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Design of a fixed-dose paediatric combination of artesunate and amodiaquine hydrochloride

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ABSTRACT

Fixed-dose combinations of artesunate and amodiaquine hydrochloride provide challenges in product development due to the incompatibility of the two agents. This is particularly critical for paediatric preparations which can often be presented in liquid form. The studies reported in this article aimed to develop an understanding of the factors responsible for this incompatibility, whilst assessing the feasibility of developing a stable paediatric formulation. The stability characteristics of fast-disintegrating granular formulations containing intimate mixtures of both agents and single agent granules blended prior to production of unit doses were therefore studied under a range of storage conditions. The granular products remained stable over the 3-month period under stressed accelerated conditions, in contrast to control samples containing both drugs in combined granular form, which demonstrated reductions in artesunate content at elevated humidity. It was hypothesized that loss of active agent content for artesunate was accelerated by access to the water of crystallization of amodiaquine as demonstrated by the more facile dehydration of amodiaquine when a mixture of the two agents was analysed by differential scanning calorimetry (DSC). It was therefore concluded that a stable, versatile paediatric preparation of the two drugs could be prepared by blending pre-formulated granules containing the individual constituents rather than producing a combined granule comprising intimate mixtures of the two agents.

1. Introduction

Resistance to anti-malarial drugs is caused by the ability of the parasite to survive or multiply in the presence of the anti-malarial drug concentrations that normally destroy the parasite or control their multiplication (WHO, 2005). The resistance to older and affordable anti-malarial drugs has been implicated as the key factor leading to the increasing rate of morbidity and mortality from malaria (WHO, 2003). This has led to the advocacy for new chemical entities or combination therapies. Combination therapy (CT) can be used to enhance drug efficacy and prevent resistance and is defined as the simultaneous use of two or more blood schizontocidal drugs with independent mechanism of action and different biochemical targets in the parasite giving synergistic or additive effects (Majori, 2004; Olliaro and Taylor, 2004). The compounds artesunate and amodiaquine hydrochloride (amodiaquine) are an example of one of the artemisinin combination therapies (ACT) approved by World Health Organisation (WHO) for use in malaria endemic regions (Roll Back Malaria, 2004; WHO, 2006). Artesunate is a semi-synthetic derivative of artemisinin, which has improved pharmacological profile when used as a combination partner (International Pharmacopoeia, 2003; Davis et al., 2005). Amodiaquine is a 4-aminoquinoline, which has been used as an anti-malarial drug for more than four decades. It has been reported that these two drugs in combination exhibit greater efficacy than amodiaquine alone (Barennes et al., 2004; Durrani et al., 2005). This combination is currently available as co-packed combination kit and more recently as fixed-dose combination products.

Fixed-dose combination treatment as opposed to multiple drug therapy has numerous advantages including lower cost, rapid effect, simplified administration, improved patient compliance, prevention of treatment failure and prevention of resistance (DNDI, 2003). However, multiple drug therapies present many difficulties and challenges to health care providers, care givers and the patients. When these drug combinations are provided as co-packed kits, health care providers especially pharmacists are typically obliged to provide clear instructions to the patients and care givers on methods of administration for these medicines. This can be problematic for inexperienced and poorly educated patients and can often lead to noncompliance, although presentation as combined formulations can help to minimise these issues.

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In addition, the formulation of fixed-dose combinations often presents many challenges for researchers and industrial pharmacists in designing stable, efficacious medicines. Primary issues often relate to incompatibility between therapeutic agents and consequent chemical instability. Artemisinins are thermally labile and chemically reactive and therefore might be prone to degradation in the presence of other drugs and also during manufacturing processes (Haynes et al., 2007). Other important factors to be considered are the physical stability and release profile of the individual drugs delivered from the dosage forms in addition to their absorption and pharmacokinetic properties. Differences in drug loading and mechanical properties of active agents can also result in problems with achieving uniformity of content and also producing mechanically robust dosage forms respectively. The use of dual combination formulations, for which each drug is incorporated into the dosage form in a manner that prevents direct interaction should therefore be considered (Haynes et al., 2007). In this regard, fixed-dose combinations of artesunate and amodiaquine are now available as bi-layer tablets (Sanofi Aventis, 2006). Paediatric formulations are however required, which are stable under the range of climatic conditions that are typically experienced in malaria endemic regions. For paediatric patients, it is necessary to consider the use of dosage forms which are easy to swallow, disintegrate rapidly in the mouth and which have pleasant taste and appearance. Liquid formulations which are often used to treat children can often suffer from stability issues, particularly for labile drugs. Storage and transportation costs are also increased through the large volume of these formulations relative to solid dosage forms. We have therefore decided to provide simple palatable readily dispersible granules of artesunate and amodiaquine at relevant strengths, which can be encapsulated or filled into primary packs such as sachets. This presentation should enable flexibility of dose selection for different age groups whilst also providing fast disintegration which can be exploited through dispersion in water prior to dosing or through oro-dispersion as a means of administration. The aim of this study was to identify a suitable approach to preparation of products with acceptable chemical stability and explore the factors responsible for incompatibility of the two active agents when incorporated into different product options.

