Chapter 6: API release – Dissolution and disintegration

Introduction

Quinine sulfate tablets, being an important medicine in the treatment of malaria, should be of high quality and safe to use for patients with this life threatening disease. Tablets failing to disintegrate and release the API could be fatal to patients who need prompt medical treatment. Disintegration of the solid oral dosage form, together with the dissolution and permeability of the API, are important factors that determine the oral absorption of the API from a solid oral dosage form and ultimately determines the product's fate regarding its efficacy (Shargel *et al.*, 2005:413).

Disintegration tests evaluate if the solid oral dosage form will break into smaller particles and ensure the increase in effective surface area from which the API can be released. (Shargel *et al.*, 2005:414). The dissolution rate of a solid oral dosage form is greatly influenced by the disintegration of the tablet or capsule, and also the solubility of the API (Shargel *et al.*, 2005:413).

During the research and development phase (R&D) *in vitro* dissolution protocols are developed to analyse the medicinal product and used as a predictive tool for *in vivo* bioavailability (Azarmi *et al.,* 2007:13).

The general discussion on dissolution methodology presented in Chapter 3 (section 3.3) indicated that:

- dissolution testing measures the release of the API as a function of time in specified conditions (Shargel *et al.*, 2005:421);
- a certain amount of API should be released from the solid oral dosage form and dissolved in the dissolution medium within a specified period for the FPP to comply with the dissolution specifications (Shargel *et al.*, 2005:424).

The amount of API (expressed as a percentage of the label claim of the FPP) that should be released and dissolved in the dissolution medium at the final withdrawal time (single point dissolution) is represented by the Q-value (Vaghela *et al.,* 2011:53). At stage 1 (S_1), six tablets are tested, all of which must achieve Q + 5% dissolution to comply with S_1. If the criterion is met at S_1 the test complies and no further testing is required. However, if the product does not comply with S_1, dissolution testing will continue (S_2 or S_3) until the criteria have been met or when all the subsequent stage/s have been exhausted (Shargel *et al.*, 2005:428). The

aforementioned stages of dissolution testing apply unless specified otherwise by the individual monograph – which is the case for the dissolution method of quinine sulfate tablets of the *Ph.Int*. The different stages of dissolution testing is presented in Table 6-1.

Table 6-1: The dissolution acceptance criteria specified in the general chapters of the USP, BP and *Ph.Int.* (USP, 2013; BP, 2013 and *Ph.Int.*, 2013)

Stage	Number of tablets tested	Acceptance criteria
S_1	6	Each unit shows a % dissolution of not less than Q+5%
S_2	6	Average % dissolution of the 12 units ($S_1 + S_2$) is equal to or greater than Q, and the % dissolution of no unit is less than Q - 15%
S_3	12	Average % dissolution of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, the % dissolution of not more than 2 units are less than Q - 15% and the % dissolution of no unit is less than Q - 25%

This chapter presents the disintegration and dissolution results obtained using the BP, USP and *Ph.Int*. quinine sulfate tablets dissolution methods. It furthers to describe additional experimental work (i.e. solubility and profile dissolutions) in order to provide insight into the differences between the results obtained using the different pharmacopoeial methods, ultimately allowing to propose an alternative dissolution method (and accompanying specifications) for the revision of current dissolution methods of the pharmacopoeias where deemed necessary.

Single point dissolutions were initially performed as required by each pharmacopoeia. Multiple-point (also known as profile) dissolutions were thereafter performed to evaluate the API release profiles from the tablets.

6.1 Dissolution requirements/specifications of the USP, BP and *Ph.Int.* monographs for quinine sulfate tablets

The different dissolution conditions, procedures and specifications for each of the quinine sulfate tablet monographs from the different pharmacopoeias are summarised in Table 6-2.

The quinine sulfate tablet dissolution methods described in the USP, BP and *Ph.Int.* monographs differ significantly from one another (as seen in Table 6-2). Furthermore the specifications of the quinine sulfate tablets dissolution methods of the *Ph.Int.* monograph differed from that of the general conditions for dissolution (Table 6-1 vs Table 6-2). The *Ph.Int.* monograph for quinine sulfate tablets specifies that after 30 minutes, 80% dissolution must be achieved (S_1). If not, the test may continue to a second and final stage (S_2), requiring the average percentage dissolution of the 12 tablets ($S_1 + S_2$) tested to not be less than 75% and

that no individual tablet show a % dissolution less than 60%. There are no S_3 conditions specified for the quinine sulfate tablets dissolution method of the *Ph.Int.* monograph.

Table 6-2: Dissolution conditions, specifications and procedures as required by the different pharmacopoeia for quinine sulfate tablets (USP, 2013; BP, 2013 and *Ph.Int*., 2013)

	BP	USP	*Ph.Int.*
Apparatus:	Basket assembly	Basket assembly	Paddle assembly
Dissolution medium:	0.1 M HCl	0.01 M HCl	Phosphate buffer pH 6.8
Medium volume:	900 ml	900 ml	500 ml
Rotation speed:	100 rpm	100 rpm	75 rpm
Acceptance criterion	Q=70% (normal stages as specified in Table 6-1)	Q=75% (normal stages as specified in Table 6-1)	S_1 = Not less than 80% S2 = Average of 12 (S1+S2) $\geq$ 75% and no unit less than 60%
Withdrawal time	45 minutes	45 minutes	30 minutes
Quantitation technique:	UV-Vis spectrophotometry	UV-Vis spectrophotometry	UV-Vis spectrophotometry
Wavelength of detection:	348 nm	248 nm	330 nm

6.2 Results and discussion for the dissolution and disintegration testing according to the specified pharmacopoeias

6.2.1 Disintegration

The *Ph.Int.* quinine sulfate tablets monograph provides the analyst an option of performing either a dissolution test (test A) or dinsintegration (test B). The *Ph.Int.* monograph state that should test B (disintegration) be selected and found to be non-compliant, test A (dissolution) should be performed. The ICH Q6A guidelines (ICH, 1999:11) state that dissolution testing may be replaced by disintegration testing if the product is an immediate release product containing a highly water soluble API which is rapidly released from the dosage form (% dissolution > 80% after 15 minutes at a pH range 1.2 – 6.8) (ICH, 1999:11). From the three pharmacopoeias (BP, USP and *Ph.Int.*) the *Ph.Int.* monograph is the only one that specifies a disintegration test for quinine sulfate tablets (as a potential choice).

All three pharmacopoeias do however have general conditions and specifications for disintegration in their general chapters. The norm for disintegration testing of immediate release oral solid dosage forms (not modified release etc.) is to use water as medium, at 37 ± 0.5°C, with a specification of 15 minutes (BP, 2013). The disintegration test for quinine sulfate tablets by the *Ph.Int.* method uses the aforementioned conditions, but a limit of 10 minutes is specified in contrast to 15 minutes.

The disintegration test results for Products 1 - 4 are presented in Table 6-3. All the samples disintegrated within ± 5 minutes. The results complied with the general specifications for disintegration by USP and BP monographs (15 minutes) and the specific limits for quinine sulfate tablets by *Ph.Int.* monograph (10 minutes).

Table 6-3: Disintegration testing results for Products 1 - 4 as specified in the *Ph.Int.* monograph for quinine sulfate tablets

	Product 1	Product 2	Product 3	Product 4
Time: Tablet 1	Within 5 minutes	Within 4 minutes	Within 2 minutes	Within 2 minutes
Time: Tablet 2	Within 5 minutes	Within 4 minutes	Within 2 minutes	Within 2 minutes
Time: Tablet 3	Within 5 minutes	Within 5 minutes	Within 3 minutes	Within 3 minutes
Time: Sample 4	Within 5 minutes	Within 5 minutes	Within 3 minutes	Within 3 minutes
Time: Tablet 5	Within 5 minutes	Within 6 minutes	Within 4 minutes	Within 3 minutes
Time: Tablet 6	Within 5 minutes	Within 6 minutes	Within 4 minutes	Within 3 minutes

6.2.2 Dissolution

All four products were tested according to the dissolution test methods as described in Table 6-2. Results are summarised in Table 6-4.

Table 6-4: Dissolution results of Products 1 - 4 using the dissolution procedures of the BP, USP and *Ph.Int.* monographs

% dissolution at final withdrawal as specified in the respective monographs				
	Tablet	BP	USP	*Ph.Int.*
Product 1	1	93	96	50
	2	95	96	54
	3	92	97	62
	4	95	97	56
	5	96	96	56
	6	95	96	47
	7			55
	8			52
	9			55
	10			51
	11			51
	12			53
Average		**94**	**96**	**54**
%RSD		**1.8**	**0.8**	**9.4**
Product 2	1	94	98	59
	2	94	96	59
	3	92	96	68
	4	94	99	60
	5	95	95	59
	6	90	94	56
	7			63
	8			52
	9			67
	10			62
	11			55
	12			61
Average		**92**	**96**	**60**
%RSD		**2.3**	**1.8**	**7.7**
Product 3	1	93	96	68
	2	94	94	71
	3	95	96	73
	4	97	100	75
	5	91	100	71
	6	96	95	70
	7			73
	8			70
	9			69
	10			71
	11			71
	12			69
Average		**95**	**97**	**71**
%RSD		**2.5**	**2.8**	**2.7**
Product 4	1	93	96	49
	2	91	96	52
	3	95	92	54
	4	93	97	56
	5	93	95	49
	6	92	96	53
	7			46
	8			49
	9			47
	10			50
	11			55
	12			53
Average		**92**	**95**	**51**
%RSD		**1.9**	**1.8**	**6.5**

As seen in Table 6-4, all four products were compliant with the S_1 specifications of the USP and BP monographs and did not require any further testing. For the *Ph.Int.* monograph however, none of the Products were found to comply with the S_1 specifications. For this reason another 6 tablets of each product (referred to as tablets 7 - 12) were tested, serving as S_2 for the *Ph.Int.* monograph dissolutions. For S_2 the average percentage dissolution for Products 1, 2, 3 and 4 (tablets 1 - 12) did not achieve 75% and/or had individual units below 60%, and therefore failed to comply with the dissolution specifications.

The single point dissolution results indicated that the outcomes (i.e. complies with S_1 specifications) for dissolutions were comparable between the USP and BP monographs, whereas none of the samples managed to comply with the *Ph.Int*. monograph specifications.

Of concern is that the dissolution and disintegration tests (choice of tests) of the *Ph.Int.* monograph did not provide with comparable outcome (i.e. compliance with both dissolution and disintegration specifications). None of the products could achieve a compliant outcome by means of dissolution, whereas the results for all products were well within limits of disintegration testing. It can therefore be concluded that contradictory results were obtained within the same monograph (*Ph.Int.* monograph) – dissolution vs. disintegration, and that, only by first choice of test B (disintegration) the outcomes of all the monographs (*Ph.Int.* vs BP vs USP) are comparable.

6.3 Dissolution profiles (from pharmacopoeial dissolution methods)

It was decided to further investigate quinine sulfate's dissolution behaviour by performing multiple-point dissolutions (profile dissolutions).

The multiple-point dissolutions were performed using the same dissolution media, apparatus, medium volume and agitation speed as specified by the different monographs. Samples for multiple-point dissolutions were withdrawn at 7.5; 15; 22.5; 30; 45 and 60 minutes. The averages and % RSD for the percentage dissolution obtained are presented in Table 6-5, Table 6-6 and Table 6-7 and Figure 6-1, Figure 6-2 and Figure 6-3. The same volume of medium that was withdrawn at each interval was replaced with fresh medium after every withdrawal. Samples were suitably diluted and analysed using a Cary UV-Vis spectrophotometer (Shargel *et al*., 2005:424).

