID-19 among which are chloroquine, hydroxychloroquine (HCQ) and azithromycin (AZM) (12).

HCQ (an analogue of chloroquine), sold under the brand name Plaquenil®, was long approved by the FDA for the treatment of malaria and certain inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus (13,14). On long-term use, HCQ has a clinical safety profile better than that of chloroquine, with fewer concerns about drug-drug interactions (15). AZM is a broad-spectrum macrolide antibiotic used for the treatment of respiratory, enteric and genitourinary infections with susceptible organisms(16).

In March, 2020 two studies in India conducted with chloroquine and HCQ have shown significant improvement in some parameters in enrolled COVID-19 patients (17), with others showing HCQ having a relatively higher *in-vitro* potency against SARS-CoV-2 (13). Another small study in France reported that HCQ alone or in combination with AZM, reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with a non-randomized control group (13). Despite the limited number of clinical studies performed, and under the urgent demand of therapeutic agents for the treatment of the rapidly spreading COVID-19, the US Food and Drug Administration (FDA), in March 29th, 2020 issued an emergency use authorization for HCQ and chloroquine for treatment of eligible hospitalized COVID-19 patients (18).

This paper tries to discuss the pharmaceutics aspects for possibility to develop a new cost-effective pharmaceutical product combing HCQ and AZM, by waiving the *in vivo* bioavailability and bioequivalence studies for the conventional solid oral dosage forms available in the global pharma market based on an approach termed the Biopharmaceutics Classification System (BCS).

Conventional dosage forms of HCQ and AZM in the global market:

In view of the growing global urgency to identify potential treatments for the SAR-COV-2 infection, scientists around the globe are conducting diversified researches and clinical studies on already available therapeutic agents in attempt to fulfill this universal need as soon as possible. Despite the small sample size, studies on the use of HCQ in combination with AZM in COVID-19 patients have shown some promising results. On March 16th, 2020 a group of researchers, in coordination with The Mediterranean Infection University Hospital Institute in Marseille, France, have conducted an open-label non-randomized clinical trial on 36 hospitalized confirmed COVID-19 patients (16 of which were in the control group). All the patients in the test group were given oral HCQ sulfate 200 mg, three times per day for a duration of ten days. Among these HCQ-treated patients, six patients received oral AZM (500mg on the first day, followed by 250mg per a day for the next four days) to prevent bacterial super-infection, under daily electrocardiogram control. At day six of this study, results revealed that 70% of patients on HCQ monotherapy were virologically cured compared to 100% of patients receiving the HCQ-AZM combination. Fig. 2 summarizes these results, reproduced from Gautret *et al*., 2020 (15).

This positive outcome has encouraged the researchers of this study to perform an additional trial on a larger sample size of patients, where, on March 26th, 2020 a group of 80 COVID-19 in-patients were given the combination of HCQ and AZM in the same previous regimen. The findings of this trial disclosed that virus cultures from patient respiratory samples were negative in 97.5% patients at day5, which confirmed the efficacy of the HQC and AZM combination in the treatment of SARS-CoV-2 positive patients (19). Based on these findings, and owing to the emergent need of therapies to stop the epidemic devastation, clinicians in various countries have begun to use these medications in clinical practice, and several randomized trials are being initiated (20). On April 1st, 2020 the Ministry of Health of India, for example, authorized the use of HCQ (400mg twice a day for day1, followed by 200mg twice a day for 4 days) in combination with AZM (500 mg once a day for 5 days) for critically ill COVID-19 patients requiring intensive care unit (ICU) management (21). Furthermore, Kansas City physicians in Missouri, USA, have adopted the former regime and begun to prescribe it with noticeable improvements (22).