2. Materials and methods

2.1. Chemicals and reagents

Artesunate and amodiaquine were obtained from Mangalam Drugs (India) through ERICA Pharma (India). Mannitol was supplied by Roquette (UK), polyvinylpyrroridone K29-32 (PVP) was obtained from BASF (Germany), croscarmellose sodium (Ac-Di-Sol®) was obtained from FMC Polymer (Republic of Ireland) and aspartame was purchased from Sinosweet (India). Absolute ethanol analytical grade, ethanol HPLC grade, and acetonitrile HPLC grade were all purchased from Fisher (UK). Aerosil 200 was purchased from Degussa (India), whilst potassium dihydrogen orthophosphate and orthophoshoric acid were obtained from BDH (UK). Dihydroartemisinin USP reference standard was purchased from Sigma–Aldrich (UK).

2.2. Thermal analysis

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were employed to determine the thermal behaviour of both drugs, with a view to investigating interactions between artesunate and amodiaquine.

DSC analysis was performed on the DSC module of the TA instruments Q2000 Series Thermal Analysis System (TA Instruments, West Sussex, UK). Samples of 2–6 mg (artesunate, amodiaquine and 1:4 blend of artesunate:amodiaquine) were accurately weighed into an aluminium pan. An aluminium lid, with central pierced hole, was crimped on to the pan. The samples were then heated under a stream of nitrogen gas from 25 to 200 °C using a heating rate of 10 °C/min and triplicate samples were studied for each drug and mixture. The instrument was calibrated using a pure indium standard (melting point 156.6 °C) with verification of performance using a zinc standard (melting point 419.5 °C).

TGA analysis was performed on the TGA module of the TA instruments Q5000 Series Thermal Analysis System (TA Instruments, West Sussex, UK). Samples of 1.5–2 mg (artesunate, amodiaquine and 1:4 blend of artesunate:amodiaquine) were loaded into an open pan attached to a microbalance and triplicate experiments were performed for each drug and mixture. The samples were heated at 10 °C/min from 25 to 200 °C under dry nitrogen purge. The sample weight was monitored throughout the experiment by the microbalance. The temperature control system was calibrated using a ferromagnetic standard.

2.3. Formulations

Fast-disintegrating, dispersible granules containing either artesunate or amodiaquine were formulated by wet granulation using water as the granulating fluid. The qualitative and quantitative composition of each ingredient and the batch sizes manufactured are presented in Table 1. Each ingredient including the drug(s), mannitol, PVP, aspartame and Ac-Di-Sol® were weighed and transferred into the caleva mixer torque rheometer which was used as a small scale granulator. The mixer was operated at the rate of 100 rotations per minute (rpm) and the dry powders were mixed for 10 min after which the granulating liquid was added. Mixing was then continued for another 10 min until a wet mass of suitable consistency was produced. The wet material was passed through a 1700 μm screen and then dried in a vacuum oven (Gallenkamp, UK) at 60 °C for 1 h. The dried granules were then passed again through a 1400 μm screen and further screened with a 355 μm sieve to remove fine materials. The granules retained by the 355 μm sieve (coarse granules) were collected. Appropriate amounts of the coarse granules were filled into a folded aluminium foil sachets (0.033 mm thickness) at a 1:4 ratio in order to obtain a unit dose strength of 50 mg for artesunate and 200 mg for amodiaquine hydrochloride dihydrate (which is equivalent to 150 mg amodiaquine base) per sachet. The ratio is based on the dosing schedule for artesunate and amodiaquine as recommended by WHO (2006).

A control batch of granules was also manufactured, which contained both artesunate and amodiaquine in the same granules at identical ratios to the individual granular products.

Table 1
Quantitative composition of artesunate and amodiaquine formulations.