Table 6-5: **Multiple-point dissolution results for Products 1 - 4 using the BP monograph dissolution conditions (n = 12)**

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	76	97	97	96	94	93
%RSD	22.7	2.5	1.8	2.1	1.8	1.8
Product 2						
Average	63	94	93	92	92	91
%RSD	17.8	2.4	2.6	2.3	2.3	2.6
Product 3						
Average	99	98	97	96	95	94
%RSD	2.2	2.3	2.0	2.2	2.5	2.3
Product 4						
Average	97	95	94	93	92	91
%RSD	2.0	1.9	2.0	1.9	1.9	1.7

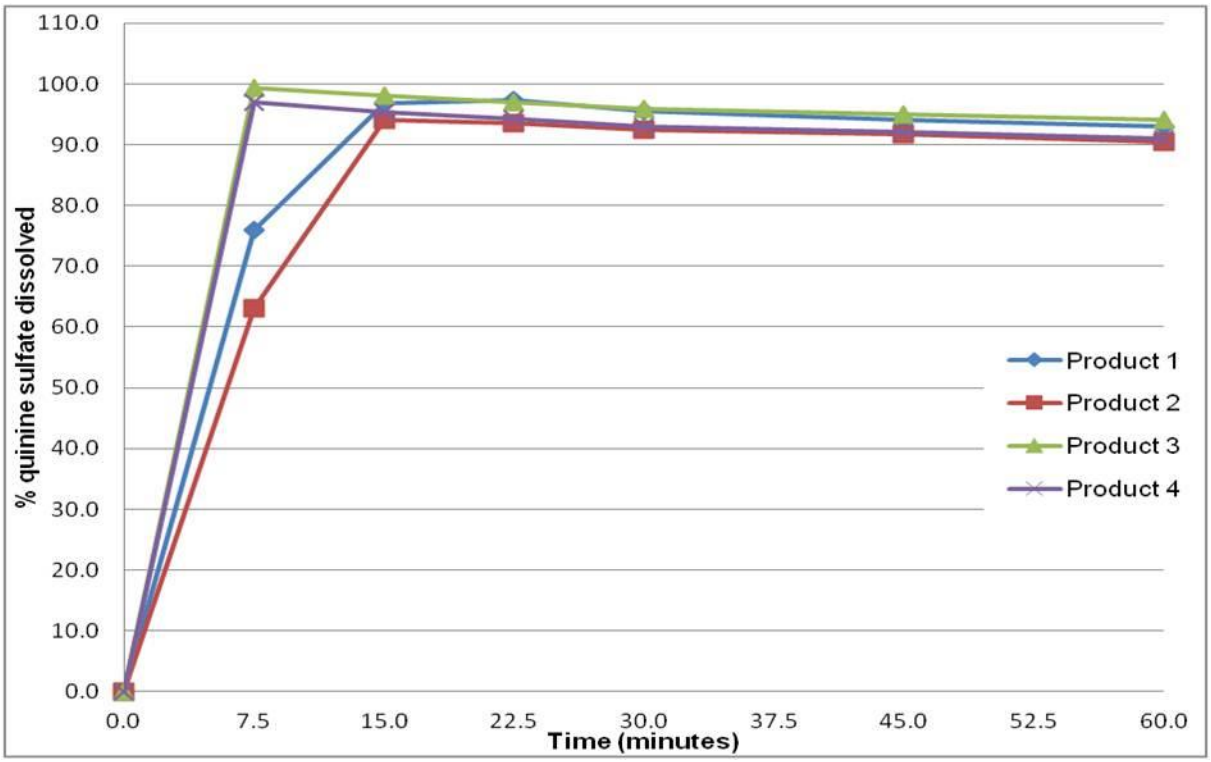

Figure 6-1: **Dissolution profiles for Products 1 - 4 using the BP monograph dissolution conditions.**

Table 6-6: Multiple-point dissolution results for Products 1 - 4 using the USP monograph dissolution conditions (n = 12)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	84	94	97	97	96	95
%RSD	2.3	2.3	2.7	0.8	0.8	1.3
Product 2						
Average	87	99	98	96	96	95
%RSD	6.3	1.9	1.6	2.1	1.8	1.7
Product 3						
Average	98	99	99	100	97	98
%RSD	1.8	2.4	2.3	2.0	2.8	3.5
Product 4						
Average	93	94	93	95	95	96
%RSD	1.4	2.0	2.1	1.8	1.8	2.0

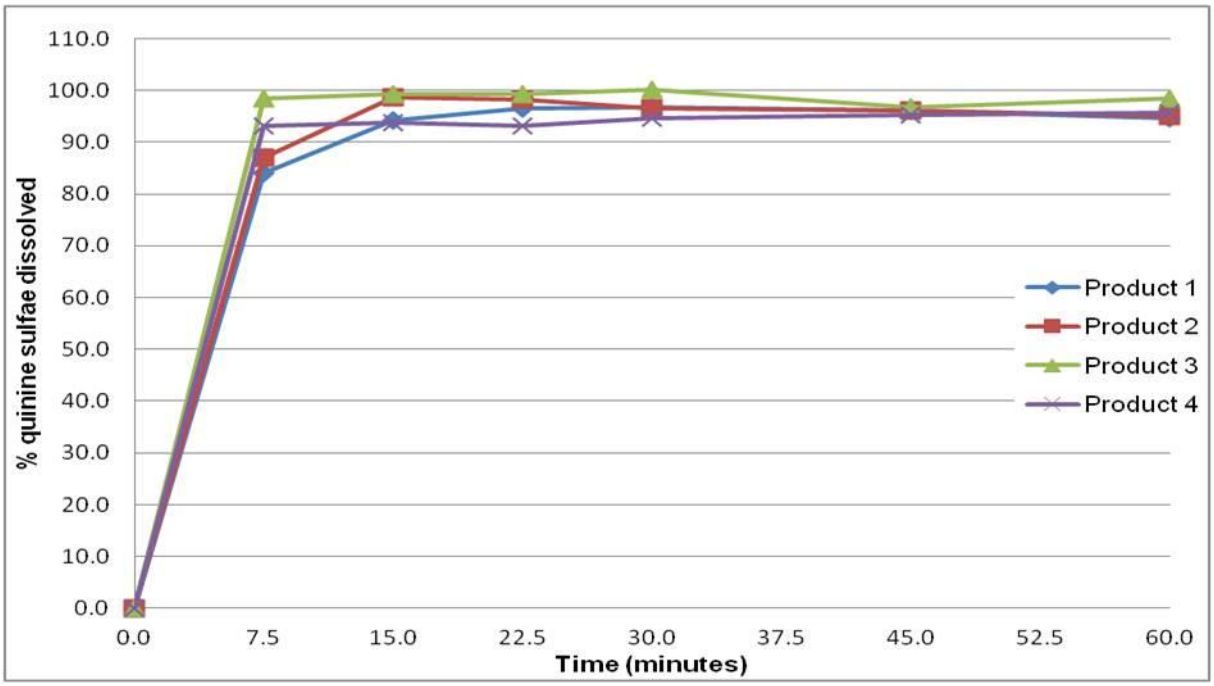

Figure 6-2: Dissolution profiles for Products 1 - 4 using the USP monograph dissolution conditions

Table 6-7: Multiple-point dissolution results for Products 1 - 4 using the *Ph.Int.* monograph dissolution conditions (n = 12)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	37	47	51	54	57	59
%RSD	10.7	8.7	9.7	9.4	10.0	10.6
Product 2						
Average	41	52	57	60	66	66
%RSD	11.3	9.3	8.0	7.7	7.3	7.7
Product 3						
Average	50	63	70	71	75	75
%RSD	7.9	3.9	3.3	2.7	1.9	3.2
Product 4						
Average	25	39	46	51	58	62
%RSD	7.9	7.2	8.9	6.5	6.0	5.4

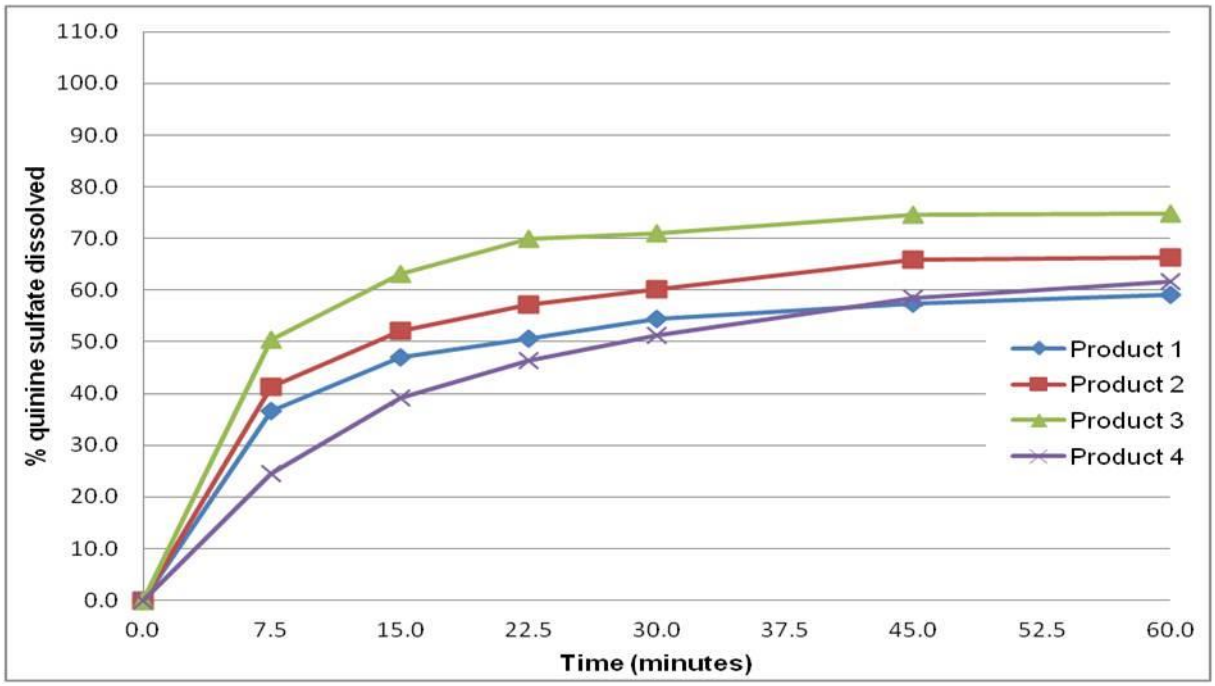

Figure 6-3: Multiple-point dissolution results for Products 1 - 4 using the *Ph.Int.* monograph dissolution conditions (n = 12)

All the products when tested according to the dissolution conditions of the BP monograph (Table 6-5, Figure 6-1) and USP monograph (Table 6-6, Figure 6-2), achieved an average percentage dissolution ranging between 90% and 100% within the first 15 minutes of testing. These dissolution profiles (BP and USP monographs) suggested an impaired ability of these methods to distinguish between the different quinine sulfate tablet formulations. The dissolution profiles obtained using the *Ph.Int.* monograph showed an improved discriminatory ability, since the profiles were clearly separated and showed gradual dissolution over time.

The dissolution profiles obtained using the *Ph.Int.* monograph further showed that none of the samples reached a plateau, even after 60 minutes, suggesting that under these conditions, the dissolution of the samples were incomplete. The disintegration test results indicated that products disintegrated within 5 minutes. The first withdrawal time was at 7.5 minutes. Complete disintegration was observed at 7.5 minutes. Therefore, it could be concluded that disintegration was not the rate limiting factor for dissolution.

The model independent approaches and a similarity factor (f_2)) were used to assist in the evaluation of the dissolution profiles. The f_2-value is used to measure the agreement between two dissolution profiles (equation 6.1) (FDA, 1997:8; Shargel *et al*., 2005:482).

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-5} \times 100\right\} \qquad \text{Equation 6.1}$$

Where:

n = the number of withdrawals

R_t = % reference sample dissolved at time t

T_t = the % sample dissolved at time t

For dissolution profiles to be deemed similar, an average difference of 10% is allowed at all measured time points. A 10% difference at each time point will result in an f_2-value of 50, and any lesser difference will result in a f_2-value between 50 and 100, which indicates similarity between the two dissolution profiles (Shargel *et al.*, 2005:482 ; MCC, 2011:3). A difference of more than 10% at each time point will result in an f_2-value below 50 (dissimilar).

