



Formulation and Evaluation of Quinine sulfate Dispersible Tablets with Emphasis on Taste Masking using Cyclodextrin

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Abstract:

Dispersible tablets (DTs), also termed quick dissolving, fast melting, fast dissolving, fast disintegrating and rapid dissolving tablets, are uncoated or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. Conventional quinine tablets have bitter taste when broken or dispersed to allow administration for children. Cyclodextrins (CDs) are cyclic oligosaccharides whose structural feature gives a hydrophobic interior and a hydrophilic exterior are widely used to increase the solubility of poorly soluble drugs. Recent studies showed that CDs masked taste of bitter drugs. The main objective of the present study was to formulate Quinine Sulphate as dispersible tablets via direct compression using different ratios of super-disintegrants. Three formulae were prepared (F1: Crosspovidone 5%, F2: Crosscarmellose 5% and F3: combination of crosspovidone 2.5% + crosscarmellose 2.5%). Further formulation development was done for taste improvement; four formulae were prepared based on the ratio of Quinine: Hydroxy propyl β - Cyclodextrin (HP- β CD) and the method of preparation. The prepared dispersible tablets were then evaluated for various parameters like thickness, hardness, friability, weight variation, assay

of content and dispersion time. *In vitro* drug release profile was also determined. F3 was selected as optimized formula since it showed good dispersion time (58 sec.), acceptable limits of quality control tests and highest percentage of drug released at the end of 10 minutes. Acceptable taste for F3 was achieved when Quinine was complex at the ratio of 1:2 Quinine HP- β CD and the complex dried from water as solvent. More studies using other concentrations and/or complication methods for Cyclodextrin or other approaches are recommended for better taste masking.

Keywords: Quinine, Dispersible tablets, Cyclodextrin, Dissolution, Dispersion time

1. Introduction:

Dosage forms are the means by which drug molecules/ Active pharmaceutical ingredients (APIs) are delivered to sites of action within the body to produce optimum desired effects and minimum adverse effects. Solid dosage forms are preferred by both patients and manufacturers. These include tablets, capsules, granules, sachets and powders. Solid dosage form contains unit dose of one or more medicament and excipients such as, fillers, binders, glidants, sweeteners, etc[1]. Tablets are the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease of manufacturing. However, it is not suitable for geriatrics, pediatrics and patients experiencing difficulties in swallowing. To overcome this weakness, scientists have developed innovative drug delivery systems known as dispersible tablets[2]. Dispersible tablets also known as quick dissolving, fast melting, fast dissolving, fast disintegrating and rapid dissolving tablets are uncoated or film-coated tablets intended to be dispersed in water before administration

giving a homogeneous dispersion[3]. A pleasant taste is achievable with appropriate taste masking and flavoring, which is most often a mandatory requirement for such drug products. Based on extensive work on taste masking, variable formulation concepts were provided to achieve rapidly or fast disintegrating tablet formulations with excellent organoleptic properties. Advantages of dispersible tablets include, (i) ease of administration to the patients who cannot swallow such as pediatrics, geriatrics, bedridden, stroke victim and institutionalized patients (especially for mentally retarded and psychiatric patients). (ii) Rapid onset of action due to the fast disintegration of tablets which leads to quick dissolution and rapid absorption. (iii) DTs offer all the advantages of solid dosage forms and liquid dosage forms. (iv) Convenience of administration and accurate dosing compared to liquids[4].

Malaria constitutes a major public health problem in Sudan and other tropical countries; transmission of malaria parasites is highly linked with climatic conditions[5]. Sudan Malaria Treatment Protocol,

2017 and the malaria technical advisory committee recommended the use of Artemether-Lumefantrine (AL) as first-line therapy, Dihydroartemisinin-piperaquine (DHAP) as a second-line treatment. The protocol recommended the use of Quinine or intravenous Artesunate for treatment of severe malaria at hospital level. The therapeutic options previously recommended by WHO for the pediatric group included intravenous Artesunate, in preference to Quinine for the management of severe malaria in children[5]. Quinine is a cinchona alkaloid that belongs to the aryl amino alcohol group of drugs. It is an extremely basic compound and is, therefore, always presented as a salt and the dihydrochloride and sulfate are the most widely used[6]. Quinine is solid, bulky, white, amorphous powder or crystalline alkaloid odorless, with very bitter taste. $pK_1 = 5.07$; $pK_2 = 9.7$ Solubility. Quinine is class I according to biopharmaceutics classification system (high solubility, high permeability). Quinine has rapid schizonticidal action against intra-erythrocytic malaria parasites. It is also gametocytocidal for *Plasmodium vivax* and *Plasmodium malarie*, but not for *Plasmodium falciparum*. Quinine also has analgesic, but not antipyretic effect, it is proved that Quinine has antifungal activity and can ameliorates doxorubicin-induced autophagy-dependent apoptosis[6]. Quinine demonstrate infection inhibition in human cell lines with SARS-CoV-2[7]. The recommended dose of Quinine is 10 mg