Name	Batch size (g)	Drug content (%, w/w)	Mannitol (%, w/w)	PVP (%, w/w)	Ac-Di-Sol® (%, w/w)	Aspartame (%, w/w)
Artesunate granules	30	50	35	2	5.0	8
Amodiaquine granules	80	50	35	2	5.0	8
Combined drugs	40	50[a]	35	2	5.0	8

[a] Comprising 10% (w/w) artesunate and 40% (w/w) amodiaquine hydrochloride dihydrate salt.

2.4. Active agent content

The active agent content of the two drugs in each sachet was determined using a suitable HPLC–UV method, which was capable of resolving and quantifying the levels of both species. The contents of each sachet were emptied into a suitable container and the resultant granules mixed with HPLC grade ethanol. The resultant samples were filtered using a Millipore syringe filter 0.2 μm (Millex-GP, 33 mm) to remove undissolved excipients. Appropriate dilution of the solution was made using acetonitrile (ACN):water 50:50. The concentrations of the active drug concentrations were determined using a modified HPLC assay method proposed in the International Pharmacopoeia for artesunate (International Pharmacopoeia, 2003). The mobile phase consisted of ACN:potassium dihydrogen orthophosphate (50 mM) 50:50 adjusted to pH 2.9 with orthophosphoric acid which was pumped through a Waters C_{18} (ODS2) 250× 4.6 μm i.d. × 5 μm at a rate of 1 ml/min. The mobile phase of pH 2.9 was prepared by first dissolving 6.8 g of potassium dihydrogen orthophosphate in 1 l of distilled water which was added to the required volume of ACN and adjusted to the pH 3 with orthophosphoric acid. The pH of the 50:50 mixture was reduced to 2.9 by the further addition of orthophosphoric acid. The solution was filtered via a membrane filter with the aid of vacuum.

This method was shown to be suitably accurate, sensitive, precise and robust with limits of detection (LOD) and quantification (LOQ) of 2.0 and 7.0 μg/ml respectively for artesunate. LOD and LOQ were not determined for amodiaquine, because this molecule absorbs much more strongly in the UV part of the electromagnetic spectrum than artesunate. These parameters are likely to exist at low ng/ml levels for amodiaquine using this method, which are markedly below the μg/ml concentrations that were typically analysed for amodiaquine in this study. The formulations were also produced at a ratio of one part artesunate to four parts amodiaquine, meaning that the method was sufficiently sensitive to quantify levels of amodiaquine in the formulations selected for analysis. The uniformity of content of the granular formulations was established through evaluation of active agent content for replicate samples ($n = 6$). In these experiments, uniformity of content was considered acceptable if the active content of each sachet was within ±10% of nominal levels with relative standard deviation (RSD) less than 6%.

2.5. Moisture content

The moisture contents of the pure drugs, individual granules and the granule mixtures were determined using a Karl Fischer CSC Aquapal III coulometer (CSC Scientific Company Inc., UK). The instrument was allowed to condition for at least 24 h before use after the addition of the reagents. Samples were weighed and dispensed into the titration chamber. The instrument was then allowed to titrate the water present in the sample back to dryness which enables calculation of water content from weight of the sample.

2.6. Dispersibility

The disintegration time and dispersibility of the granules was determined using the method described below. The intention of this test was to assess the ability of the granules to disperse in small volumes of water at room temperature with no agitation. This evaluation provides some insight into the dispersibility of the granules at the point of use prior to administration. It is likely that small volumes of fluid will be used to disperse the granules when delivering these medicines to infants.

(1) The sample contained in one aluminium sachet was transferred to a 25 ml vial containing 10 ml of water and a small 355 μm sieve sitting just below the meniscus. The time taken for the total content of a sachet to disperse in 10 ml water at 22 °C with no agitation and pass through the 355 μm sieve was observed using a stop watch and recorded.
(2) The pictorial representation of the process of dispersion of the granules in 10 ml of water was recorded using a 13.6 mega pixel digital camera (Sony Cyber-shot).

2.7. Granules flow

The flow properties of the granules were assessed using the angle of repose technique described by Staniforth (2002). In this test, a funnel was mounted on a tripod stand resting on a flat surface, with granules being filled into the funnel. The height of the funnel was adjusted to allow flow of granules onto the surface with continual adjustment of funnel height to maintain its position at the peak of the subsequent conical powder bed. The distance between the tip of the funnel and the flat surface and the diameter of the conical bed at its base were measured. The angle of repose was then calculated using Eq. (1):

$$A_R = \tan^{-1} h/r \quad (1)$$

where h is the height of the cone formed by the cone, r is the radius of the cone and A_R is the angle of repose.