When the % dissolution reaches 85% within 15 minutes, it is not necessary to calculate the f_2-value, as similarity is implicated (MCC, 2011:6).

Dissolution studies performed during the research and development phase require that only three individual units be tested (Pablo *et al.,* 2009:106,107). However when comparing dissolution profiles in a QCL with the model independent method, the following requirements have to be abided to (MCC, 2011:6):

- 12 individual units (tablets) need to be tested per product;
- a minimum of three withdrawal time points (excluding point zero) should be used and only one withdrawal time measurement after 85% dissolution should be included;

- the %RSD should not be greater than 20% at <15 minutes or greater than 10% at time points > 15 minutes (MCC, 2011).

Dissolution profiles obtained from each product under different dissolution conditions where compared to evaluate the effect of different dissolution conditions on the dissolution of the products (Tale 6-8). Inter-product (one product against a different product) comparisons were not considered since different products may have different formulations, which may result in dissolution profiles not related to differences in dissolution methods.

Determined by means of two-dimensional matrix analysis, f_2-values were calculated to evaluate differences in the dissolution profiles for the following:

- BP vs USP
- BP vs *Ph.Int.*
- USP vs *Ph.Int.*

The f_2-values for the different profile comparisons are summarised in Table 6-8.

Table 6-8: Similarity (f_2) calculations for the different dissolution profile comparisons obtained from performing the dissolution methods obtained in the BP, USP and *Ph.Int.* monograph

	BP vs. USP	**BP vs. *Ph.Int.***	**USP vs. *Ph.Int.***
Product 1 vs Product 1	Similar (> 85% within 15 minutes)	19	18
Product 2 vs Product 2	Similar (> 85% within 15 minutes)	25	21
Product 3 vs Product 3	Similar (> 85% within 15 minutes)	25	24
Product 4 vs Product 4	Similar (> 85% within 15 minutes)	15	16

As anticipated, the comparison of the dissolution profiles obtained using the BP and USP monographs revealed that the dissolution profiles were similar (% dissolution > 85% within 15 minutes). The only difference between the dissolution methods of the USP and BP monographs is the dissolution medium. Both monographs (USP and BP monographs) specify

hydrochloric acid, but in different concentrations (0.1 M vs 0.01 M). The results revealed that the dissolution profiles of the samples were not significantly affected by the change from 0.1 M to 0.01 M HCl dissolution medium.

The *Ph.Int.* monograph specifies a different dissolution medium and volume, different apparatus and a different agitation speed when compared to the BP and USP monographs (Table 6-2). The f_2-values (*Ph.Int.* monograph vs. USP monograph and *Ph.Int.* monograph vs BP monograph) indicated that dissolution profiles of the products were different from that seen from the BP/USP monograph due to the differences in medium, agitation speed and medium volume, which may be explained using the Noyes-Whitney equation (as presented in section 6.4).

6.4 The Noyes-Whitney equation and dissolution rate

The Noyes-Whitney equation (equation 6.2) defines the process of dissolution which was used to identify areas of further investigation (Shargel *et al.*, 2005:414):

$$\frac{dC}{dt} = \frac{DA}{h}(Cs - C) \qquad \text{Equation 6.2}$$

Where:

$\frac{dC}{dt}$ = rate of API dissolution at time t

D = diffusion rate constant

A = surface area of the particle

C_S = concentration of the API (equal to the solubility of the API) in the stagnant layer

C = concentration of the API in the bulk solvent

h = thickness of the stagnant layer

From this equation it is clear that the rate of API dissolution is dependent on the D, A, C_s, C and *h*.

This equation can be used to explain the differences in the extent of dissolution of quinine sulfate tablets with the specified dissolution conditions of the respective monographs. C_s and C define the concentration of the API in both the stagnant layer and the bulk solvent, which is dependent on the solubility of the API as well as the level of saturation in the medium. Bearing in mind the differences in the dissolution methods (medium, medium volume, agitation speed) it may be hypothesised that the solubility of quinine sulfate and the thickness of the stagnant layer

(*h)* be the causes for the differences in dissolution behaviour observed. The following were investigated:

- the solubility of quinine sulfate was determined in the different dissolution media - section 6.5;
- the extent of dissolution of the samples were evaluated under varying dissolution conditions (medium, volume, agitation speed) – section 6.6.

6.5 Solubility and the Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System (BCS) is used as a guideline to classify an API according to its solubility and permeability. The BCS is used to relate physico-chemical characteristics of an API to its *in vivo* behaviour (Shargel *et al.*, 2005:482 - 483). The BCS classes are summarised in Table 6-9.

Table 6-9: The Biopharmaceutics Classification System (Shargel *et al*., 2005:483)

Class	Solubility	Permeability	Comments
Class I	High	High	API dissolves rapidly and is well absorbed. Bioavailability problem is not expected for immediate release drug products.
Class II	Low	High	API solubility is limited but well absorbed. Bioavailability is controlled by the dosage form and rate of release of the drug substance.
Class III	High	Low	The permeability of the API is limited. Bioavailability may be incomplete if drug is not released and dissolved within absorption window.
Class IV	Low	Low	Difficulty in formulating a drug product that will deliver consistent drug bioavailability. An alternate route of administration may be needed.

An API is considered highly soluble when the highest recommended dose is soluble in 250 ml or less of aqueous media:

- over the pH range 1.0 – 7.5 according to the US Food and drug administration (FDA) (Strauch *et al*., 2012:503);
- over the pH range 1.0 – 6.8 according to the European Medicines Agency (EMA) (Strauch *et al*., 2012:503);
- over the pH range of 1.2 – 6.8 according to the WHO (Strauch *et al*., 2012:503).

Any API of which the highest dose is not soluble in 250 ml or less media, is not considered highly soluble.

The highest recommended dose of quinine sulfate is described as follows:

- available in the USA, is Qualaquin® tablets which contain 324 mg quinine sulfate per tablet with a recommended dosage of one to two tablets/dose (dose of 628 mg quinine sulfate);
- according to the EMA the recommended dosage of quinine sulfate is one to two 300 mg tablets/dose (dose of 600 mg quinine sulfate);
- listed in the WHO Model List of Essential Medicines, is 300 mg/tablet and the recommended dosage is 1 tablet/dose (dose of 300 mg quinine sulfate) (Strauch *et al*., 2012:503).

The calculation of the dose/solubility (*D/S*) ratio assists in the clarification of an active ingredient's solubility profile (Shargel *et al.*, 2005:483). A dose/solubility (*D/S*) ratio is determined by dividing the dose (mg) by the solubility (mg/ml) to yield a value with units in ml. A *D/S* ratio of less than 250 ml over the pH range is indicative of a highly soluble API (Shargel *et al.*, 2005:483).

The solubility results of quinine sulfate presented by Strauch *et al.* (2012:501) are summarised in Table 6-10 (standard shake-flask method at 37.0 °C). From these data it can be concluded that quinine sulfate could be classified as a poorly soluble API at a pH range of 1.0 to 7.5.

Table 6-10: Solubility of quinine sulfate as reported by Strauch *et al*. (2011:501) with the appropriate calculated D/S ratios

Medium	pH	Solubility (mg/ml)	*D* (300 mg)/*S* (ml)	*D* (600 mg)/*S* (ml)	*D* (648 mg)/*S* (ml)
Simulated gastric fluid	1.0	10.5	28.7	57.1	62.0
Simulated gastric fluid	1.2	12.0	25.2	50.0	54.4
Acetate buffer	4.5	5.4	55.5	111.1	119.8
Simulated intestinal fluid	6.8	1.3	230.8	461.5	498.5
Simulated intestinal fluid	7.5	0.3	1010.2	2000.0	2182.0

The results of Strauch *et al.* (2012:501) are contradictory with that reported by Lindenberg *et al.* (2004:270), which classified quinine sulfate as either a BCS Class I or III (highly soluble, differing in permeability).

Due to the contradictory classifications (with reference to the solubility of quinine sulfate) in the available literature it was decided to perform equilibrium solubility studies on quinine sulfate API. The solubility of quinine sulfate API was measured in the following four physiological media: 0.1 M HCl (pH 1.2), 0.01 M HCl (pH 2.0), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8). The four media that were selected are representative of the WHO guidelines which requires a pH-solubility profile of the API at 37 ± 1°C in aqueous media in the pH range 1.2 – 6.8 (WHO, 2006:379). The procedure that was followed for solubility testing has been described in Chapter 3, section 3.7.1. The results obtained are summarised in Table 6-11.

Table 6-11: Solubility of quinine sulfate in different media over the pH range of 1.2 - 6.8 at 37 ± 0.5°C with the calculated appropriate D/S ratios

Medium	pH	Solubility (mg/ml)		*D* (300 mg)/*S* (ml)	*D* (600mg)/*S* (ml)	*D* (648 mg)/*S* (ml)
0.1 M HCl	1.2		41.12 41.19 40.89	7.3	14.6	15.8
		Average %RSD	41.07 0.37			
0.01 M HCl	2.0		6.01 6.01 5.91	50.3	100.5	108.5
		Average %RSD	5.97 0.001			
Acetate buffer	4.5		3.99 3.99 4.02	75.0	150.0	162.0
		Average %RSD	4.00 0.41			
Phosphate buffer	6.8		0.74 0.75 0.74	405.4	810.8	875.7
		Average %RSD	0.74 0.94			

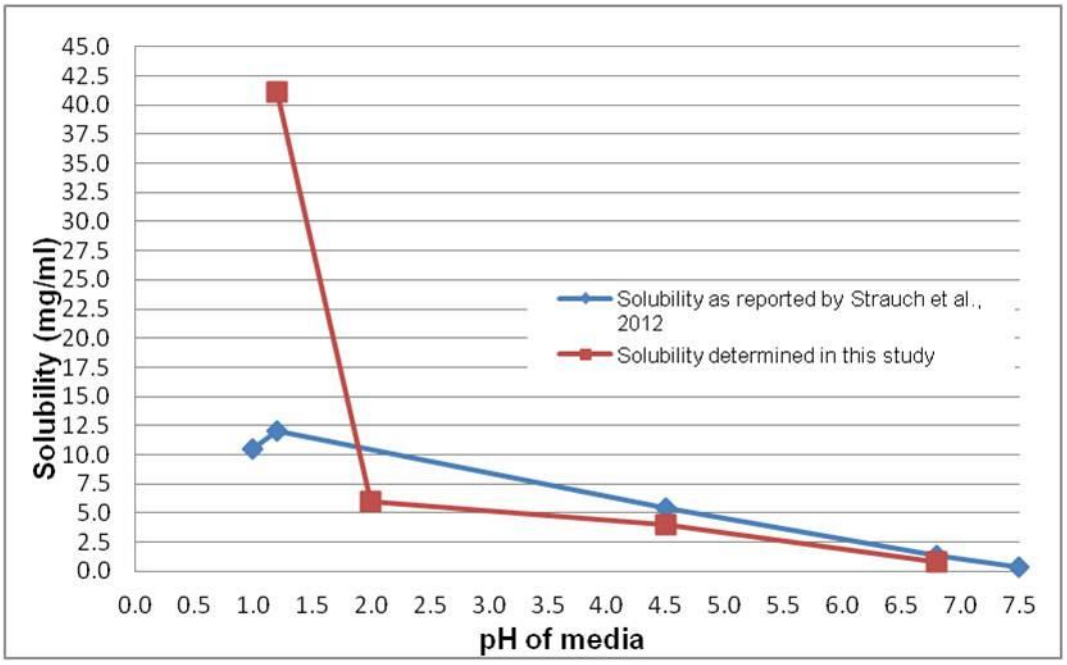

Figure 6-4: The pH-solubility profiles of quinine sulfate API as determined in this study and that reported by Strauch *et al*. (2012:501).

