Magistral preparation of chloroquine phosphate capsules for the treatment of lupus patients : Example of an active principle with a narrow therapeutic range requiring manipulation under conditions

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Introduction

Hydroxychloroquine (HCQ) is the only initial pharmacological option for the chronic treatment of lupus. However, in rare cases, HCQ is responsible for significant cutaneous hyperpigmentation. Given this intolerance, an alternative is chloroquine phosphate.

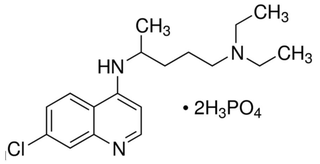

Fig.1 : Chloroquine (di)phoshate molecule (CAS : 50-63-5)

Characteristics of chloroquine (di)phosphate (CAS: 50-63-5, European Pharmacopoeia monograph: 01/2017:0544):

- Class I active ingredient in the biopharmaceutical classification system.
- Toxicity of the active ingredient: reprotoxic (Category 1A) and organ toxicity (cardiovascular - Category 2)
- 160 mg is equivalent to 100 mg of chloroquine base

***Objective*: assess the feasibility of a magistral preparation of chloroquine phosphate (PCQ), taking into account production constraints and the narrow therapeutic range of PCQ.**

Materials and Methods

Formulation based on:

Chloroquine Phosphate Tablets, USP Monograph (i.e., 30 mg microcrystalline cellulose, CMC, filling excipient)

Protective equipment used considering the toxicity of chloroquine (di)phosphate:

- Handling of the active ingredient under isolator
- Personal protective equipment :
  - FFP3 mask
  - Gown
  - Overblouse
  - Overshoes
  - Gloves

Controls:

1. The homogeneity of the PCQ powder mixture was assessed macroscopically by **observing the fluorescence of the mixture under a UV lamp** (254 and 312 nm).
2. A **UV spectrophotometric assay** for PCQ in the PCQ/CMC mixture was developed to perform an **uniformity of content assay** after dissolving and then diluting the contents of 10 capsules in reverse osmose-purified water.
3. **Uniformity of mass** was determined by weighing 20 capsules.
4. A Fourier transformed **infrared spectrum** of the PCQ/CMC mixture was obtained.

References:

1. Pubchem. Compound summary Chloroquine phosphate. [En ligne]. 28/05/2024. https://pubchem.ncbi.nlm.nih.gov/compound/64927
2. Rising pharmaceuticals Inc. United states pharmacopea. Chloroquine Phosphate Tablet, USP. – Revised : Oct 2018
3. Conseil de l'Europe. 11ème édition de la Pharmacopée européenne. Strasbourg, France : Chloroquine (phosphate de), 2023. 2484-2485 p.
4. Conseil de l'Europe. 11ème édition de la Pharmacopée européenne. Strasbourg, France : Cellulose microcristalline, 2023. 2441-2445 p.
5. K Desta and M Amare. **Validated UV-Visible spectrometry using water as a solvent for determination of chloroquine in tablet samples.** Chemistry International 2017 ; 3 : 288-295.

Results

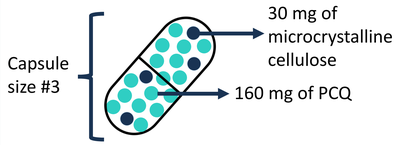

Fig.2 : Formulation of a capsule of PCQ 160 mg

Preparation:

1. Mixing the powders for 10 minutes in an automatic mixer.
2. Filling of empty capsules in a semi-automatic capsule filler.

Storage:

- High-density polyethylene container sealed with a lid containing a silica desiccant (DUMA twist-off®).
- Room temperature.

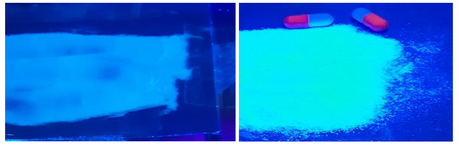

Fig.3 : Fluorescence at 312 nm of CMC (left) vs PCQ/CMC mixture (right)

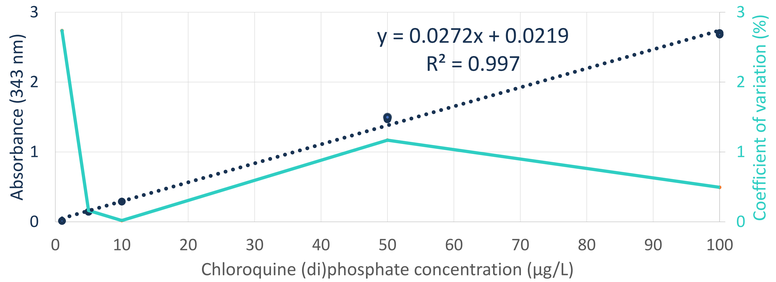

Fig.4: 5-point UV spectrophotometer calibration line for the determination of chloroquine phosphate and coefficient of variation (%) of absorbance as a function of measured concentration (µg/ml) - 343 nm

Table.1: Results of content and mass uniformity tests on chloroquine (di)phosphate capsules produced

Test	Maximum deviation from average
Uniformity of mass (2.9.5)	9,26%
Uniformity of content (2.9.6)	4,21%

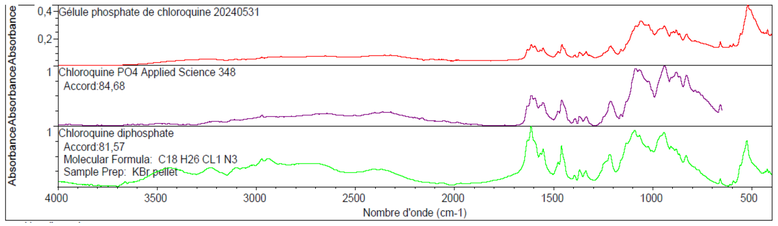

Fig.5: Fourier transformed infrared spectrum of the PCQ/CMC mixture

Conclusions

This study demonstrates the **feasibility of preparing PCQ capsules** for the treatment of lupus patients in response to cutaneous intolerance to HCQ. Our approach guarantees the **quality and safety** of customised PCQ formulations tailored to specific patient needs.

Despite the difficulties involved in handling PCQ, our method for preparing PCQ capsules as a magistral preparation has been rigorously developed and **validated** by the content uniformity test and by the uniformity of the mixture demonstrated by UV fluorescence.

In addition, spectrophotometric assays have demonstrated a **reliable linear relationship** for quantifying PCQ in capsules. The assay method will need to be validated before a hospital preparation of PCQ can be offered.