/kg bodyweight 3 times a day for 7 days for treatment of malaria in children. Sometimes administration started via intravenous infusion followed by oral route via splitting of higher strength adult conventional oral tablets. Definitely, this practice may lead to poor dose adjustment and noncompliance due to the bitter taste[8,9]. Many drugs are marketed as dispersible tablets for pediatric use. Antimalarial Artemether-Lumefantrine is one example. In recent studies, many drugs were formulated as dispersible tablets, these includes Chlorpheniramine[10], Valsartan [11], Lomefloxacin [12], Aceclofenac [13], Pyridostigmine[14] and Levofloxacin[15] in which Cyclodextrin and its derivatives were used for taste masking. This work aimed at formulation of Quinine sulfate 100 mg dispersible tablets with emphasis on the bitter taste masking using aspartame and Hydroxy propyl β - cyclodextrin (HP- β CD).

2. Materials and methods:

2.1 Materials:

Quinine sulfate, lactose, peppermint and aspartame, were kindly gifted by Amipharma Pharmaceutical Company (Khartoum, Sudan). Microcrystalline cellulose and cyclodextrin were kindly gifted by Blue Nile Pharmaceutical Company (Sudan). Crosscarmellose, crosspovidone and magnesium stearate were purchased from Techno Pharmchem (India).

Talc was obtained from Central Drug House (P) Ltd. (New Delhi, India).

2.2 Methods:

2.2.1 Construction of calibration curve for UV analysis:

Aqueous Quinine stock solution 0.1% was prepared using IsoLab Laborgerate GmbH sonicator. Then five concentrations (4µg/ml, 8µg/ml, 12µg/ml, 16µg/ml and 20µg/ml) were prepared by serial dilution. The UV absorbance at λ_{max} of 236 nm was recorded in triplicate using 7315 UV/VIS spectrophotometer, (Jenway®, England).

2.2.2 Formulation of dispersible tablet:

Three formulae containing variable amounts of super-disintegrants were prepared (Table 1). All

Table 1: Composition of Quinine dispersible tablets:

ingredients were passed through sieve No.12, and then weighed using sensitive balance (KERN®, Germany). Inclusion complex of Quinine sulphate and hydroxy propyl β - cyclodextrin in different ratios was prepared by dissolving the drug and hydroxy propyl β - cyclodextrin in solvent (water/methanol) with continuous stirring. Solvent was completely evaporated at 40-50°C[12]. Tablets were prepared by direct compression. Quinine- HP- β CD was then mixed with directly compressible diluents and super disintegrants in a mortar with the help of pestle, finally aspartame as sweetener, Mg stearate as lubricant, peppermint as flavoring agent, lactose as filler were added. The blend was then compressed using a tablet compression machine[2].

Components	Amounts (mg)		
	F 1	F 2	F 3
Quinine/ Quinine- HP- β CD equivalent to	100	100	100
Microcrystalline cellulose	60	60	60
Crosscarmellose	-	5%	2.5%
Crosspovidone	5%	-	2.5%
Talc	1%	1%	1%
Magnesium stearate	1%	1%	1%
Aspartame	2	2	2
Peppermint	2	2	2
Total tablet weight completed using Lactose	450	450	450

2.2.3 Preparation of Quinine- HP- β CD complex by inclusion complication method:

Quinine sulphate and HP- β CD were prepared in two molar ratios 1:1 and 1:2 by triturating them with minimum quantity of methanol (about 8 ml) with continuous stirring. Solvent was completely evaporated from the resulting mixture at 40-45°C with continuous stirring to obtain dry complex. When Quinine sulphate and HP- β CD 1: 2 complex was prepared using water, Quinine was needed with mixture of HP- β CD and water with continuous stirring. Water was completely evaporated at 50 °C using rotary evaporator to obtain dry powder[12].