From the solubility results obtained (Table 6-11 and Figure 6-4) it can be concluded that the dissolution behaviour of quinine sulfate is pH dependent. Quinine sulfate was found to be soluble at a pH of 1.2 (0.1 M hydrochloric acid) and pH 2.0 (0.01 M hydrochloric acid), explaining the greater extent of dissolution in these media (refer to Table 6-5 and Table 6-6). The solubility of quinine sulfate API was found to be 0.74 mg/ml in phosphate buffer (pH 6.8). The dissolution conditions of the *Ph.Int.* monograph specify the use of 500 ml phosphate buffer as dissolution medium (Table 6-2). With the solubility of quinine sulfate in phosphate buffer now known, it is feasible that under these conditions, the dissolution of a 300 mg tablet be impaired since the medium was close to saturation. It is common to use a volume of medium larger than what is required to completely dissolve a certain amount of API as to prevent saturation of the medium in which case no further dissolution will take place (Shargel *et al.*, 2005:424). This is referred to as sink conditions and allows the solid oral dosage form to continuously dissolve during the dissolution testing. The USP monograph defines sink conditions as "the quantity of medium used should be not less than 3 times that required to form saturated solution of the drug substance" (USP, 2013). When sink conditions are considered for the dissolution of quinine sulfate in phosphate buffer, pH 6.8 the medium volume should be close to 1200 ml. This medium volume however is not practical since conventional dissolution vessels used do not exceed a 1000 ml. It is not uncommon (when justified) to use a dissolution medium volume less than the theoretical volume necessary for sink conditions (USP, 2013).

From the solubility results (Table 6-11) it is evident that quinine sulfate does not conform to the criteria to be classified as a highly soluble API (*D/S* ratio < 250ml, BCS Class I or III). It is therefore possible that any decisions based on this classification, be erroneous. Approximately 90% of quinine sulfate is absorbed after oral administration (Strauch *et al*., 2012:502), thus the permeability of the API is not a problem. It can therefore be concluded that quinine sulfate may be classified as a BCS Class II API.

It is current practice of the *Ph.Int.* monograph to use the following dissolution conditions for all solid oral dosage forms containing BCS Class I or III API's (Paleshnuik, 2009):

- 500 ml phosphate buffer pH 6.8 as medium,
- the paddle apparatus,
- an agitation speed of 75 rpm, and
- a specification of not less than 80% in 30 minutes.

The wrongful BCS classification of quinine sulfate (Lindenberg *et al.,* 2004:270) may explain why these conditions were selected by the *Ph.Int.* monograph for the dissolution of quinine sulfate tablets (Table 6-2).

This study was furthered by evaluating the extent of dissolution of quinine sulfate tablets under varying different dissolution conditions – section 6.6.

6.6 Dissolution of quinine sulfate under varying conditions

The objective for this part of the study was to undertake developmental dissolution studies to ultimately propose a dissolution method (and accompanying specifications) that is rugged, reproducible, and able to discriminate between different quinine sulfate formulations.

Referring to the Noyes-Whitney equation (equation 6.3), one way to control the rate of dissolution is by controlling the thickness of the stagnant layer (*h*). This can be done by adjustment of the agitation speed (rpm) or choice of medium (Shargel *et al.*, 2005:415).

The preliminary dissolution methods (developmental studies) that were considered are summarised in Table 6-12 and discussed thereafter. Justifications for the selected dissolution conditions (presented in Table 6-12) will be discussed in the sections to follow.

Table 6-12: Summary of the dissolution conditions considered for the developmental studies

	Dissolution medium	Dissolution volume	Agitation (rpm)	Apparatus
Developmental study 1	Acetate buffer, pH 4.5	900 ml	75 rpm	Paddle
Developmental study 2	Acetate buffer, pH 4.5	500 ml	75 rpm	Paddle
Developmental study 3	Acetate buffer, pH 4.5	500 ml	50 rpm	Paddle
Developmental study 4	Phosphate buffer, pH 6.8	900 ml	75 rpm	Paddle
Developmental study 5	Phosphate buffer, pH 6.8	1000 ml	75 rpm	Paddle
Developmental study 6	Phosphate buffer, pH 6.8	900 ml	100 rpm	Paddle

6.6.1 Developmental study 1

The solubility results indicated that the solubility of quinine sulfate increased with a decrease in the solvent pH. In acidic media, quinine sulfate was found to be soluble, but the dissolutions in these acidic dissolution media were not discriminatory (all products obtained a percentage dissolution > 85% in 15 minutes or less).

At a higher pH, the solubility of quinine sulfate decreased (Table 6-11), which resulted in more discriminatory dissolution conditions. Quinine is a diprotic weak base with p*K*a values of 8.5 and 4.1 at 20°C (Strauch *et al*., 2012:501). For this reason it was decided to study the dissolution of quinine sulfate tablets in acetate buffer (pH 4.5), since it was anticipated that the quinine sulfate tablets might achieve greater dissolution than in phosphate buffer, hopefully not at cost to the discriminatory ability.

Dissolution testing in acetate buffer was performed following the conditions of the Developmental study 1, 2 and 3 as specified in Table 6-12. The results of Developmental study 1 are summarised in Table 6-13 and illustrated in Figure 6-5.

Table 6-13: Multiple-point dissolution results for Products 1 - 4 using the Developmental study 1 dissolution conditions (acetate buffer pH 4.5, 900 ml, 75 rpm, paddle) (n = 6)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	64	93	94	94	93	93
%RSD	10.9	1.5	1.2	1.7	2.6	1.2
Product 2						
Average	74	93	94	94	94	93
%RSD	10.1	1.3	0.3	0.8	0.8	0.4
Product 3						
Average	92	97	95	94	93	91
%RSD	2.2	3.9	3.0	2.9	3.1	3.2
Product 4						
Average	86	93	94	93	92	91
%RSD	1.6	1.7	1.9	2.0	2.0	1.7

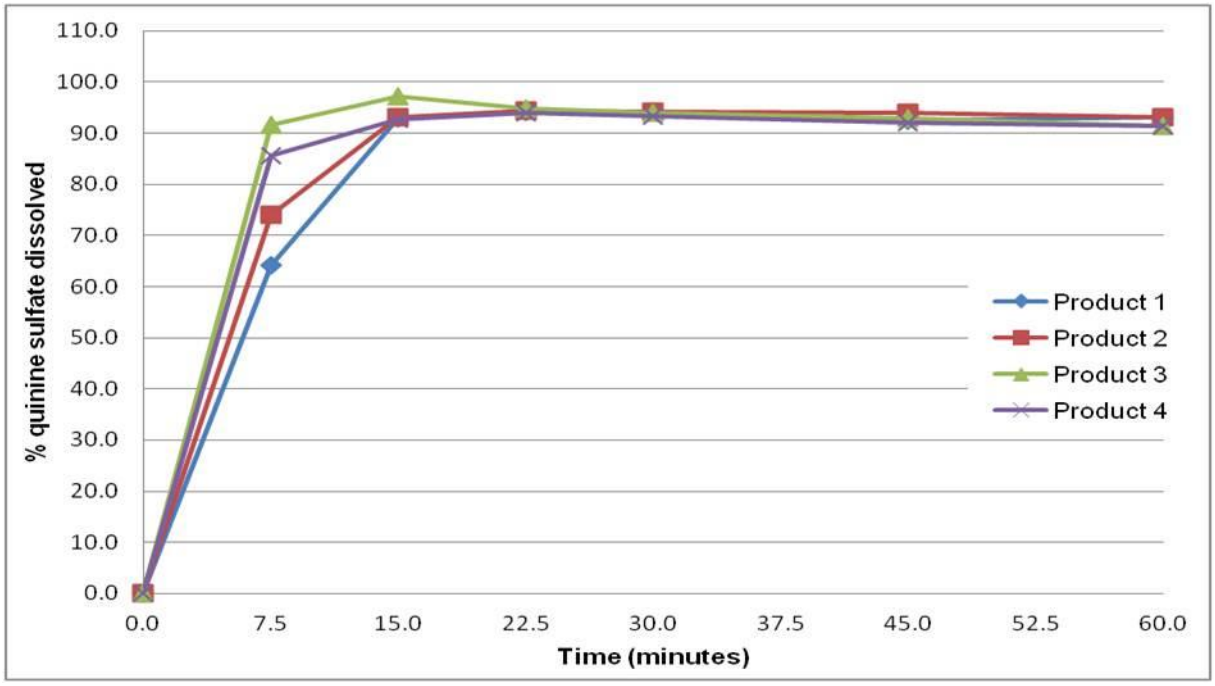

Figure 6-5: Dissolution profiles for Products 1 - 4 using the Developmental study 1 dissolution conditions (acetate buffer pH 4.5, 900 ml, 75 rpm, paddle).

From Table 6-13 and Figure 6-5 it can be seen that all the samples achieved percentage dissolution > 85% within 15 minutes. This behaviour is similar to that achieved using the BP and USP monograph dissolution methods and are not desirable. The conditions of

Developmental study 1 were therefore considered not suitable as an alternative dissolution conditions.

6.6.2 Developmental study 2

To further the investigation, it was decided to evaluate the influence on the dissolution of quinine sulfate when changes were made to the dissolution medium volume (acetate buffer, pH 4.5). It is postulated that an increase in dissolution medium volume will result in even better dissolution (in comparison with that achieved in Developmental study 1), therefore in an attempt to improve the discriminatory ability of acetate buffer, pH 4.5, by altering the dissolution medium volume, a decrease in the volume was investigated. Developmental study 2 was conducted to investigate the influence of a decrease in the acetate buffer (pH 4.5) volume on the dissolution properties of quinine sulfate tablets (Table 6-14 and Figure 6-6).

Table 6-14: Multiple-point dissolution results for Products 1 - 4 using the Developmental study 2 dissolution conditions (acetate buffer pH 4.5, 500 ml, 75 rpm, paddle) (n = 6)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	51	65	73	78	80	82
%RSD	7.0	4.4	3.5	3.1	2.8	2.4
Product 2						
Average	61	76	82	80	86	87
%RSD	14.1	4.0	2.6	7.0	1.4	1.7
Product 3						
Average	87	95	94	92	91	89
%RSD	0.9	1.6	2.0	2.2	2.0	2.0
Product 4						
Average	86	93	93	92	90	88
%RSD	2.3	1.3	1.3	1.8	1.6	1.9

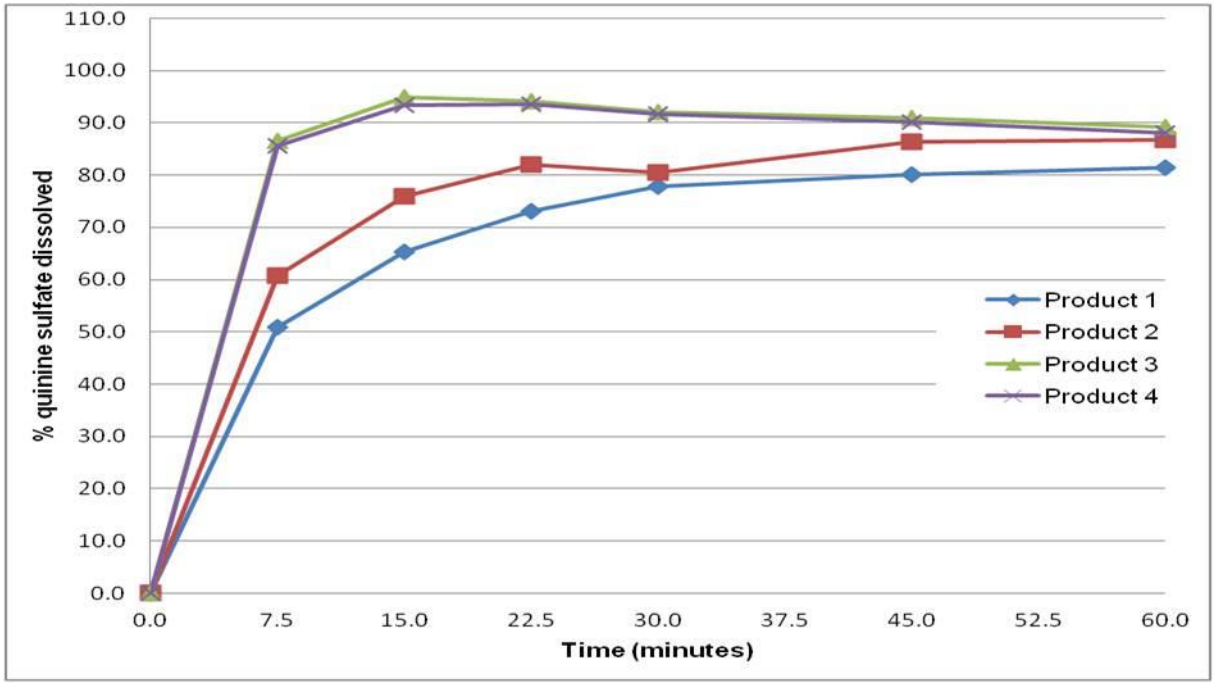

Figure 6-6: Dissolution profiles for Products 1 - 4 using the Developmental study 2 dissolution conditions (acetate buffer pH 4.5, 500 ml, 75 rpm, paddle).