2.8. Stability study

The various formulations were stored at 10 °C/60% relative humidity (RH), 40 °C/75% RH and 50 °C ambient RH and the tests described above (Sections 2.4–2.7) were repeated at 4, 13 and 26 weeks. Samples subjected to analysis of moisture content were also stored at 30 °C/65% RH for 13 weeks. The conditions for accelerated stability testing are detailed in the draft consensus guideline stability data package for registration in climatic zones III and IV (ICH, 2002).

3. Results and discussion

3.1. Formulation stability

Figs. 1–3 show the active agent content as a percentage of the nominal strength for artesunate and amodiaquine respectively following 26 weeks storage at 10 °C/60%, 40 °C/75% RH and 50 °C/10% when presented as separately mixed granules (granules of individual drugs) and combination granules (intimate mix-

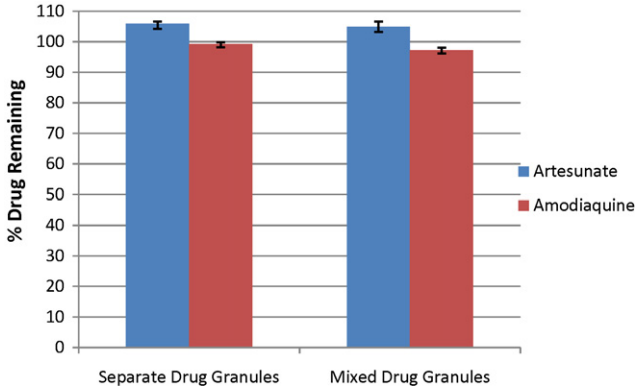

Fig. 1. Twenty-six-week drug stability at 10 °C for blends of granules containing individual drugs (separate drug granules) and for granules containing an intimate mix of both agents (mixed drug granules).

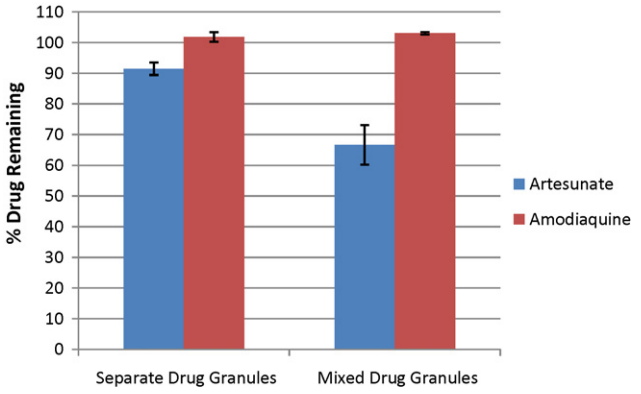

Fig. 2. Twenty-six-week drug stability at 40 °C/75% RH for blends of granules containing individual drugs (separate drug granules) and for granules containing an intimate mix of both agents (mixed drug granules).

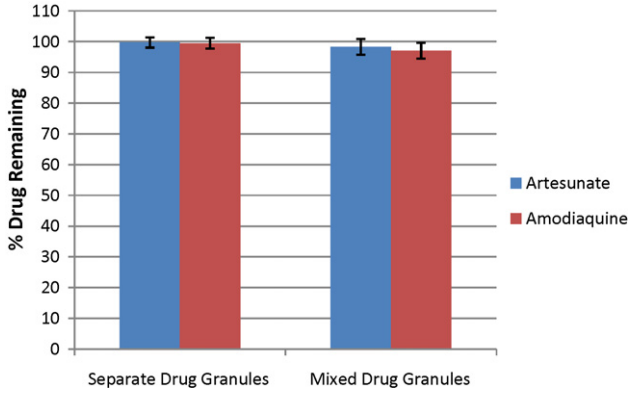

Fig. 3. Twenty-six-week drug stability at 50 °C Ambient RH for blends of granules containing individual drugs (separate drug granules) and for granules containing an intimate mix of both agents (mixed drug granules).

tures of both drugs in the same granule), all stored in aluminium sachets.

