Formulation Development And Evaluation Of Immediate Release Tablets Of Anti-Malarial Drug For Effective Management Of Malaria.

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Abstract

A quinoline called hydroxychloroquine sulfate, or HCQ, is used to treat and prevent rheumatoid arthritis, lumpus erythematosus, and simple malaria. HCQ is a weight-based treatment option for pediatric and adolescent patients for each indication; however, there isn't a pediatric medication that is specifically designed for this market. It is possible to combine a pediatric taste-masking system with an adult immediate-release formulation to make it possible to make a palatable suspension with water using standard excipients. An ion-pairing system that is somewhat buffered has been shown to dramatically lessen the bitterness of HCQ, according to preliminary study. Since HCQ is a medication classified as Class 1 in the Biopharmaceutics Classification System, adding taste-masking and suspending substance to an adult tablet formulation would not change the pharmacokinetics of the adult immediate-release formulation.

Keywords **:** *Suspension Formulation, Immediate-release Formulation, Biopharmaceutics Classification System, Pharmacokinetics, Dosing accuracy.*

Introduction

In the pharmaceutical production, oral delivery is currently the gold standard since it is thought to be the safest, most practical, cost-effective, and patient-compliant mode of drug delivery. (DrugBank.com) A drug's solubility behavior, in addition to its permeability, is a crucial factor in determining its oral bioavailability. There have always been some medications whose solubility has made it difficult to create an oral formulation that works well[1]. I instantly think of examples like sulphathiazole, digoxin, phenytoin, griseofulvin, and chloramphenicol. Drug solubility and permeability have a major role on oral bioavailability. Drugs are categorized into four classes, known as the Biopharmaceutical Classification System (BCS), which are listed in Table 1, based on these two parameters[2].

BCS Class	Solubility in aqueous environment	Permeation over(intestinal)membrane
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Benefits of a drug delivery method with quick release[3]

A pharmaceutical formulation with quick release provides:

1. Enhanced convenience and compliance.
2. Improved stability.
3. Fit for active ingredients with regulated or prolonged release.
4. Permits a lot of drug loading.
5. The capacity to offer liquid medication's benefits in a solid form.
6. Flexible and compatible with current packaging and processing equipment.
7. Economical.

Drug selection criteria for Immediate release tablet[4]

1. The mouthfeel of the drug should be pleasant.

2. It must to show minimal susceptibility to external factors like temperature and humidity.

3. It ought to be produced affordably with standard processing and packaging machinery.

4. It ought to dissolve quickly and be absorbed from the stomach.

5. After oral administration, it shouldn't leave behind much or any residue in the mouth.

Mode of Action

The exact mechanism of action of hydroxychloroquine is unknown, however it may have something to do with its ability to bind and alter DNA. Furthermore, it has been found that the parasite absorbs hydroxychloroquine within the acidic feeding vacuoles of the erythrocyte. The pH of the acid vesicles increases as a result, interfering with their regular operation and possibly blocking the metabolism of phospholipids. When administered as a suppressive medication, hydroxychloroquine prevents the erythrocytic stage of plasmodia development. During acute malaria episodes, it halts the erythrocytic schizogony of the parasite. Their ability to concentrate in parasitized erythrocytes may account for their unique toxicity against the erythrocytic phases of plasmodial infection. As a mild immunosuppressive that inhibits the synthesis of rheumatoid factor and acute phase reactin, hydroxychloroquine is an antirheumatic[5].

Pharmacokinetics

• **Type of Route**: Oral

• **Absorption**: Very quickly and totallydigested following oral consumption

Plasma half-life: 3–4 hours.

Peak duration: 4–8 hours

Duration:Within 24 hours, 60% of the peak serum sodium elevation is sustained

Protein bound: around 45%

• **Metabolism:**Hepatic metabolism contributes to the production of active de-ethylated metabolites.

• **Excretion**: Stools

Pharmaceutical Interaction

Pharmaceutical products that alter heart rhythm: hydroxychloroquine shouldn't be combined with other medications that increase the risk of cardiac arrhythmias, or irregular heartbeats. Combining these medications with hydroxychloroquine may result in harmful arrhythmias[6].

A few examples of these medications: Clarithromycin, amiodarone, and chlorpromazine.

• Digoxin: Digoxin levels in the body may rise when taken with hydroxychloroquine, which may raise the possibility of digoxin side effects.

• Caution on alcohol interaction: excessive alcohol consumption may harm your liver, which may impact the way hydroxychloroquine functions in your body. When using this medication, abstain from alcohol.

• Insulin and other diabetic medications: diabetes medications, hydroxychloroquine, and insulin all lower blood sugar levels. Combining these medications with hydroxychloroquine may result in hypoglycemia, or low blood sugar. Your insulin dosage may need to be lowered by your doctor

Examples of other diabetes drugs include: - Chlorpropamide, Glimepiride, Rapaglinide[7].