The results of Developmental study 2 showed more promise than that of Developmental study 1, since a greater degree of discrimination was achieved between the profiles. Products 3 and 4 achieved > 85% dissolution within 15 minutes, and the dissolution profiles may therefore be regarded as similar. Product 1 and 2 showed a gradual increase in dissolution, with clear gradual ascending dissolution curves and plateau phases, which are desirable. Developmental study 2 was not considered as the most ideal dissolution conditions, as the discriminatory ability of the dissolution method was not completely satisfactory for Products 3 and 4 (half of the sample population).

6.6.3 Developmental study 3

The next step in the investigation was to decrease the agitation speed (rpm) – Developmental study 3 (Table 6-15 and Figure 6-7).

Table 6-15: Multiple-point dissolution results for Products 1 - 2 using the Developmental study 3 dissolution conditions (acetate buffer pH 4.5, 500 ml, 50 rpm, paddle) (n = 6)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	41	48	54	55	59	61
%RSD	9.4	10.0	6.2	5.5	5.9	4.7
Product 2						
Average	41	49	56	60	63	64
%RSD	14.1	11.4	9.6	9.1	6.8	5.4

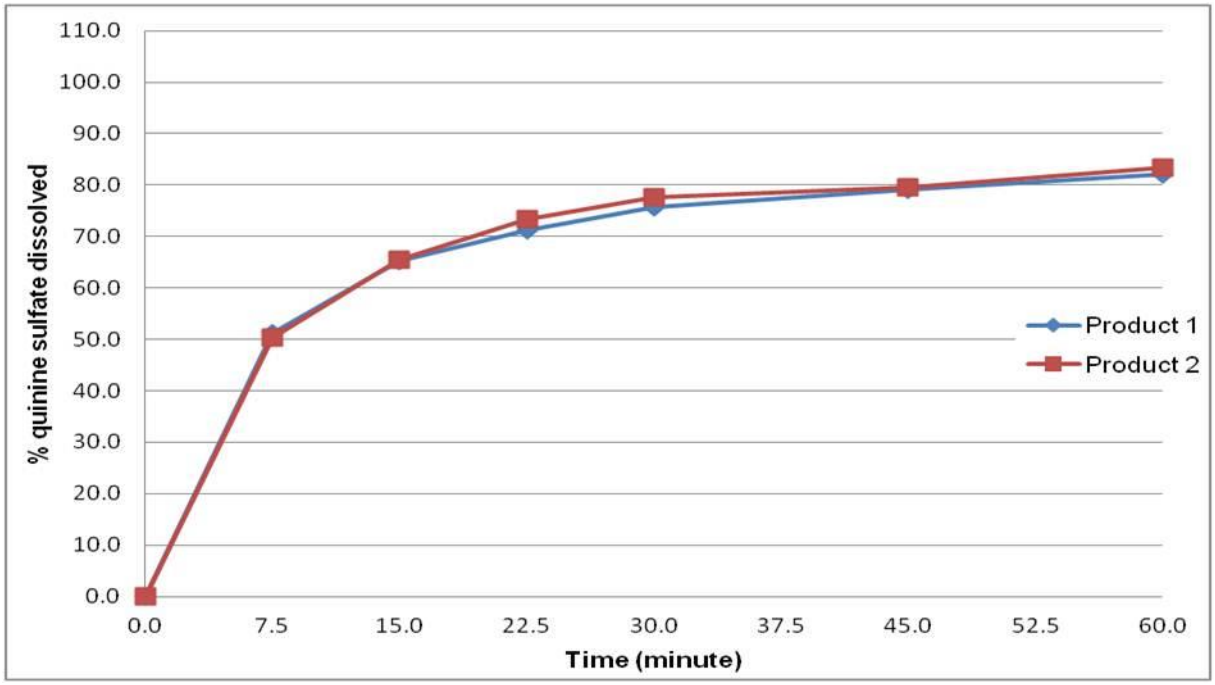

Figure 6-7: Dissolution profiles for Products 1 and 2 tested using the Developmental study 3 dissolution conditions (acetate buffer pH 4.5, 500 ml, 50 rpm).

Developmental study 3 was aborted after two dissolution tests as Product 1 and Product 2 presented with coning (Figure 6-8). Only a limited amount of tablets were available for this study. Since the fate of Developmental study 3 could be decided at this stage, it was decided

not to subject Product 3 and Product 4 to Developmental study 3 (the tablets could be saved for more promising studies). Coning results in incomplete dissolution due to the entrapment of particles within the cone, causing large variance in results (USP, 2012). As seen in Table 6-15, the % RSD was greater than 10% at 15 minutes. A % RSD greater than 10% at time points > 10 minutes is considered as highly variable (USP, 2012) and will result in the method not being repeatable. Developmental study 3 was therefore not considered a suitable candidate as an alternative dissolution method.

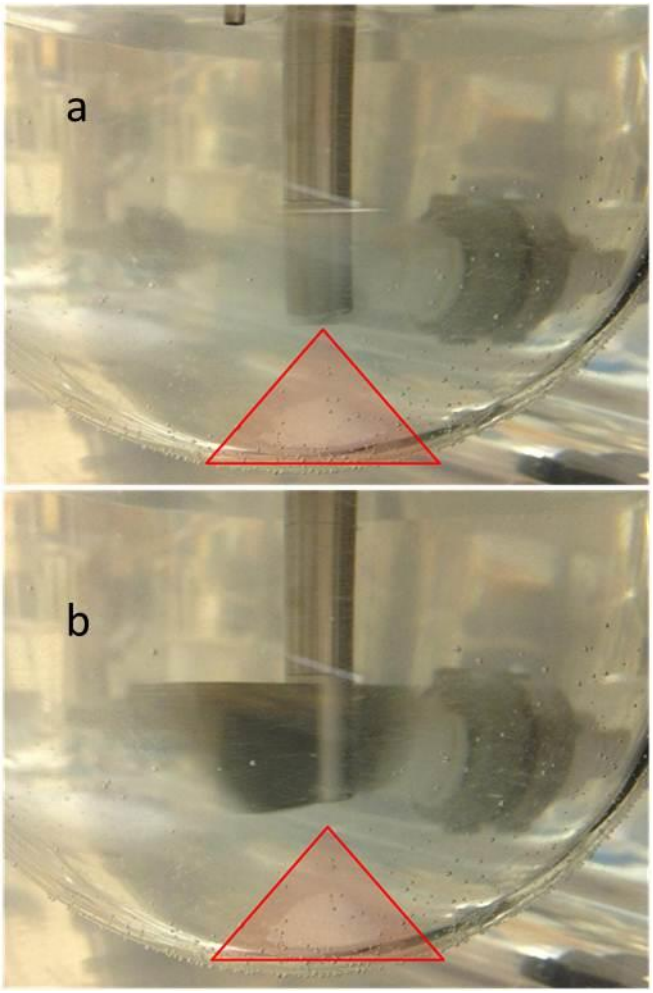

Figure 6-8: Examples of the coning that occurred during the Developmental study 3 for (a) Product 1 and (b) Product 2.

From the results of Developmental studies 1 - 3 it was concluded that acetate buffer, pH 4.5 may not be a suitable choice as dissolution medium.

6.6.4 Developmental study 4

It has already been established (from the *Ph.Int.* monograph dissolution results, Table 6-7, Figure 6-3) that phosphate buffer was a discriminatory dissolution medium. However none of the products met the dissolution specifications of the *Ph.Int.* monograph. For this reason the idea to use phosphate buffer as dissolution medium was revisited for Developmental studies 4 - 6. It was decided to create a more favourable environment for quinine sulfate in phosphate buffer by increasing the medium volume and the agitation speed (*Ph.Int.* monograph prescribes 500 ml, 75 rpm), thereby anticipating improved extent of dissolution without a loss in discriminatory ability. The results of Developmental study 4 are summarised in Table 6-16 and illustrated in Figure 6-9.

Table 6-16: Multiple-point dissolution results for Products 1 - 4 using the Developmental study 4 dissolution conditions (phosphate buffer pH 6.8, 900 ml, 75 rpm) (n = 12)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	48	62	69	72	77	80
%RSD	4.2	3.0	2.9	2.6	2.1	1.7
Product 2						
Average	55	69	75	79	82	86
%RSD	7.6	4.6	3.8	3.0	2.0	2.6
Product 3						
Average	52	63	71	75	80	84
%RSD	12.2	2.3	1.8	1.8	3.5	1.6
Product 4						
Average	32	48	59	61	70	72
%RSD	11.5	10.8	6.5	14.7	9.7	9.2

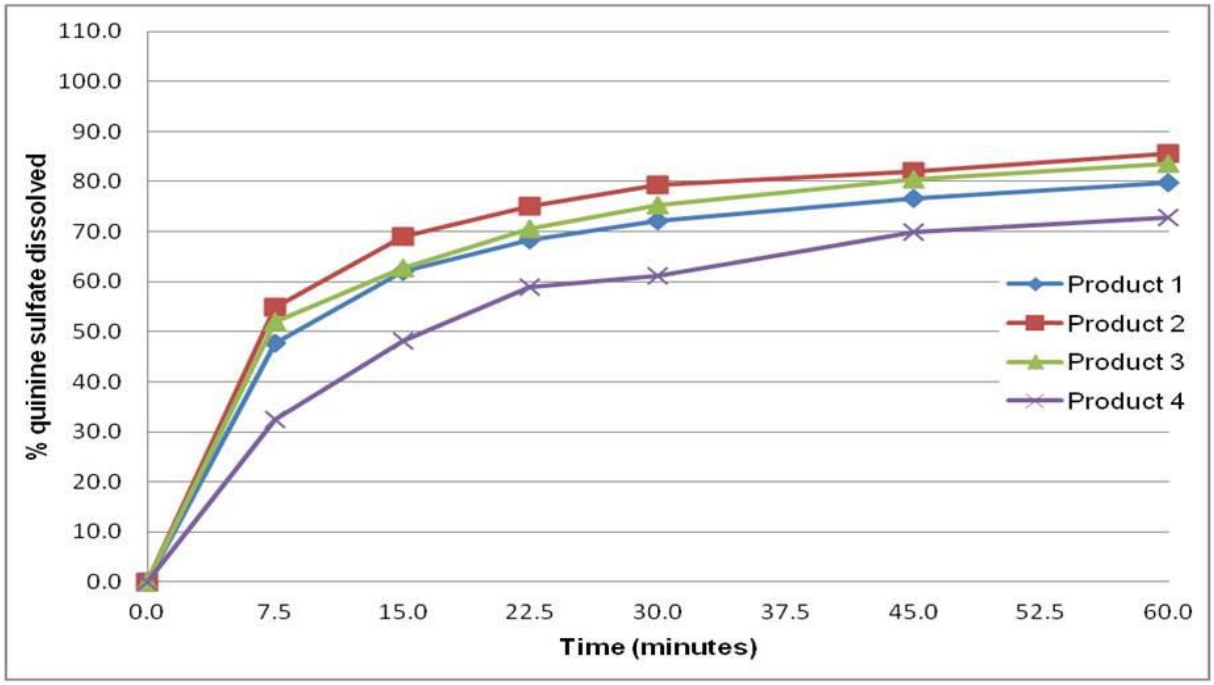

Figure 6-9: Dissolution profiles for Products 1 - 4 using the Developmental study 4 dissolution conditions (phosphate buffer pH 6.8, 900 ml, 75 rpm).