2.2.4 Post compression evaluation of quinine dispersible tablets:

2.2.4.1 General appearance:

Colors, shape, smoothness of surfaces were evaluated by visual inspection.

2.2.4.2 Tablets thickness:

Thickness of individual tablets was measured using digital Caliper Vernier. Tablet thickness should be controlled within a $\pm 5\%$ variation of a standard. Thickness must be controlled to facilitate packaging[16].

2.2.4.3 Tablets hardness:

Tablet hardness tester (Gouming®, China) was used to determine the crushing strength of the tablets. Ten tablets were randomly selected and the pressure at which each tablet broken was measured [17].

2.2.4.4 Friability test:

Friability test was performed to monitor the resistance of the tablets to abrasions or fractures during manufacturing, packaging and transportation. 20 tablets were randomly selected from each formulation, degusted, weighed using sensitive balance (Kern®, Germany) and then subjected to a uniform tumbling motion in a friability tester (Gouming®, China) at 25 rpm for 4 min. Tablets were degusted again after the end of rotation and reweighed. The friability loss was determined as a percentage weight loss and calculated as follow:

$$\% \text{ Weight loss} = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is the initial weight of tablets prior to the test and W_2 is the final weight of tablets at the end of the test.

A maximum weight loss of less than 1% is considered acceptable according to USP standards[18].

2.2.4.5 Tablets content and conformity:

Ten tablets were powdered using mortar and pestle. A quantity equivalent to 10 mg of Quinine was accurately weighed using sensitive balance (Kern®, Germany) and then transferred to a 50 ml volumetric flask and completed to 50 ml with water. The resulting solution was filtered through 0.45 μ m membrane filter, suitably diluted and

analyzed spectrophotometrically at 236 nm using 7315 UV–VIS spectrophotometer (Jenway®, England). Conformity with content uniformity test achieved when the % amount of Quinine found not less than 85% and not more than 115% of the labeled quantity according to (USP, 2010).

2.2.4.6 Dispersion time:

Tablets were added to 10 ml of water and the time required for complete dispersion was recorded in seconds. Ten tablets from each formulation were randomly selected and examined for dispersion time[2].

2.2.4.7 Disintegration test:

Disintegration test is a measure of the time required for a group of tablets to break up into particles under a given set of conditions. Six tablets were randomly selected from each brand; one tablet was placed in each tube of the basket. The basket rack was positioned in one liter beaker containing distilled water maintained at 37°C as disintegration medium. The apparatus was started to move the basket assembly containing the tablets (raising and lowering occurred in approximately 28- 32 cycles per minute) and the time required for the six tablets to break into particles and to pass the screen to the disintegration medium was recorded. The tablets considered complying with USP standards if all tablets disintegrate between 5 to 30 minutes [2].

2.2.4.8 Dissolution test:

In vitro dissolution test was carried out using six tablets, one tablet was placed into USP apparatus II

ZBS-8GD Dissolution tester (Erweka®, Germany). The stirrer motor, dissolution vessel and paddles were assembled, and the stirrer motor was switched onto speed of 50rpm. 900 ml of water as dissolution medium was added into each vessel and maintained at 36.5°C-37.5° . 5 ml sample was removed from the dissolution vessel every 2 min, 4min, 6min, 8min, 10min, 15min, 20min, 30min, 45min and 60 min using a syringe with a wide gauge cannula. The sample removed was replaced with an equal volume of fresh dissolution medium (5 ml). These samples were then filtered through 0.45 µm membrane filter and the absorbance of filtered solutions was determined using UV spectrophotometer at 236 nm[19].

3.4.9 Taste evaluation of the dispersible tablet:

Taste evaluation of the dispersible tablet was carried out using twelve human volunteers. Quinine pure drug was used as a base to overcome the individual variation in taste measuring and for the comparative purpose. Tablets containing Quinine sulphate without HP- βCD (F1, F2 and F3) and the optimized formulation containing different ratios of Quinine: HP- βCD (1:1 and 1:2) evaporated from methanol or water as solvent was tested (F4, F5, F6 and F7). Volunteers were provided with adequate rinsing and drinking of water and a break time of 15 minute between each sample to avoid carry over[20].

Table (2) below shows the scale used for evaluation of the taste.