The HCQ 200 mg oral tablet, patented under the brand name Plaquenil® by Concordia Pharmaceuticals Inc., was first approved as a prescription medicine by the FDA on 14 April 1955. It is currently available in the Pharma market under the generic names of Quineprox® and Apo-hydroxyquine® 200mg tablets (23,24). On the other hand, Pfizer was the first producer of AZM, It obtained the FDA approval for Zithromax® 250mg oral capsules in November 11th, 1991 (25). In 1994, 2005, and 2007 respectively, the FDA approved Pfizer's Zithromax® oral suspension EQ 1gm Base/Packet, Zmax® ER oral suspension EQ 2gm Base/Bot, and AzaSITE® 1% ophthalmic solution/drops (26–28). AZM is also found in various generic products, including, but not limited to, Azithromycin® 250mg or 600mg oral tablets, Azithromycin® 2.5 g/23mL or 500mg/4.8mL IV injection, and Zithromax® 250mg or 500mg film-coated oral tablets (29). Table II summarizes the conventional dosage forms available in the existing Pharma market for HCQ and AZM, reproduced from DrugBank database (30,31)

A proposed fixed-dose combination (FDC) of HCQ and AZM

In the light of the current practices, we are exploring the possibility of developing a fixed-dose combination (FDC) of HCQ and AZM to be used as a cost-effective treatment in the fight against SARS-CoV-2 infection, to simplify the

dosing schedule with a consequent enhancement of patient compliance. Such an approach would involve waiving of the *in-vivo* bioavailability (BA) and bioequivalence (BE) studies for both medicines' conventional solid oral dosage forms. Regulatory agencies accept three types of biowaiver, the BCS-based biowaiver, the well-established use/bibliographical applications, and the Literature-based submissions. The former will be discussed in this section (32).

Biopharmaceutics Classification System

In 1995, the Biopharmaceutics Classification System (BCS) was established as a scientific framework to classify drug substances based on their aqueous solubility and intestinal permeability(33,34). When combined with drug product dissolution, the BCS takes into account the three major factors that govern the rate and extent of drug from immediate release (IR) solid oral dosage forms (33,35). This concept behind the BCS led to the possibility of repealing the regulatory requirement for in-vivo BA and/or BE studies in favor of specific comparative in-vitro testing to conclude BE of oral IR products with systemic actions (33,35,36).

According to the BCS, a drug substance falls under one of following four categories, depending on its aqueous solubility and permeability(37,38). Fig. 3 demonstrates the classification of drugs according to the BCS, (reproduced from the Lubrizol Corporation, 2019 (37).

- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability
- Class 4: Low Solubility – Low Permeability

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of water over a pH range of 1–7.5 at 37 °C. While it is said to be highly permeable when the extent of absorption in humans is greater than 90% of an administered dose, based on mass-balance or compared with an intravenous reference dose. On another note, rapid dissolution becomes a drug's characteristic when 85% or more of the labeled amount dissolves within 30 min using USP Apparatus 1 or 2 in a volume of 900 mL or less of buffer solutions (34).

It is important to note that drugs in each of the four BCS classes have their own set of unique characteristics. Those will be discussed below:

Class I drugs: are known for their rapid dissolution and bioavailability, which act in vivo like an oral solution wherefore gastric emptying is often the rate governing parameter. Thus, BA and BE are unnecessary for the products of such drugs (39).

Class II: drugs have high permeability but low aqueous solubility, hence, the dissolution rate becomes the governing parameter for their absorption. These drugs exhibit variable bioavailability ,therefore, methods that enhance their dissolution rate are required to improve their bioavailability (39).

Class III drugs: have the permeation through the intestinal membrane as the rate-limiting step for their absorption. Since the dissolution is rapid, the variation in the rate and extent of absorption is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. Therefore, permeability enhancers are generally necessary (39,40).

Class IV drugs: are not well absorbed through the intestinal mucosa with consequent poor bioavailability. Therefore, drugs that come under this BCS class are troublesome for successful oral administration. Several variables such as the rate of dissolution, gastric emptying, and permeability form the rate limiting steps for the drug absorption(34,39,40).

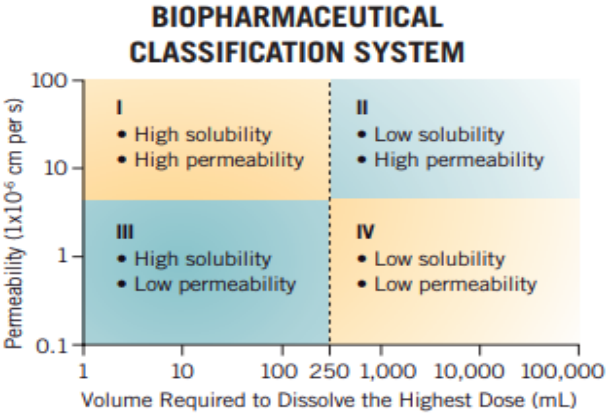

Fig. 3: Classification of drugs according to the BCS (adopted from reference 37).