The results from Developmental study 4 showed improved extent of dissolution in comparison with that obtained using the prescribed conditions of the *Ph.Int.* monograph (500 ml, 75 rpm). The f_2-values presented in Table 6-17 showed that the extent of dissolution in Developmental study 4 was significantly different ($f_2 < 50$) from that obtained from the original *Ph.Int.* method for Products 1, 2 and 4. The extent of dissolution of Product 3 from Developmental study 4 was found to be similar to that obtained under original *Ph.Int.* monograph conditions.

Table 6-17: The f_2-values calculated for the Developmental study 4 with reference to the original *Ph.Int.* method dissolution results

Scenario	f_2-value	Similar
Product 1 (Developmental study 4) vs. Product 1 (original *Ph.Int.)*	38	No
Product 2 (Developmental study 4) vs. Product 2 (original *Ph.Int.)*	38	No
Product 3 (Developmental study 4) vs. Product 3 (original *Ph.Int.*)	75	Yes
Product 4 (Developmental study 4) vs. Product 4 (original *Ph.Int.*)	49	No

Should the original specifications of the *Ph.Int*. (S_1 = 80% within 30 minutes, S2 = average of 12 = 75% with no unit less than 60%) be used in the evaluation of the results of Developmental study 4 one can conclude the following – Table 6-18.

Table 6-18: Comparison of the outcomes of Developmental study 4 and original *Ph.Int.* monograph conditions between the four products

		Original *Ph.Int.* monograph conditions outcomes	**Developmental study 4 outcomes**
% dissolution after 30 minutes	Product 1	54% dissolution Do not comply with specifications	72% dissolution Do not comply with specifications
	Product 2	60% dissolution Do not comply with specifications	79% dissolution Complies with S_2 specifications
	Product 3	71% dissolution Do not comply with specifications	75% dissolution Complies with S_2 specifications
	Product 4	51% dissolution Do not comply with specifications	61% dissolution Do not comply with S_2 specifications

From the results it is clear that the conditions of Developmental study 4 were an improvement to the original conditions prescribed by the *Ph.Int.* monograph. The conditions of Developmental study 4 allowed the samples a fairer chance for improved dissolution, without loss of the discriminatory ability (Products 1 and 4 was non-compliant under original *Ph.Int.* monograph conditions and still non-compliant under Developmental study 4 conditions).

Although Developmental study 4 showed great promise of being a suitable alternative method, two concerns were observed:

- Product 4 presented with a high degree of variance (% RSD of ± 10% at 15 minutes), and
- none of the profiles showed a plateau phase (Figure 6-9), indicating that dissolution was still incomplete.

6.6.5 Developmental study 5

It would be ideal if the products presented the potential to achieve complete dissolution within a reasonable time and that none of the samples presented with high variance (as in Developmental study 4). High variance impairs the ability to identify trend, true batch variations and effects of formulation changes (Vaghela, *et al.,* 2011). In an attempt to improve the dissolution conditions further, it was decided to evaluate what a further increase in dissolution medium volume would achieve. For Developmental study 5, all the conditions were the same

as for Developmental study 4, except for an increase in dissolution medium volume (1000 ml). The results of Developmental study 5 are presented in Table 6-19 and Figure 6-10.

Table 6-19: Multiple-point dissolution results for Products 1 - 2 using the Developmental study 5 dissolution conditions (phosphate buffer pH 6.8, 1000 ml, 75 rpm) (n = 6)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	51	65	71	76	79	82
%RSD	3.4	2.7	2.7	2.8	2.0	2.1
Product 2						
Average	50	65	73	78	80	83
%RSD	7.1	3.2	2.6	1.8	1.3	1.1

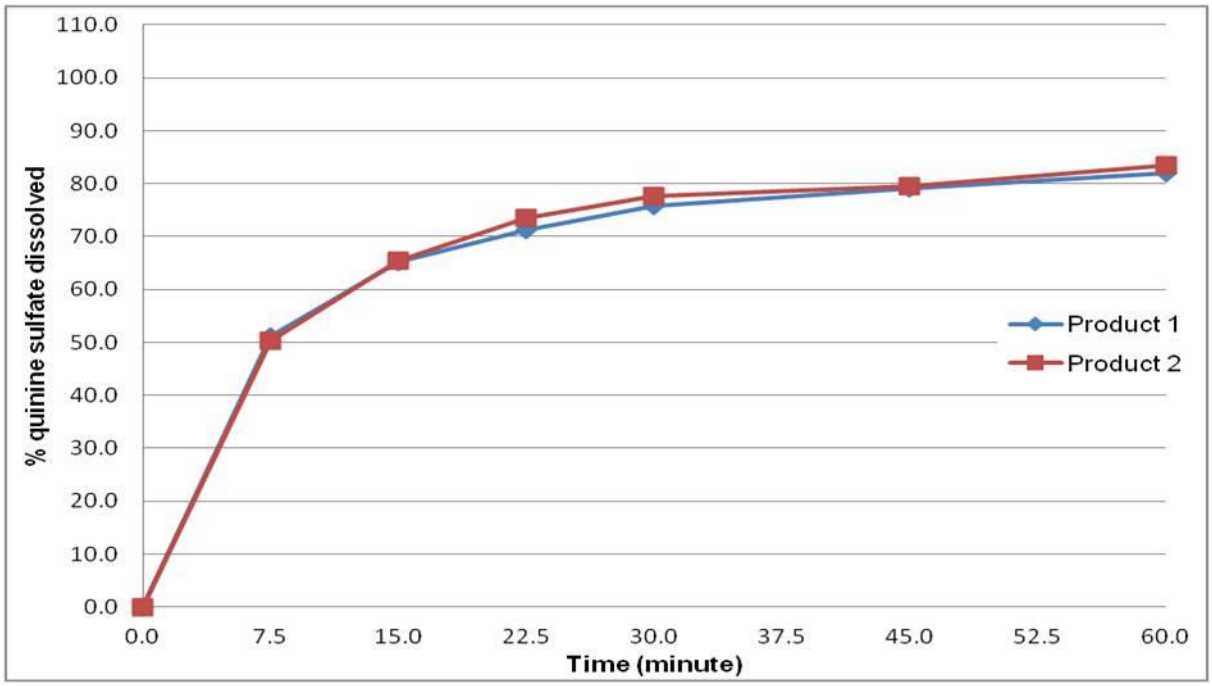

Figure 6-10: Dissolution profiles for Products 1 - 4 using the Developmental study 5 dissolution conditions (phosphate buffer pH 6.8, 1000 ml, 75 rpm).

As with Developmental study 3 the conditions of Developmental study 5 was investigated using the minimal amount of sample (to minimise wastage should the study not produce a positive outcome). Product 1 and Product 2 showed no significant improvement in the extent of dissolution in comparison with that obtained using the conditions of the Developmental study 4

(900 ml, 75 rpm) – Table 6-20. The f_2-values calculated (Table 6-20) showed that Developmental study 4 and Developmental study 5 did not differ significantly.

Table 6-20: The f_2-values calculated for the Developmental study 4 with reference to the Developmental study 5 of Products 1 and 2

Scenario	f_2 value
Product 1 $_{\text{(Developmental study 4)}}$ vs Product 1 $_{\text{(Developmental study 5)}}$	75
Product 2 $_{\text{(Developmental study 4)}}$ vs Product 2 $_{\text{(Developmental study 5)}}$	76

6.6.6 Developmental study 6

Developmental study 6 differed from the original *Ph.Int.* quinine sulfate tablet monograph by increasing the agitation rate (100 rpm) and the medium volume (900 ml). The results of Developmental study 6 are presented in Table 6-11 and Table 6-21. The results of Developmental study 6 showed that it allowed the best dissolution conditions for the products while maintaining the ability to discriminate – Table 6-21.

Table 6-21: Multiple-point dissolution results for Products 1 - 4 using the Developmental study 6 dissolution conditions (phosphate buffer pH 6.8, 900 ml, 100 rpm) (n = 12)

Time	7.5 min	15 min	22.5 min	30 min	45 min	60 min
Product 1						
Average	56	70	75	78	83	85
%RSD	3.7	2.2	1.8	1.9	1.7	1.8
Product 2						
Average	60	73	78	82	85	88
%RSD	5.0	2.3	1.9	2.0	3.1	3.5
Product 3						
Average	55	66	74	77	82	85
%RSD	1.9	5.9	2.6	3.3	2.0	2.4
Product 4						
Average	41	58	68	73	79	84
%RSD	3.3	1.8	1.5	1.5	1.1	2.3

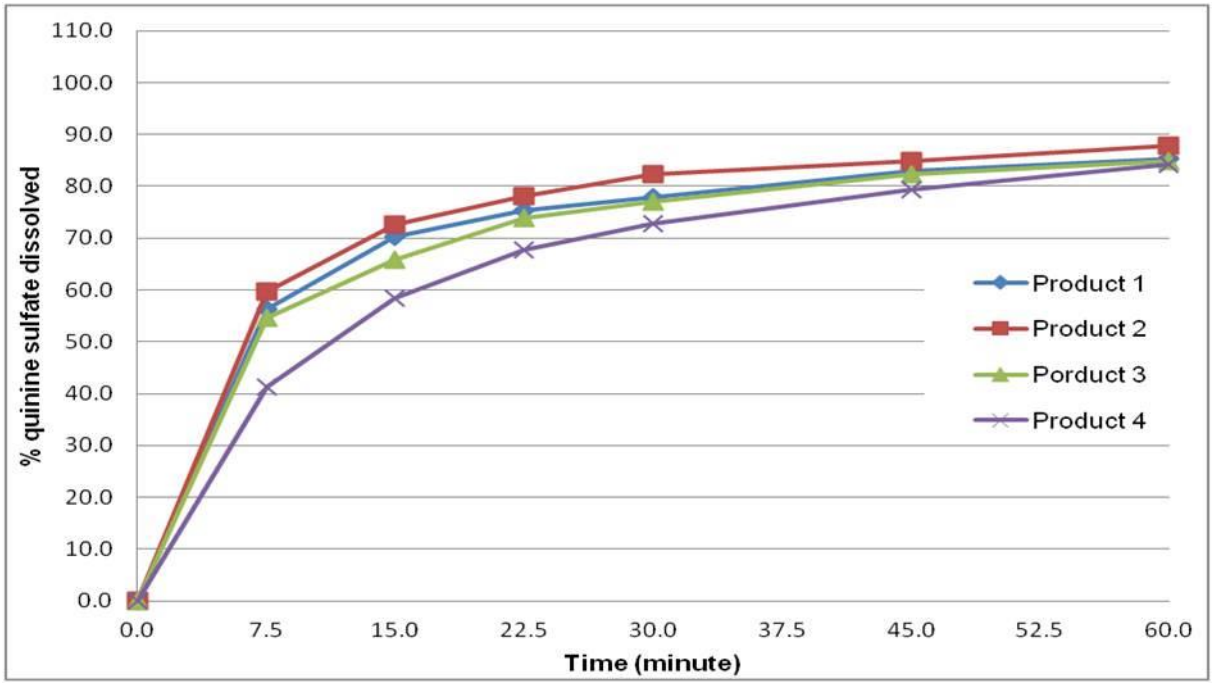

Figure 6-11: Dissolution profiles for Products 1 - 4 using the Developmental study 6 dissolution conditions (phosphate buffer pH 6.8, 900 ml, 100 rpm).