Table 2: Bitterness evaluation scale:

Scale	-	+	++	+++
Bitterness	No bitter taste	Slightly bitter	Moderately bitter	Very bitter

3. Results and Discussion:

3.1 Calibration curve of Quinine:

Linear calibration curve (Figure 1) was obtained for Quinine at the conc. range between 4-20 µg/ml

as $Absorbance = 0.0613 * Concentration + 0.0387$, with a regression coefficient (R^2) = 0.9997.

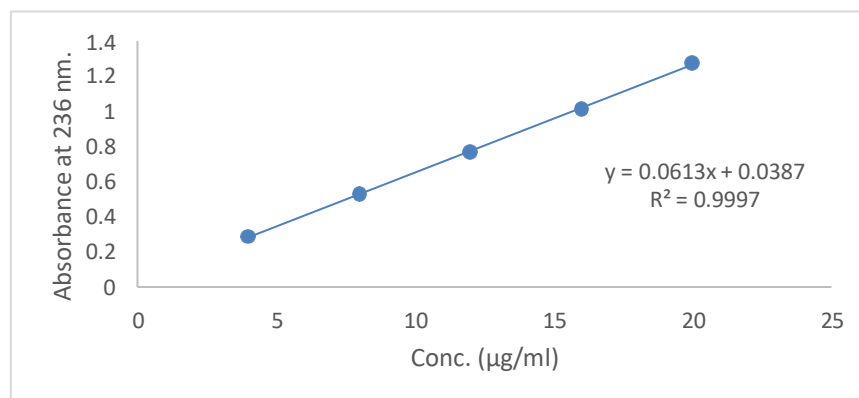


Figure 1: Calibration curve of Quinine

3.2 Post compression evaluation of Quinine dispersible tablets:

3.2.1 Dispersion Time test:

Dispersion time was measured in seconds; average dispersion time for each formula is shown in Table

[3]. Crosspovidone containing formula showed rapid dispersion ($\approx$ 40 Sec.), while crosscarmellose containing formula showed the slowest dispersion time (178 Sec.).

Table 3: Dispersion time and taste of the three quinine dispersible tablets formulations:

Formula	Dispersion time (Sec.)	Bitterness
F1	039.5± 0.58	+++
F2	178.0± 2.50	+++
F3	058.5± 0.87	+++

3.2.2 In-vitro Dissolution Study:

The three formulations were subjected for the *in vitro* dissolution studies using tablet dissolution tester. The plots of cumulative% drug released versus time and the results obtained for the formulations F1, F2 and F3 are shown in Figure [2]. The dissolution was found to increase rapidly in F2 and F3 in the first 15 minutes ($\approx 100\%$) compared to F1 which showed only 15.77%. Croscarmellose have recorded highest drug release compared to Crosspovidone and combined super-disintegrants, 100% drug release in F2 and F3 formulations was achieved within 6 and 15 minutes respectively. The relative efficiency of different super-disintegrants to improve the dissolution rate of tablets was in order, $F3 > F2 > F1$. This is in accordance with a study done by Veerendra K. et al [12]. The rapid increase in

dissolution of Quinine when croscarmellose sodium was used may be attributed to rapid swelling and disintegration of tablet into apparently primary particles while Crosspovidone exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrates the tablets rapidly but into larger masses of aggregated particles [21]. Generally, dissolution of dispersible tablets was found mainly dependent on the type and amount of super-disintegrants used in the formulation. The amounts of super-disintegrants used in this study were within the stated limits (crosspovidone up to 3% w/w and croscarmellose sodium up to 5% w/w) for preparation of dispersible tablets through different technologies like direct compression, wet granulation, sublimation, spray drying, freeze drying, tablet moulding and mass extrusion [22,23].