The results showed that artesunate which demonstrated a retention time of approximately 11.4 min was markedly less stable when presented in combined granule form compared to a blend of granules containing the different active species (Figs. 2 and 4). Although the active agent content of artesunate was shown to decrease slightly at 40 °C/75% RH for the blend of granules containing the individual drugs, loss of active agent was markedly greater for the granules containing the intimate mixture of the two compounds. The reduction in assay levels occurred alongside concomitant appearance of a degradation product peak at a retention time of approximately 12.6 min (Fig. 5). The peak of the degradation product corresponds with that of β-dihydroartemisinin which has

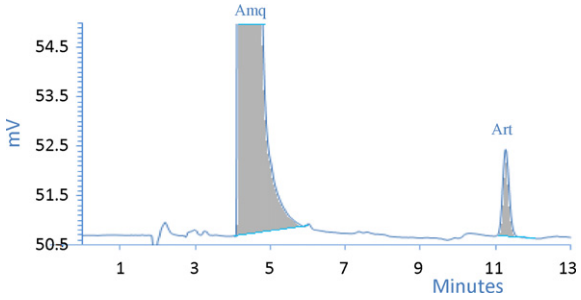

Fig. 4. Chromatogram of solution containing 100 μg/ml artesunate and 400 μg/ml amodiaquine HCl.

been reported in previous evaluations of artesunate (Gaudin et al., 2007). This peak eluted at a similar retention time to that observed for the β-dihydroartemisinin reference standard in experiments to demonstrate specificity of the method.

Although marked loss of active agent content was observed for artesunate in the combined granules at 40 °C/75% RH, stability was improved at 10 °C/60% and 50 °C/10% RH, suggesting that the instability is primarily moisture mediated at elevated temperatures. Amodiaquine stability on the other hand, was adequate regardless of its presentation. The amodiaquine peak with a retention time of 4.2 min was not adversely affected by temperature, humidity or by intimate contact with artesunate, suggesting that the reduction in artesunate content is not necessarily related to a chemical reaction with amodiaquine (Fig. 5). It is possible therefore that the artesunate is interacting with the water of crystallization of amodiaquine, for which two water molecules exist for every molecule of the drug. It is hypothesised that access to water through the intimate mixing process for the combined granules, could be the factor leading to increased loss of active content (Gabriëls and Phaizier-Veicammen, 2004). The thermal studies described in Section 3.4 give further insight into the interaction between the water of crystallization of amodiaquine and artesunate.

The stability of artesunate and amodiaquine in formulations containing blends of the granules containing the individual agents and in formulations containing each drug alone stored at 40 °C/75% RH were compared during a 13-week study period. It was found that there was no statistically significant difference between the percentage of drug remaining for granular blends and when presented as single drug granules (p values for artesunate and amodiaquine were 0.91 and 0.16 respectively by Student's t-test (95% confidence interval)) indicating that stability of both drugs was not adversely affected by blending of granular formulations. These data suggest combination formulations of adequate stability can be produced through blending of granules containing the individual active agents. The intimate contact of the two drugs in granules containing both drugs is therefore responsible for the increased loss of active content of artesunate shown in Fig. 2. Reduction of contact between the two agents is therefore sufficient to prevent marked loss of potency and enable provision of a stable formulation.

In order to ascertain whether the degradation of artesunate was attributed to incompatibility between formulation ingredients, a sample of artesunate drug substance was placed in a vial and stored at 50 °C/75% RH for 1, 4, and 13 weeks. The active agent levels present in the drug substance were compared with that of the formulated product placed at the same storage condition. Statistical analysis using the Student's t-test (95% confidence interval) was undertaken to determine any differences in stability data for the drug substance and formulated product. The results given in Table 2 show a rapid decrease in active content of artesunate drug substance within the first week of storage. This decrease when compared with formulated artesunate was statistically significant (p value: 3.3×10^{-5}). At weeks 4 and 13, there was however no significant difference in the stability of artesunate when presented as drug substance alone or as the formulated product (p values:

Table 2
Comparison between the stability of artesunate drug substance and formulated granules.

Time (weeks)	Pure artesunate (percent remaining)	Formulated artesunate (percent remaining)
0	100	99.3 ± 0.6
1	90.9 ± 0.5	100.2 ± 1.0
4	89.7 ± 2.7	89.1 ± 2.2
13	70.3 ± 1.6	63.9 ± 5.1

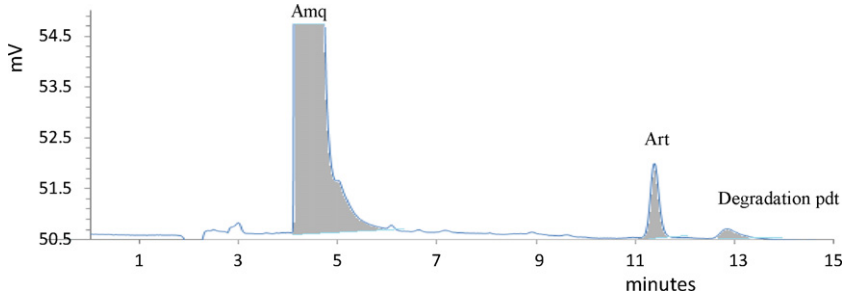

Fig. 5. The chromatogram of the solution from mixed granule formulation at week 26.

