The discriminatory ability of analytical quality control test methods: A comparison of test results from different international monographs of quinine sulfate tablets

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Abstract

Malaria is a parasitic disease claiming one million lives worldwide annually. Unfortunately, malaria-endemic countries in need of good quality medicines are also overwhelmed with counterfeit or substandard medicine. This results in treatment inefficacy, resistance towards treatment and death. Counterfeit or substandard quinine sulfate tablets are known to have infiltrated the market, however at this point in time, treatment efficacy of quinine sulfate has fortunately not yet been significantly impaired by resistance, but immediate action is required to prevent it from becoming obsolete.

Validated analytical methods with justified specifications are effective in controlling the quality of medicines and to minimise the effect of poor quality medicines. Pharmacopoeia specifies analytical quality control procedures and accompanying specifications to standardise acceptable levels of product quality. Understandably, different monographs of different pharmacopoeias are developed by different independent laboratories and therefore their respective test procedures/specifications for the same FPP may differ from each other. Institutions such as the Pharmacopoeial Dicussion Group (PDG) aim to harmonise pharmacopoeia in order to synchronise final outcomes.

This study evaluated the relevancy of differences in analytical procedures, results and specifications for quinine sulfate tablets set by the United States Pharmacopoeia (USP), British Pharmacopoeia (BP) and International Pharmacopoeia (*Ph.Int*.) in an aim to ensure that these different methods all provide with similar final outcomes and that they be effective in successfully evaluating the quality of quinine sulfate tablets. Four quinine sulfate tablet products were obtained from different manufacturers and were subjected to the tests of all three pharmacopoeia – BP, USP and *Ph.Int*.

The results from identification, assay and related substance testing concluded that the outcomes were the same between the pharmacopoeia despite their differences in techniques/procedures/specifications. The assay, identification and related substances methods and specifications set by each respective monograph were deemed appropriate to evaluate the quality of quinine sulfate tablets.

Even with differences in methodology, quantitative techniques and specifications, the USP and BP dissolution methods for quinine sulfate tablets shared the same final outcome at the first stage of dissolution, whereas none of the products achieved a compliant outcome using the *Ph.Int.* dissolution method.

Possible reasons for the poor dissolution (when using the *Ph.Int.* method) were identified and investigated. Investigation into the solubility of quinine sulfate found *the Ph.Int.* dissolution method conditions to be too stringent, as the solubility of quinine sulfate in phosphate buffer pH 6.8 (dissolution medium specified by the *Ph.Int.*) was found to be much less than in acidic media (as proposed by the BP and USP dissolution methods). Several adapted dissolution methods (called developmental studies) were investigated to serve as potential alternatives for the *Ph.Int.* dissolution method. The developmental studies investigated an alternative dissolution medium, agitation rates (50 rpm, 75 rpm, 100 rpm) and medium volumes (500 ml, 750 ml, 900 ml and 1000 ml). Developmental study 6 was proposed as an alternative dissolution method. Developmental study 6 stipulates the use of the same medium as the original *Ph.Int.* method, as it was deemed the medium of choice for its discriminatory ability. To address the impaired solubility of quinine sulfate in phosphate buffer, the medium volume and agitation were increased (in reference to the original method) to 900 ml and 100 rpm respectively. The same analytical quantitation technique (UV-Vis spectroscopy) is proposed for Developmental study 6. The newly proposed method provided with final outcomes comparable to that of the USP and BP, however having more discriminatory power than the USP and BP.

Keywords: quinine sulfate tablets, dissolution, malaria, pharmacopoeia, validated analytical methods, harmonisation

Uittreksel

Malaria is ‘n parasitiese siekte wat jaarliks ‘n miljoen lewens wêreldwyd eis. Malaria-endemiese lande wat goeie kwaliteit medisynes benodig, word ongelukkig oorstroom met medisyne wat vervals of substandaard is. Dit lei tot oneffektiewe behandeling, weerstand teen behandeling en die dood. Dit is bekend dat vervalste of substandaard kiniensulfaattablette die mark infiltreer het. Op hierdie tydstip is die behandelingseffektiwiteit van kiniensulfaat gelukkig nog nie beduidend deur weerstand belemmer nie, maar onmiddellike optrede is nodig om te voorkom dat dit uitgedien raak.

Gevalideerde analitiese metodes met geregverdigde spesifikasies is effektief om die kwaliteit van medisynes te beheer en om die uitwerking van swak gehalte medisynes te minimaliseer. Farmakopeë spesifiseer analitiese kwaliteitsbeheerprosedures en gepaardgaande spesifikasies om aanvaarbare vlakke van produkkwaliteit te standaardiseer. Dit is verstaanbaar dat verskillende monograwe van verskillende farmakopeë ontwikkel word deur verskillende onafhanklike laboratoriums en gevolglik mag hul onderskeie toetsprosedures/spesifikasies vir dieselfde finale farmaseutiese produk van mekaar verskil. Instellings soos die Pharmacopoeial Dicussion Group (PDG) (Farmakopeë Besprekingsgroep) beoog om farmakopeë te harmoniseer sodat die eindresultaat gesinchroniseer kan wees.