BCS-based biowaiver

As far as 2006, the BCS Guidance of the United States Department of Health and Human Services, FDA (HHS-FDA) recommended the biowaiver only for IR solid oral dosage forms containing Class I drugs (High Solubility–High Permeability) (41). However, in subsequent publications, and according to the 2017 updates, the HHS-FDA suggested that biowaiver can be extended to Class III and Class II drugs that meet certain criteria (33,41). Generally, requirements for a BCS-based biowaiver study include(42):

a. Dissolution Test in 3 different media (in 900 ml and at 37°C) which are:
   - Buffer pH 1.2, simulated gastric fluid without enzymes or 0.1N HCl.
   - Buffer pH 4.5.
   - Buffer pH 6.8 or simulated intestinal fluid without enzymes.

b. 12 samples in each media, paddle rotating at 50 rpm or basket at 100 rpm

c. Sampling times are 10, 15, 20, 30, 45 and 60 minutes.

d. The profiles of the test and reference products must be similar in all three media.

e. The products are similar if the similarity factor f2 ≥ 50 and both products show ≥ 85% dissolution in 15 min.

Knowing that HCQ and AZM are BCS class I and II, respectively (43,44), we looked into available literature reviews to investigate if any has proposed the eligibility of APIs belonging to the same BCS classes for a BCS-based biowaiver, and we found some interesting data.

Table III: Summary of Biowaiver Monographs Conducted on Some BCS-Class I and Class II APIs.

API	BCS Classification	Characteristics	Eligibility For Biowaiver	Reference No.
Levetiracetam	Class I	High Solubility High Permeability	Eligible	(50)
Chloroquine Phosphate Chloroquine Sulfate Chloroquine Hydrochloride	Class I	High Solubility High Permeability	Eligible	(51)
Bisoprolol	Class I	High Solubility High Permeability	Eligible	(52)
Codeine Phosphate	Class I	High Solubility High Permeability	Eligible	(53)
levofloxacin	Class I	High Solubility High Permeability	Eligible	(54)
Piroxicam	Class II	Low Solubility High Permeability	Eligible	(55)
Diclofenac Potassium Diclofenac Sodium	Class II	Low Solubility High Permeability	Eligible	(56)
Ketoprofen	Class II	Low Solubility High Permeability	Eligible	(57)
Rifampicin	Class II	Low Solubility High Permeability	Not eligible	(58)

In April, 2005 for instance, a biowaiver monograph on paracetamol (acetaminophen), a BCS class I(45), concluded that an IR acetaminophen solid oral dosage form is a good candidate for BCS-biowaiver (46,47). Another monograph, in Jan,2005, reviewed existing literature data on Ibuprofen properties related to the BCS, which was assessed to be a BCS class II drug. It stated that, as long as the dosage form is rapidly dissolving (85% in 30 min or less) in pH 6.8 buffer, the test product shows dissolution profile similarity to the reference product in pH 1.2, 4.5, and 6.83, and contains only the specified excipients, biowaiver for IR ibuprofen solid oral dosage form is scientifically justified(48). Similar biowaiver monographs on other drug substances belonging to BCS class I and II were established with positive results. Some of those are summarized in Table III.

In Addition, we found that a fixed-dose combination product containing the above discussed APIs, Paracetamol and Ibuprofen, was produced by AFT pharmaceuticals and marketed as Maxigesic® (49). These data could support the proposal of developing a FDC of HCQ and AZM as stated earlier.

CONCLUSION

Available data on BCS-based biowaiver for BCS class I and II drugs, in accordance with existing marketed FDC products containing drug substances that belong to these classes support our proposal to develop a new cost-effective pharmaceutical product combing HCQ and AZM for the therapeutic management of wide spread SARS-CoV-2 infections.

Conflict of interest

Authors declare that there is no conflict of interest.

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