0.94 and 0.083 respectively). The degradation of artesunate in the formulated product is therefore related to the drugs instability at high temperature and high relative humidity rather than as a consequence of excipient incompatibility, although degradation is accelerated in the presence of amodiaquine dihydrate. The excipient composition and method of manufacture are therefore not responsible for accelerating the degradation of artesunate.

3.2. Moisture content

The results of moisture analysis show that under storage conditions of 10 °C/60%, 30 °C/65% RH and at 40 °C/75% RH for 13 weeks, the moisture content of granules increased, providing increased potential for moisture-mediated degradation of artesunate. However, at 50 °C and ambient humidity, a slight decrease in moisture content was experienced. On measuring the humidity of the air at the 50 °C condition, RH of 10% was observed. Under this combination of high temperature and low % RH, the equilibrium moisture content of the samples is likely to be lower than that of other conditions. The good stability of samples stored at 50 °C shown in Fig. 6 compared to 40 °C/75% RH provides additional support to the hypothesis of moisture-mediated loss of active content. At the same time the granules stored at 10 °C/60% also showed good stability despite the increased moisture content suggesting that high relative humidity leads to the degradation of artesunate only at elevated temperatures.

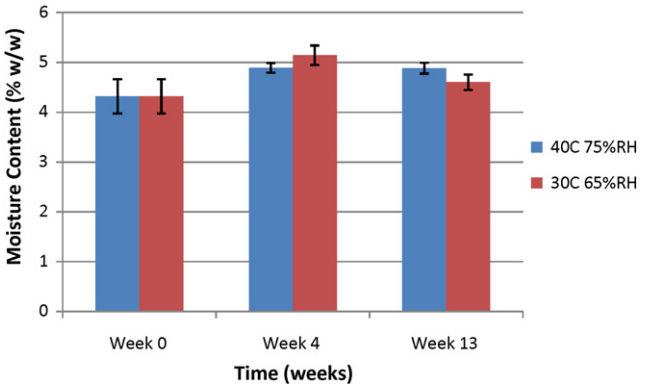

Fig. 6. The moisture content of a batch of blended granules stored at 40 °C/75% RH and 30 °C/65% RH.

Table 3
The dispersibility time of blends of granules containing the individual drugs in 10 ml of water.

Storage time/condition	Dispersibility time (min)		
	10 °C/60% RH	50 °C/10% RH	40 °C/75% RH
Week 0	0.5	0.5	0.5
Week 1	0.5	0.5	1
Week 13	1	1	1

3.3. Other physical tests

The dispersion time for the granular formulations was determined in 10 ml of water. All samples including those stored under stress accelerated conditions for 13 weeks were shown to disintegrate at times in the range 0.5–1.0 min indicating that environmental conditions did not affect markedly the dispersibility of the samples, although slightly longer dispersion times were observed over longer storage durations (Table 3). The photographic presentation showing the dispersion of granules in 10 ml of water is presented in Fig. 7.

Assessment of flowability of samples showed that all granules (combination granules and blends of samples containing individual drugs) remained free flowing with an angle of repose <30° except for the combined dual-drug granular system stored at 40 °C/75% RH where caking occurred at week 13. This indicates that not only does