Hierdie studie het die tersaaklikheid van verskille in analitiese prosedures, resultate en spesifikasies vir kiniensulfaattablette, soos gestel deur die United States Pharmacopoeia (USP), British Pharmacopoeia (BP) en International Pharmacopoeia (*Ph.Int*.) geëvalueer, met die doelwit om te verseker dat hierdie verskillende metodes almal dieselfde finale uitkomste bied en dat hulle effektief is om die kwaliteit van kiniensulfaattablette suksesvol te evalueer. Vier kiniensulfaattablet produkte is verkry van verskillende vervaardigers en is onderwerp aan die toetse van al drie farmakopeë – BP, USP en *Ph.Int*.

Die gevolgtrekking uit die resultate van toetsing van identifikasie, essai en verwante middels, was dat die uitkomste dieselfde was tussen die farmakopeë, ten spyte van die verskille in tegnieke/prosedures/spesifikasies. Die essai, identifikasie en verwante middel metodes en spesifikasies soos gestel deur elke onderskeie monograaf, is gereken om geskik te wees om die kwaliteit van kiniensulfaattablette te evalueer.

Selfs met verskille in metodologie, kwantitatiewe tegnieke en spesifikasies, het die USP en BP se dissolusiemetodes vir kiniensulfaattablette dieselfde finale uitkoms gehad by die eerste stadium van dissolusie, terwyl geen van die produkte ‘n uitkoms gehad het wat aan die vereistes voldoen met gebruik van die *Ph.Int.* dissolusiemetode nie.

Moontlike redes vir die swak dissolusie (wanneer die *Ph.Int.* metode gebruik is) is geïdentifiseer en ondersoek. Ondersoek na die oplosbaarheid van kiniensulfaat, het bevind dat die *Ph.Int.* dissolusiemetode se vereistes te streng is, aangesien gevind is dat die oplosbaarheid van kiniensulfaat in fosfaatbuffer pH 6.8 (dissolusiemedium gespesifiseer deur die *Ph.Int.*) baie minder is as in suur media (soos voorgestel deur die BP en USP dissolusiemetodes). Verskeie aangepaste dissolusiemetodes (genaamd ontwikkelingstudies) is ondersoek om te dien as potensiële alternatiewe vir die *Ph.Int.* dissolusiemetode. Die ontwikkelingstudies het 'n alternatiewe dissolusiemedium, agitasiesnelhede (50 rpm, 75 rpm, 100 rpm) en volumes van die medium (500 ml, 750 ml, 900 ml en 1000 ml) ondersoek. Ontwikkelingstudie 6 is as 'n alternatiewe dissolusiemetode voorgestel. Ontwikkelingstudie 6 bepaal die gebruik van dieselfde medium as die oorspronklike *Ph.Int.* metode, aangesien dit weens die diskriminasievermoë daarvan as die voorkeurmedium geag word. Om die belemmerde oplosbaarheid van kiniensulfaat in fosfaatbuffer aan te spreek, is die volume van die medium en agitasie (met verwysing na die oorspronklike metode) tot 900 ml en 100 rpm onderskeidelik verhoog. Dieselfde analitiese kwantifiseringstegniek (UV-Vis spektroskopie) word voorgestel vir Ontwikkelingstudie 6. Hierdie nuut voorgestelde metode verskaf finale uitkomste wat vergelyk kan word met dié van die USP and BP, alhoewel dit meer diskriminerend is as die USP en BP.

Sleutelwoorde: kiniensulfaattablette, dissolusie, malaria, farmakopeë, gevalideerde analitiese metodes, harmonisering

Aims and Objectives

The following was considered the objectives for this study:

To conduct a literature review of malaria, how to effectively prevent and treat it and how the quality of medicine affect effective treatment thereof. It was found that the presence of poor quality anti-malarial medicine on the market (with African countries mostly affected) contributed to a large number of malaria deaths. Counterfeit or substandard variations of quinine sulfate were found to be among some of the medications reported to be available on the market. When tested by independent laboratories, quinine sulfate tablets presented with poor quality dissolution results. A summary is given on what analytical tests are deemed necessary to confirm the quality of medicine and to prove its quality, safety and efficacy. Analytical quality control procedures and specifications of quinine sulfate tablets, set by three international monographs were evaluated. **(Chapter 1)**.

To conduct a literature review of the history, chemical, pharmaceutical and pharmacological properties of quinine sulfate **(Chapter 2)**.

To obtain an understanding of the analytical principles/techniques required to successfully complete quality testing and analysis of quinine sulfate tablets in a laboratory. To ensure that the correct grade of materials was sourced for testing and to ensure that equipment was set up and maintained in accordance with GLP requirements **(Chapter 3)**.

To investigate the validation parameters considered in the process of monograph validation. To investigate which of these parameters are necessary to be repeated and confirmed when method verification is performed in a quality control laboratory. To ensure that the methods still perform as intended (fit for its purpose) as when it were validated at the original developing laboratory **(Chapter 4)**.

To compare the results obtained from conducting quality analyses as prescribed by the three different monographs (*Ph.Int*., USP and BP). When the final outcome of results is similar this might indicate interchange ability (the possibility of harmonisation) of analytical tests prescribed by the three monographs **(Chapter 5)**.

To investigate the factors influencing the dissolution behaviour of solid oral dosage forms at certain dissolution conditions. To perform dissolution tests to investigate if discrepancies between the methods prescribed by the three different monographs (*Ph.Int.,* USP and BP) exist. To obtain a dissolution method as close as possible to the ideal dissolution test. The ideal dissolution test is able to discriminate between different formulations without failing quinine

sulfate tablets of good quality. If necessary, to propose a dissolution method most suitable for the dissolution testing of quinine sulfate tablets (**Chapter 6)**.

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