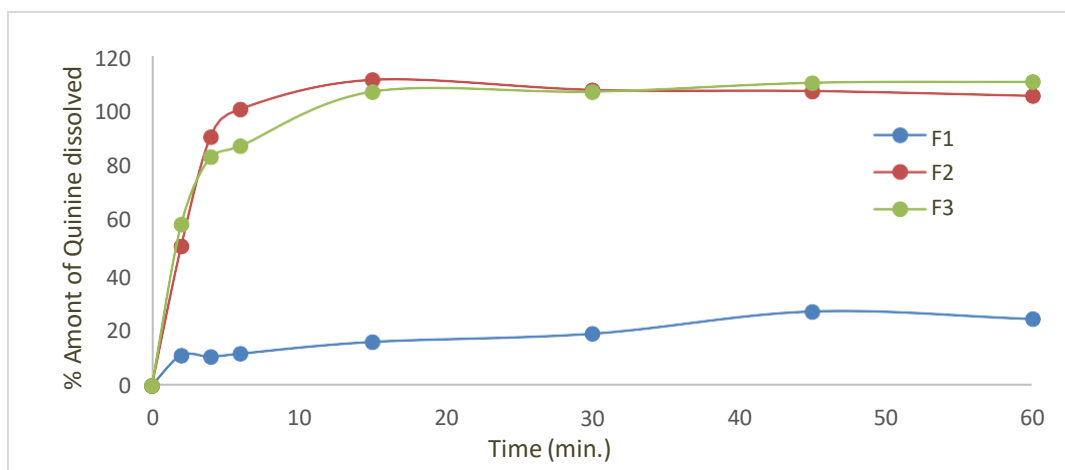


Figure 2: Dissolution profile of different formulations of Quinine dispersible tablets

Based on the dispersion time and dissolution profile results, F3 was selected as an optimized formula and subjected for further studies like taste masking and post compression evaluation.

3.2.3 Physical evaluation of Quinine dispersible tablets:

Table (4) below shows results of taste masking, it is clear that taste masking effect increased as the amount of cyclodextrin increased. Simultaneously, the preparation method of dry Quinine: HP- β CD complex was found to affect the taste of the formula, drying of the complex from water gave better taste masking effect compared to drying from methanol. The sequence of bitterness was as

follow, $F4 > F5/F6 > F7$. Slight bitter taste was achieved in F7 and considered as optimized formula. F7 was then evaluated for other physical characteristics like weight variation, thickness, friability, hardness, disintegration time and dispersion time (Table 5). All results were found within the accepted limits. Addition of cyclodextrin to F3 in the ratio of 1:2 Quinine: HP- β CD (F7) decreases the dispersion time from 58.5 to 40.5 Sec. (Tables 3 and 5). On the other hand the dissolution profile was not affected upon complication of Quinine with HP- β CD; the % dissolved at 10 mins was found 94.79, 91.94% for F3 and F7 respectively.

Table 4: Taste evaluation for different formulations of Quinine dispersible tablet:

Formula	F4	F5	F6	F7
Quinine: HP- β CD	1:1	1:2	1:1	1:2
Solvent	Methanol	Methanol	Water	Water
Bitterness	+++	++	++	+

Table 5: Post-compression evaluation of the optimized formula:

Optimized formula	Weight (mg)	Thickness (mm)	Friability %	Drug content %	Hardness (N/mm ²)	Dispersion Time (Sec.)	Disintegration Time (Min.)
F7	445.7 $\pm$ 0.2	0.35 $\pm$ 0.0	0.51	98	69 $\pm$ 8.06	40.5 $\pm$ 0.51	4 $\pm$ 0.12

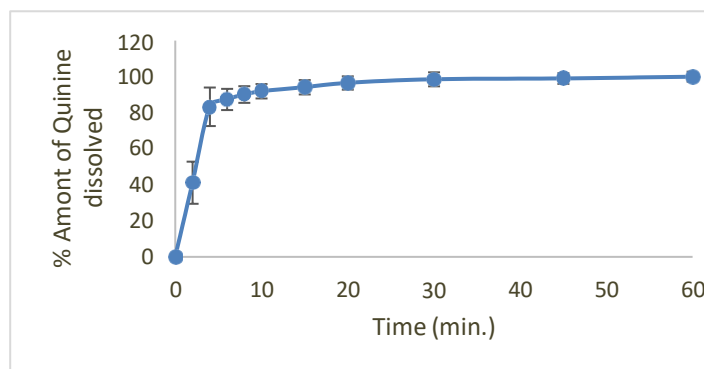


Figure 3: Dissolution profile of the optimized formula (F7).

4. Conclusion:

Quinine dispersible tablets with rapid dispersion time were formulated via direct compression method using different types of superdisintegrants (Crosspovidone and Crosscarmellose). Based on its dispersion time and *in vitro* release profile, F3 was selected as optimized formula. Accepted taste for the optimized formula was achieved in F7 when dry Quinine: HP- β CD complex was prepared at the ratio of 1:2 using water as solvent. More studies at higher ratios of Quinine: HP- β CD and/or use of other inclusion methods are recommended for better taste masking. In addition, further stability and *in vivo* studies should be conducted.

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