EXPERIMENTAL WORK

For development of immediate Release formulation following materials, chemicals and instruments were used.

Excipients:

List of excipients used in the study

Ingredient	Functional Category	Grade	Source
Dibasic Calcium Phosphate	Diluent	-	DFE
Lactose Monohydrate	Diluent	Pharmakos200 M	DFE
MCC	Avicel102	Colorcon	Diluent
PVPK 30	Binder	Kollidon30	BASF
Tween80	Surfactant	SP Tween80 MBAL -LQ - (SG)	Croda
Coprocessed starch	Disintegrant	Starcap 1500	Colorcon
Croscarmellose sodium	Disintegrant	Ac-Di-Sol	FMC
SLS	Lubricant	Kolliphor SLS Fine	BASF
Colloidal Si(o2)	Glidant	Aerosil200	Evonik
Magnesium stearate	Lubricant	-	Avantor
Opadry white	Coatingagent	-	Colorcon

Instruments:

List of instruments used in the study.

Sr. No.	Equipments	Manufacturers
1	Weighing balance	Sartorius Pvt. Ltd.
2	Sieve shaker	Electrolab
3	DCB blender	Multipex
5	Halogen moisture balance	Mettler Toledo
6	Tablet compression machine	Cadmach
7	Hardness tester	Dr.Schleuniger Pvt. Ltd.
8	Friability tester	Electrolab(EF-1W)
9	Varnier caliper scale	Omega Intrument Ltd.
10	Disintegration tester	Electrolab(ED-2AL)
11	Dissolution test apparatus	Electrolab
12	Mechanical stirrer	Remi
13	Stability chambers	Thermolab
14	HPLC	Waters
15	Ultraviolet spectrophotometer	Shimadzu

Preformulation studies[8]

Preformulation studies are intended to identify the physicochemical characteristics of drugs and excipients that could impact the final product's pharmacokinetic-biopharmaceutical qualities, manufacturing process, and formulation design.

1. DrugIdentification

a) Melting point by Thermometer

b) UV method

c) FTIR

2. Solubility study of drug

3. Physical parameter of drug

4. Drug excipients interaction

Drug excipients interaction

The main goals of this study were to determine appropriate excipients for the medicine's formulation and stable storage conditions for the drug in its solid state. Carefully choosing the excipients to add to the formulation is essential to producing a stable and effective dosage form. Glass vials are used to store two sets of each mixture at 40ºC and 75% relative humidity for a month. One set is used for initial analysis,

and the other set is kept closed to monitor any physical changes. Glass vials, both open and closed, were used to test the drug's compatibility with various excipients under particular storage conditions. The drug's physical stability was monitored often to ensure it remained unchanged. For any physical changes, the powder mixture in the vials was examined[9].

Scheme for drug substance-excipients compatibility studies

Sr. No.	Condition	Time-point	Type of packing
1	Initial	-	Glassvial
2	40°C/75% RH	upto 30days	Glassvial

Formulation Development

The data from immediate release tablet literature was used to build trial batches. For trial batches, it was determined, based on innovative sample analysis, to maintain identical tablet strength, size, and form. Optimizing the SLS concentration on it, choosing a superdisintegrant, and choosing a binder are all included in the current work experiment. All other components remained unchanged. The fast mixing granulator was used to prepare the wet and direct granulation methods in this formulation. In order to compare the final product to the innovator, powder blends were assessed for flow qualities during the formulation process, and tablets were assessed for appearance, thickness, hardness, friability, disintegration, and in-vitro release. An advanced UV and HPLC technology was used to examine the data[10].

General procedure for tablet formulation

Dispensing and Sifting
All intragranular ingredients were weighed as per the required quantities then it sifted through ASTM #50 mesh.
DryMixing
Materials were mixed together manually for 5 min.
Lubrication
Blend from dry mixing was mixed with Magnesium Stearate(#60passed)manually for 10 min LODNMT 1.5.
Compression
Lubricated blend was compressed using 11.5x5.5mmoval shaped punch, to form a tablet.

Result And Discussion

Drug idenfication

Meltingpoint

Identification of the medicinal product Melting point The drug's claimed melting point was found to be 225.0 ºC, however the capillary rise method showed that it was between 225 and 227 ºC.