The f_2-values in Table 6-22 showed that the dissolution profiles of Developmental study 6 were different from the dissolution profiles obtained using the BP or USP monographs. Developmental study 6 was not similar to the less discriminatory dissolution methods according to the f_2-value calculations.

The f_2-values for the comparison of Developmental study 4 vs 6 showed that the dissolution profiles for Products 1, 2 and 3 remained similar, whereas the dissolution profile for Product 4 was different using the different dissolution conditions. This implied that the dissolution conditions of Developmental study 6 were more favourable for Product 4 than that of Developmental study 4 (the only difference being the agitation speed). Although the dissolution profiles for Products 1, 2 and 3 were deemed similar by the f_2 – calculations, an improvement was seen in the extent of dissolution (% dissolution) - so much so that it impacted on the outcome of if the products complied and at what stage the products complied.

The f_2-values for comparison of the original *Ph.Int.* monograph dissolution profiles and that of Developmental study 6 (Table 6-22) indicated that Products 1, 2 and 4 were different. The conditions of Developmental study 6 were more favourable for all the products than that of original *Ph.Int.* monograph (the differences being the agitation speed and dissolution medium

volume). Although the dissolution profiles of Product 3 were deemed similar by the f_2-calculations an improvement was seen in the extent of dissolution.

Table 6-22: The f_2-values calculated for the different Developmental dissolution results with reference to the USP, BP and *Ph.Int.* monographs dissolution results

Scenario	f_2 value	Similar
Product 1 (Developmental study 4) vs Product 1 (Developmental study 6)	59	Yes
Product 2 (Developmental study 4) vs Product 2 (Developmental study 6)	72	Yes
Product 3 (Developmental study 4) vs Product 3 (Developmental study 6)	79	Yes
Product 4 (Developmental study 4) vs Product 4 (Developmental study 6)	49	No
Product 1 (original *Ph.Int.*) vs Product 1 (Developmental study 6)	31	No
Product 2 (original *Ph.Int.*) vs Product 2 (Developmental study 6)	34	No
Product 3 (original *Ph.Int.*) vs Product 3 (Developmental study 6)	60	Yes
Product 4 (original *Ph.Int.*) vs Product 4 (Developmental study 6)	34	No
Product 1 (USP) vs Product 1 (Developmental study 6)	35	No
Product 2 (USP) vs Product 2 (Developmental study 6)	36	No
Product 3 (USP) vs Product 3 (Developmental study 6)	28	No
Product 4 (USP) vs Product 4 (Developmental study 6)	26	No
Product 1 (BP) vs Product 1 (Developmental study 6)	37	No
Product 2 (BP) vs Product 2 (Developmental study 6)	46	No
Product 3 (BP) vs Product 3 (Developmental study 6)	29	No
Product 4 (BP) vs Product 4 (Developmental study 6)	25	No

The profiles of Products 1 - 4 using the USP, BP, original *Ph.Int*., Developmental study 4 and Developmental study 6 were plotted (shown in Figure 6-12, Figure 6-13, Figure 6-14 and Figure 6-15) to illustrate the comparison between al these methods.

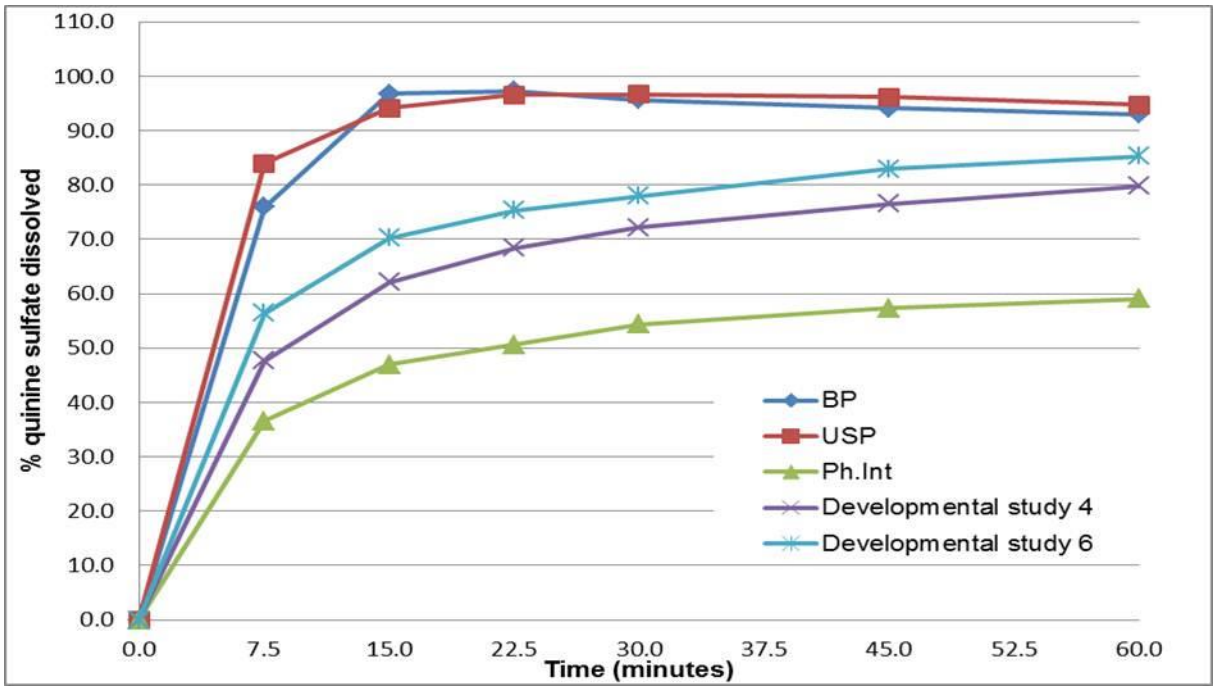

Figure 6-12: **Dissolution profiles for Product 1 (from the dissolution method of the USP monograph, BP monograph, *Ph.Int.* monograph, Developmental study 4, and Developmental study 6).**

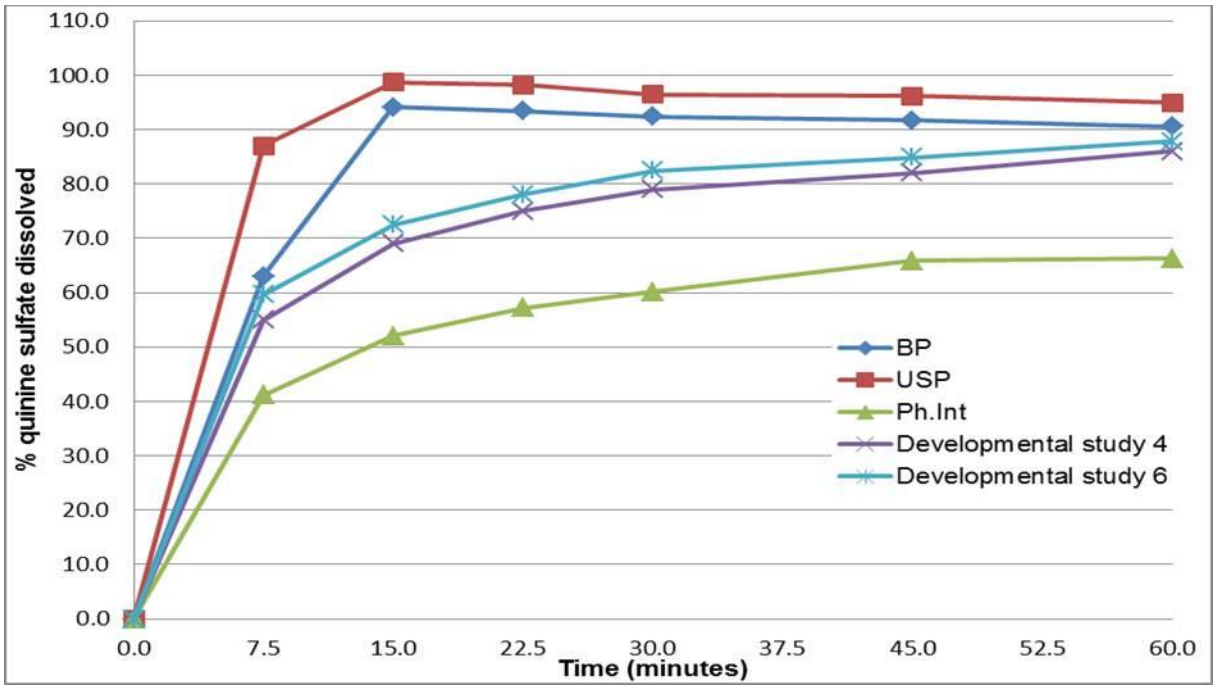

Figure 6-13: **Dissolution profiles for Product 2 (from the dissolution method of the USP monograph, BP monograph, *Ph.Int.* monograph, Developmental study 4, and Developmental study 6).**

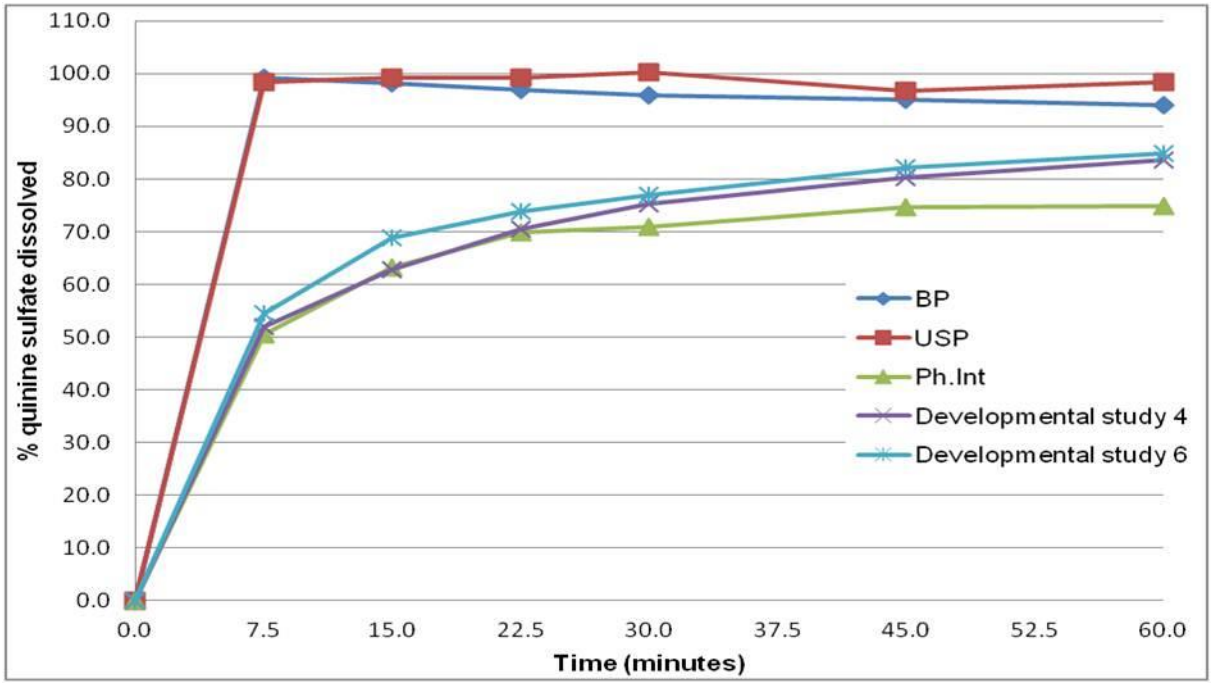

Figure 6-14: **Dissolution profiles for Product 3 (from the dissolution method of the USP monograph, BP monograph, *Ph.Int.* monograph, Developmental study 4, and Developmental study 6).**