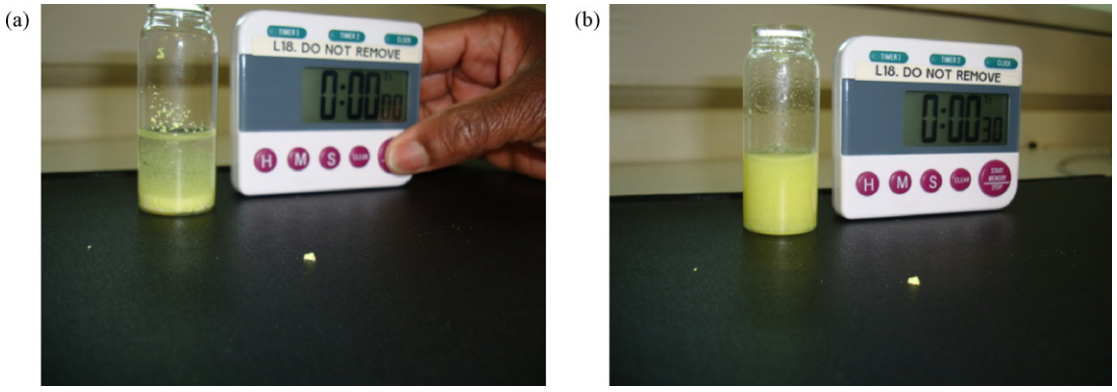

Fig. 7. Photographs showing granular product dispersibility in 10 ml of water (a) sample after dispersion at 0.0 min and (b) sample after dispersion at 0.5–1.0 min.

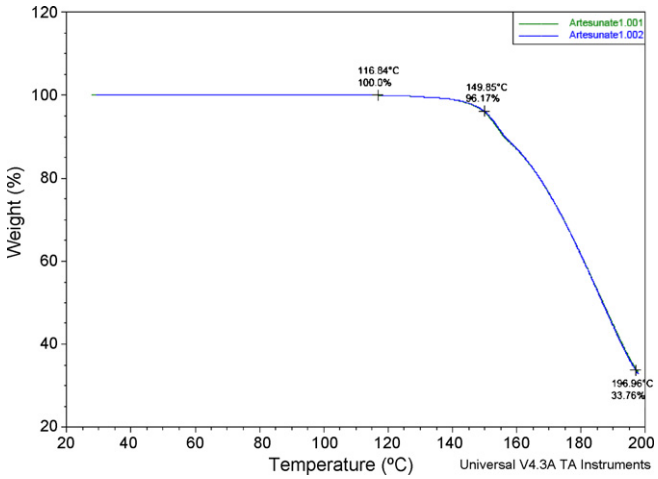

Fig. 8. Representative TGA profile for artesunate from duplicate runs.

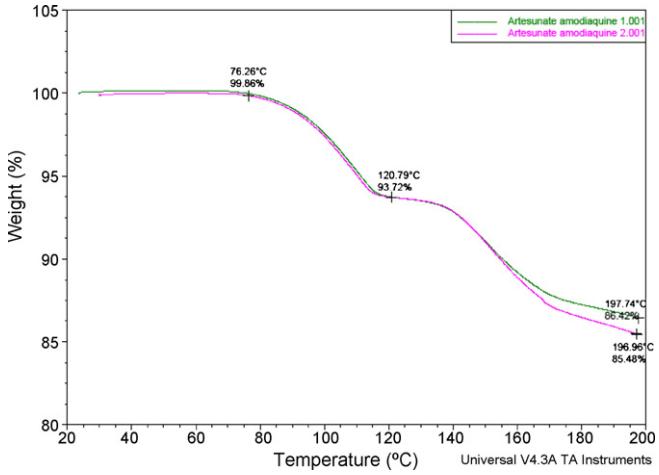

Fig. 10. Representative TGA profiles for a 1:4 mixture of artesunate and amodiaquine from duplicate runs.

moisture affect the chemical stability of samples, but also affects their physical characteristics and impairs the ability of samples to flow freely.

3.4. Thermal analysis

Figs. 8–10 show the relationship between weight loss and temperature for artesunate, amodiaquine and a 1:4 mixture of both agents. The TGA profile of amodiaquine shows the loss of weight for amodiaquine between 75 °C and 120 °C (Fig. 9). These changes in weight (7.6%, w/w), relate to the removal of the two molecules of water from the amodiaquine structure during heating. For a stoichiometric dihydrate, the weight loss would be approximately 7.75%. Between the temperature of 120 °C and 200 °C a further 1% (w/w) loss in weight occurred owing to sample decomposition, showing amodiaquine to be relatively thermally stable. For artesunate, the only weight loss event was observed at 140 °C, which also relates to the decomposition of the sample. Fig. 8 shows that the % weight loss at 200 °C was however approximately 67%.

When mixed in a 1:4 ratio (artesunate:amodiaquine), there appears to be an initial 6.3% reduction in weight associated with the initial loss of water of crystallization of amodiaquine, followed by further decrease after 140 °C due to the decomposition of artesunate (Fig. 10). No phenomena indicating interaction or reaction of the two agents were observed using TGA.