Uv Spectra

A standard solution of 20 µg/mL hydroxychloroquine sulfate was scanned in a 1.0 cm cell against solvent (water) and blank, recording the spectra between 400 and 200 nm. The Hydroxychloroquine Spectra

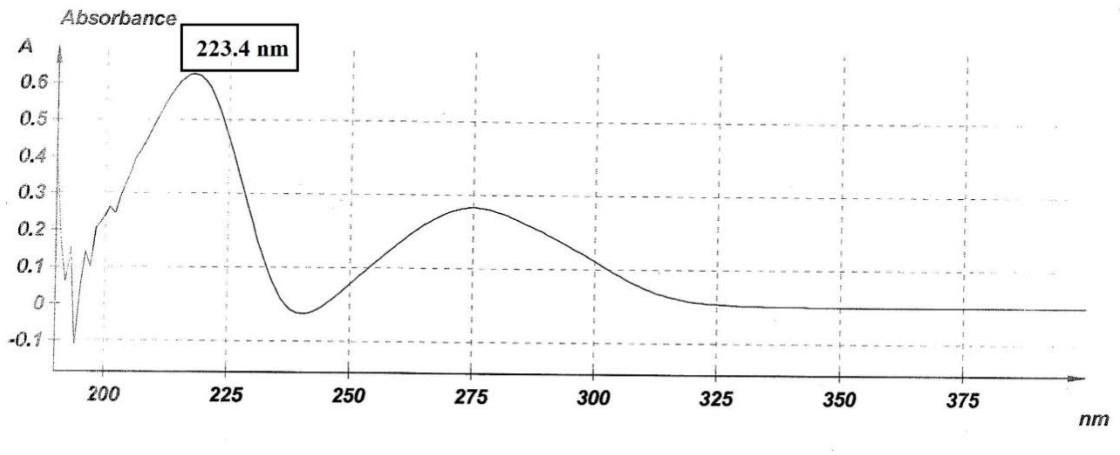

Fig. sulfate standard solution is shown

UV spectrum of Hydroxychloroquine sulphate

Absorbance of UV spectrum

Sr. No	Observed value	Reported value	
	Wavelength (λmax)	Wavelength (λmax)	Absorbance (A)
1	223nm	223nm	0.4980

The experiment was conducted as described in the experimental work. The drug's maximum absorbance is seen in the UV spectrum at a wavelength of 223 nm, which is also the reported λmax for the drug.

Solubility Study

Solubility of Hydroxychloroquine Sulfate.

Media	**Actual pH**	**Initial**	**Stability as Such Vial (at24 hr)**
mg/250ml			
0.1NHCl	0.95	199.80	199.55
0.01NHCl	2.10	199.94	200.17
Acetate Buffer(pH4.5)	4.45	198.68	199.76
Purified Water	5.70	201.18	200.88
Phosphate Buffer(pH 6.8)	6.75	202.31	201.62

This drug solubility study was conducted at several pH values in order to choose the best dissolve medium for the medication. In 0.1N HCl, pH 4.5 acetate buffer, the drug was found to be insoluble. In purified water with a pH of 6.8 phosphate, the medication was found to be soluble. The dissolving medium of choice is water.

Drug-Excipient interaction

Drug-Excipient interaction

Physical admixture	**Drug: Excipient**	**Initial description**	**Observation**
API	1	White colour powder	No Change
API+Lactose Monohydrate	1:1	White colour powder	No Change
API+MCC	1:1	White colour powder	No Change
API+PVPK30	1:1	White colour powder	No Change
API+Tween80	1:1	White colour powder	No Change
API+Coprocessed starch	1:1	White colour powder	No Change

API+Croscarmellose sodium	1:1	White colour powder	No Change
API+SLS	1:1	White colour powder	No Change
API+Colloidal Sio2	1:1	White colour powder	No Change
API+Magnesium Stearate	1:1	White colour powder	No Change
API+Magnesium Stearate	1:1	White colour powder	No Change

There have not been any notable changes in physical appearance, according to the physical data shown in the above table. Consequently, it is possible to infer from the foregoing that the medicine and excipients can be utilized in the final formulation.

Observation

Throughout the procedure, good weight homogeneity of the tablets was seen. Tablet dimensions were found to be between 2.0 and 5.5 mm, while hardness was found to be between 40 and 60 N. Tablet friability was determined to be NMT 1%.

Conclusion

The goal of the research project was to formulate and assess quick -release tablet for curing malarial disease. An effort was undertaken to create a stable, bioequivalent drug form of hydro chloroquine sulfates that would release the medication in a manner more similar to that of a pure drug and individual reference product taking into account the medication content in the finished tablet as well as the information from the literature and the characterization of the reference product.

The main goal was to create an antimalarial tablet that was generic and comparable to the reference product, hydroxychloroquine sulphates. A safe, effective generic version of IR tablets was created with a similar dissolving profile to the reference product, as well as bioequivalence.

The project entailed standardizing pure drugs. Additionally, it included figuring out the reference tablets' release pattern in order to choose a release profile in water, a dissolution medium, that might serve as a target for internally developed instant release tablet formulations.

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