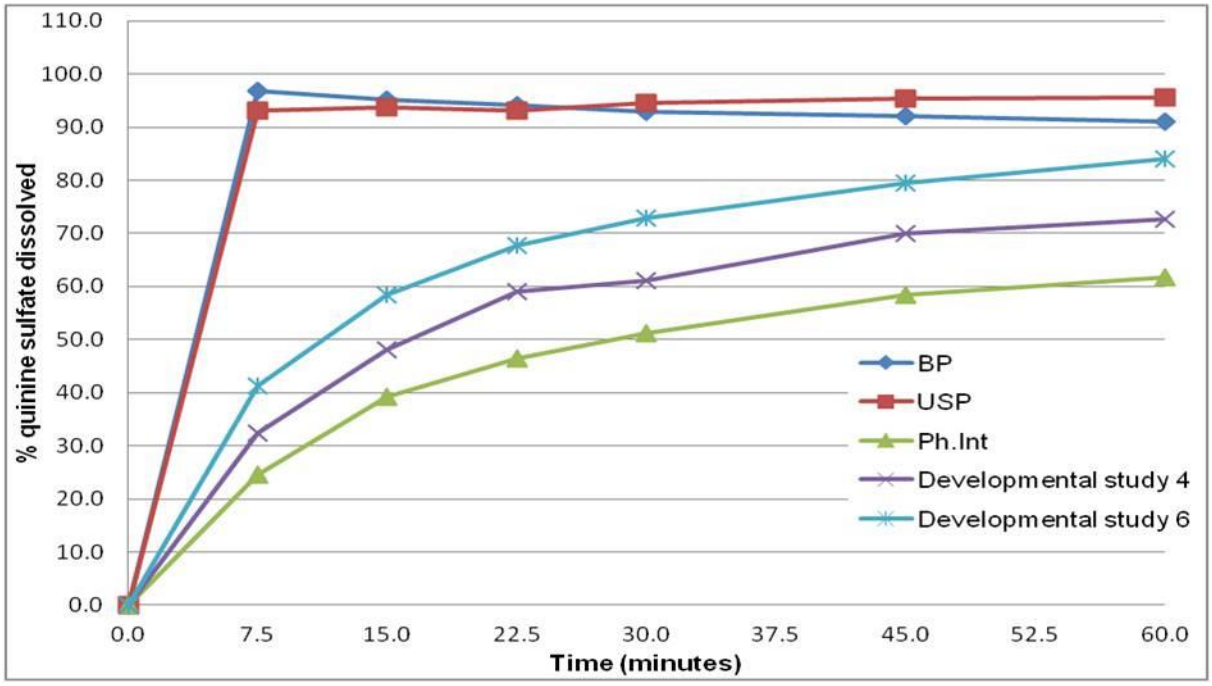

Figure 6-15: **Dissolution profiles for Product 4 (from the dissolution method of the USP monograph, BP monograph, *Ph.Int.* monograph, Developmental study 4, and Developmental study 6).**

Although the f_2-values indicated that the dissolution profiles obtained for Developmental study 4 and 6 were similar for Product 1, it is clear that Product 1's extent of dissolution was improved comparing Developmental study 4 and 6. Similarly, it can be seen that Product 2 (Figure 6-13) and Product 3 (Figure 6-14) also achieved a higher extent of dissolution in Developmental study 6 than in Developmental study 4. The difference in the extent of dissolution of Product 4 when comparing Developmental study 4 and 6 is evident in Figure 6-15.

All products showed a higher extent of dissolution with the dissolution conditions of Developmental study 6. Dissolution profiles of Developmental study 6 also showed the ascending and plateau phases of the dissolution curve, which is ideal (Figure 6-11.)

6.7 Acceptance criteria

Considering that quinine sulfate is soluble in acidic media (pKa of 8.1 and 4.5), dissolution acceptance criteria that specify a Q-value of 70% within 45 minutes might be too lenient in acidic media, as is the case for the BP monograph and USP monograph.

Even if the acceptance criteria is adjusted to a Q-value of 80% within 30 minutes in acidic media, all samples would still comply even with this more stringent specification considering the dissolution results in 0.01 M and 0.1 M HCl (Table 6-4). Although acidic media may not be the most discriminatory dissolution medium for quinine sulfate, one may propose that should acidic media be used, that the specification be made more stringent, thereby instilling improved discriminatory ability to such methods.

Quinine sulfate is less soluble in phosphate buffer compared to in diluted hydrochloric acid (section 6.5). Therefore, when phosphate buffer is considered as dissolution medium for quinine sulfate tablets it is important to bear in mind the level of saturation of quinine sulfate in this medium. The more saturated the medium becomes; the more the dissolution of quinine sulfate will be impaired, which will ultimately result in the outcomes not to be a true representation of the dissolution potential of the product.

The original *Ph.Int*. monograph acceptance criteria (S_1 = 80% within 30 minutes, S2 = average of 12 = 75% with no unit less than 60%) was without a doubt too stringent under the original conditions (no product complied). Considering the results from Developmental study 6, it is recommended that the acceptance criteria be set to the following:

- S_1 = 80% within 45 minutes (same percentage as original method, but a longer time is allowed),
- S_2 = average of 12 = 75% with no unit less than 60% (same as original method).

Using the abovementioned acceptance criteria in conjunction with the conditions of Developmental study 6, Products 1 - 3 would comply to S_1 criteria whereas Product 4 would comply to S_2 criteria.

6.8 Additional considerations

A comparison between the original *Ph.Int.* monograph's dissolution method for quinine sulfate tablets and the proposed dissolution method (herein known as Developmental study 6) have been summarised in Table 6-23. The differences between the methods are printed in **bold**.

Table 6-23: Comparison between the dissolution methods and specifications of Developmental study 6 and the original *Ph.Int.* method for quinine sulfate tablets

Parameter	*Ph.Int.*	Developmental study 6
Dissolution medium	Phosphate buffer pH 6.8	Phosphate buffer pH 6.8
Medium Volume	**500 ml**	**900 ml**
Agitation speed	**75 rpm**	**100 rpm**
Apparatus	Paddles	Paddles
Specification	S_1 = Not less than 80% in **30** minutes S_2 = Average of 12 (S_1+S_2) $\geq$ 75% and no unit less than 60% in **30** minutes	S_1 = Not less than 80% in **45** minutes S_2 = Average of 12 (S_1+S_2) $\geq$ 75% and no unit less than 60% in **60** minutes
Method of quantitation	UV	UV
Wavelength	330 nm	330 nm
Blank	Dissolution medium	Dissolution medium

As seen in Table 6-23, besides the specification and final withdrawal time (which does not impact on the method validation/verification characteristics Chapter 4, section 4.3.1), there are 3 differences between the original and proposed methods, namely medium volume, agitation speed and specifications.

As previously mentioned, dissolution testing may be replaced by disintegration testing if the product is an immediate release product containing a highly water soluble API and the API is rapidly released from the dosage form (% dissolution > 80% after 15 minute at a pH range 1.2 – 6.8) (ICH, 1999). From the dissolution results presented in this chapter it is clear that quinine sulfate did not achieve > 80% after 15 minute at all conditions over the pH range 1.2 – 6.8. This was supported by the solubility studies which found that quinine sulfate cannot be classified as a BCS I or III API, but rather a class II. It is therefore justified that the choice of disintegration

be removed from the monograph, since disintegration was not the rate limiting step and therefore not of value for quality and bioavailability testing.

The proposed changes for consideration for the replacement of the current dissolution method for quinine sulfate tablets of the *Ph.Int.* monograph as well as the proposed text is summarised in Table 6-24.

Table 6-24: The proposed changes for consideration for the replacement of the current dissolution method for quinine sulfate tablets of the Ph.Int monograph as well as wording proposed for the replacement of the current *Ph.Int.* monograph dissolution test

Current wording for *Ph.Int.* monograph dissolution test	Proposed wording for dissolution test
Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, **500 ml** of dissolution buffer, pH 6.8, TS and rotating the paddle at **75 revolutions per minute**. At **30 minutes** withdraw a sample of 10 ml of the medium through an in-line filter. Measure the absorbance (1.6) of a 1-cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 330 nm. At the same time measure the absorbance at the maximum at about 330 nm of a suitable solution of quinine sulfate RS in dissolution buffer, pH 6.8, TS, using the same buffer as a blank.	Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, **900 ml** of dissolution buffer, pH 6.8, TS and rotating the paddle at **100 revolutions per minute**. At **45 minutes** withdraw a sample of 10 ml of the medium through an in-line filter. Measure the absorbance (1.6) of a 1-cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 330 nm. At the same time measure the absorbance at the maximum at about 330 nm of a suitable solution of quinine sulfate RS in dissolution buffer, pH 6.8, TS, using the same buffer as a blank.
B. Disintegration. Comply with 5.3 Disintegration test for tablets and capsules, operating the apparatus for 10 minutes. If the tablets do not comply, carry out test A above.	~~**B. Disintegration.** Comply with 5.3 Disintegration test for tablets and capsules, operating the apparatus for 10 minutes. If the tablets do not comply, carry out test A above.~~

Conclusion

The quinine sulfate tablets dissolution methods of the different pharmacopoeias were evaluated. All the products complied with the USP and BP monographs dissolution specifications (S_1) and rendered similar outcomes. None of the products complied with the dissolution specifications of the *Ph.Int.* monograph.

The *Ph.Int*. monograph offers a choice between two different tests, Test A and Test B. Test A is a dissolution method and Test B is a disintegration method. It was found that none of the products complied with the dissolution specifications of the *Ph.Int.* monograph, but all of the products complied with the disintegration specifications. The results were thus found to be contradictory within the same monograph (Test A and B of the *Ph.Int.* monograph) and between the different pharmacopoeias (*Ph.Int.* monograph vs. USP/BP monograph).

An investigation into the dissolution behaviour was furthered by means of multiple-point dissolutions. The dissolution profiles obtained from the BP and USP monograph dissolution methods indicated that more than 85% dissolution occurred within 15 minutes. The dissolution profiles obtained from the *Ph.Int*. monograph showed a gradual ascending phase but also indicated incomplete dissolution even after 60 minutes (refer to Figure 6-3). Results from solubility experiments supported the dissolution results, as it showed that the solubility of quinine sulfate is indirectly proportional to the pH of the dissolution medium. The solubility results indicated that the dissolution medium volume specified by the *Ph.Int*. monograph for quinine sulfate dissolution testing may be the reason why the dissolution potential of the samples where impaired, causing the outcomes between the monographs to be different.

Using the Noyes-Whitney equation and the solubility results as a foundation, varying dissolution conditions (Developmental studies) were identified for consideration.

Acetate buffer (pH 4.5) as dissolution medium was considered for Developmental studies 1-3. The dissolution profiles from Developmental studies 1 - 3 were not desirable and therefore these studies were not considered for proposal as alternative dissolution conditions.

The investigation was advanced to Developmental study 4. The dissolution conditions of Developmental study 4 were similar to those of the original *Ph.Int.* monograph dissolution method, except for the difference in dissolution medium volume (900 ml instead of 500 ml). The extent of dissolution improved and f_2-values indicated a significant difference between the dissolution profiles obtained of Developmental study 4 and that of the original *Ph.Int.* monograph dissolution method. Developmental study 4 seemed to have the potential as a suitable candidate for consideration, however it did present with some concerns: Product 4 did not comply with the original *Ph.Int* monograph or Developmental study 4 dissolution specifications (assuming the same specification) and products presented with very high variance (%RSD values of more than 10%) at < 15 minutes.

Developmental study 5 evaluated the possible influence of using an increase in the dissolution medium volume (1000 ml). The f_2–values (comparing Developmental study 4 and 5) of two

samples indicated that the extra 100 ml of dissolution medium did not make a significant difference, and for this reason the study was aborted.

Developmental study 6 differed from the original *Ph.Int.* monograph dissolution conditions by using 900 ml phosphate buffer (pH 6.8) as medium (compared to 500 ml) and an agitation speed of 100 rpm (compared to 75 rpm). The dissolution conditions of Developmental study 6 seemed to be the most favourable as it was a good indication of the dissolution potential of all the products and maintained the ability to discriminate between different formulations.