The results from DSC analysis shown in Fig. 11 however indicate a subtle change in the dehydration behavior of amodiaquine when mixed with artesunate. The DSC thermogram for amodiaquine shows a broad endotherm with peak temperature approximately 140 °C relating to dehydration of the sample followed by a small overlapping endotherm at approximately 160 °C which is probably related to melting. The melting of artesunate overlaps with these transitions with a peak temperature of approximately 135 °C. In the physical mixture, artesunate is subjected to a fivefold dilution as the ratio of artesunate to amodiaquine hydrochloride in the mixture is 1:4. The melting transition of artesunate is therefore less prominent than observed for the pure sample of artesunate. The dehydration endotherm of amodiaquine, however appears to shift to slightly lower temperature with a reduced peak of approximately 127 °C. These results suggest that intimate mixing of the two drugs is leading to a physical interaction which disrupts the crystal lattice of amodiaquine and facilitates the loss of water of crystallization, increasing its availability for reaction with artesunate. In addition to the obvious consequences of artesunate degradation, this phenomenon could also have consequences for quality attributes of the formulations such as dispersibility and dissolution. Further interrogation of crystallographic changes to amodiaquine through its interaction with artesunate is however required to probe changes in structure and evaluate interactions at the molecular level.

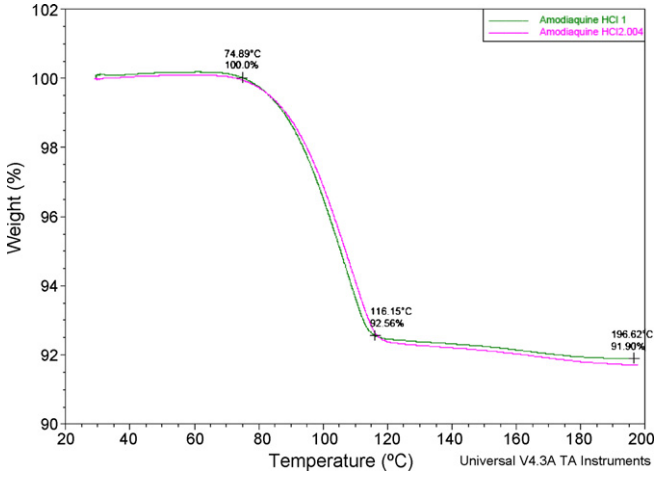

Fig. 9. Representative TGA profile for amodiaquine from duplicate runs.

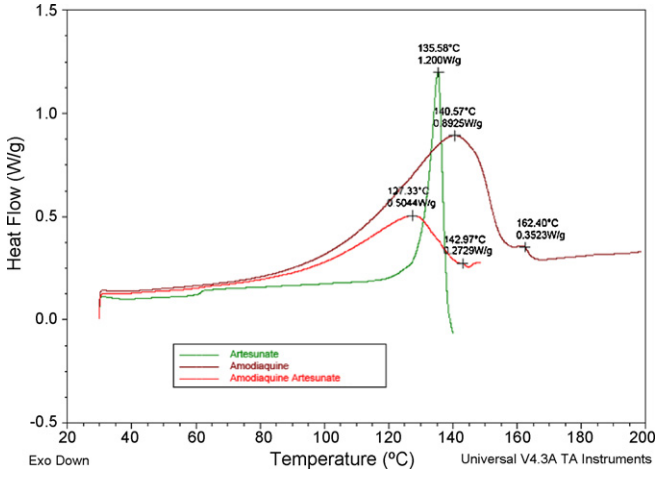

Fig. 11. Representative DSC thermal profiles for artesunate and amodiaquine alone and in combination.

4. Conclusion

Fixed-dose formulations of artesunate and amodiaquine can be produced by first preparing individual granules of each drug and mixing these systems at relevant ratios. This provides a flexible option for adjusting the dose for different age ranges within the paediatric population. The production of separate granular products for subsequent blending also gives rise to products, which are markedly more stable than formulations containing both agents combined into a single granular product. In the combined products, the loss of active content of artesunate is considered to be moisture mediated. It is believed that this loss of content is accelerated when intimately mixed with amodiaquine owing to liberation of water of crystallization from the amodiaquine lattice and hydrolysis of artesunate. This interaction not only influences the chemical stability of the product but also has potential to influence the solid form of amodiaquine and its physical stability during storage. To avoid these issues, production of granules containing the individual agents should be considered, which can then be blended prior to formulation of the final unit dosage form. To avoid moisture-mediated degradation of artesunate, formulations should be prepared to low target moisture content and should be packaged in moisture resistant packaging such as polyvinylidene dichloride (PVDC) coated polyvinylchloride (PVC), Aclar or aluminium foil.

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