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Research Article

Formulation development and stability studies of quinine sulphate suppositories for paediatric use

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ABSTRACT

Rectal administration may be preferred to oral and parenteral routes in paediatric population because it is relatively painless while avoiding nausea, vomiting and first pass metabolism. With emergence of chloroquine resistance, quinine is still one of the accepted chemotherapeutic agents against *Plasmodium falciparum*. The aim of this study is to develop paediatric suppositories of quinine sulphate using Fattibase™ to aid stability, adequate release, ease of administration and affordability. Physical appearance, weight uniformity, hardness, melting range, liquefaction time, drug content uniformity, and release profile of the suppositories were determined at 27.0±2.0 °C and 4.0±0.5 °C after 0, 1, 4 and 8 weeks. Statistical analysis was done using two-way ANOVA. For suppositories stored at 27.0±2.0 °C, hardness and liquefaction time increased significantly with time. Release of quinine from the fattibase™ was sustained (quantity released at 120 min, Q_{120} = 52.16 - 71.16%). Storage time had significant influence ($p < 0.05$) on all the parameters while storage temperature significantly influenced hardness, liquefaction time, Q_{120} and drug content. Quinine sulphate suppositories made with fattibase™ were stable throughout the period of study and will be suitable for peadiatric use.

INTRODUCTION

Rectal administration of medicines may not always be the route of first choice but is a preferred alternative to the intravenous route, being relatively painless and convenient, especially in paediatric population (Aulton and Taylor, 2013). Furthermore, a high concentration of the drug can be achieved in the rectum, making it useful when local action is desired. Some drugs administered low in the rectum are absorbed into the systemic circulation through the inferior and middle rectal veins without passing through the liver. Thus, offering an advantage for drugs that are subject to first-pass hepatic metabolism via the oral route of administration (Hua, 2019).

Suppositories are medicated solid dosage forms intended for insertion into the body orifices (e.g. rectum, vagina, urethra), where they melt, soften or dissolve and exert localized or systemic effects. The shape, volume and consistency of suppositories are suitable for rectal administration. Rectal suppositories for adults weighing up to 2g, are usually torpedo-shaped while children's suppositories weigh about 1g. Suppositories can be self-administered, implying ease of administration. Furthermore, they are suitable for those drugs that cause nausea and vomiting as well as those that are susceptible to the hostile conditions in the stomach. Suppositories can be used

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in unconscious patients as well as for babies and paediatrics that cannot be administered oral medication (Galbraith *et al*, 2015). In addition, suppositories are found suitable in cases whereby oral intake is restricted before surgery and they can be used in targeted delivery system. The poor blood flow in the rectum, results in drugs reaching their site of action with lower dose, thus reducing systemic toxicity. However, some of the drawbacks of suppositories include anal or rectal irritation due to insertion, difficulty in self-administering these dosage forms by arthritic or physically-compromised patients and unpredictable and variable absorption *in vivo* in some instances (Talevi and Quiroga, 2018; Hua, 2019). Suppositories can be prepared by hand molding, fusion and compression (Lloyd, 2008). Quality control of suppositories includes physical and chemical aspects of the products such as uniformity of weight, uniformity of texture, melting point, liquefaction time, melting and solidification time and mechanical strength, analysis of the activity and dissolution testing (Lachman *et al*, 2015).

Quinine, the drug of choice for the study, is a methanol quinolone derived from cinchona bark. It is a blood schizonticidal drug, effective against the erythrocytes forms of all four species of *Plasmodium*, but it has no effect on exo-erythrocytes forms (O'Neal *et al*, 2013). It is still used in the treatment of uncomplicated malaria during the first trimester of pregnancy (WHO, 2015). In severe and complicated malaria in children and adults, intravenous (I.V) injections of quinine are usually recommended until the patient can take oral formulations (Pussard *et al*, 1999). However, due to the lack of trained health personnel and inaccessibility to health facilities, this route of administration is not often applicable in rural areas (Barenness *et al*, 2001). Another route through which quinine can be administered is the intramuscular (I.M) route but it is a common source of complication in children, involving pain, local inflammation, abscess, tetanus, and lower extremity disability. There is therefore the need for an alternative and more convenient route of administration of quinine. The rectal route is commonly used in paediatric practice and is widely assessed as an alternative to parenteral administration (Batchelor and Marriot, 2013; Hua, 2019). Rectal quinine administered as injectable solution or cream has proven to be effective for the treatment of both uncomplicated and complicated malaria, despite their poor bioavailability and the side effect of early rejection (Achan et al, 2011). The formulation of quinine suppositories, which are more adaptable to the rectal route, is being necessitated by the need to improve the performance of this alternative route and improve its administration and compliance. In addition, quinine given by the rectal route has an acceptable safety profile and could be used in the early management of moderately severe malaria in children who are unable to take oral treatment, thereby halting progression to severe disease (Babalola *et al*, 2004; Akinjo *et al*, 2018). In order to enhance early treatment in cases of severe malaria as obtained in many rural regions where the disease is often endemic, rectal formulations of the relatively cheaper quinine is recommended. Hence, there is the need to formulate a stable quinine suppository formulation that is simple to use, requires no trained personnel or manipulation and is affordable (Bareness *et al,* 2006; Akinjo *et al*, 2018).

Thus, the aim of this study is to develop a stable quinine sulphate suppository formulation for paediatric use that meets the conditions of adequate release properties, affordability and ease of administration. Paediatric suppositories of quinine sulphate (10%w/w), with weight 1.67±0.01g; length 60mm and diameter 12mm, were formulated for paediatric dose for children of 6 to 18 months old, using Fattibase™ and characterized in terms of physical appearance, weight uniformity, hardness test, Fourier Transform Infrared (FTIR) analysis, melting range, liquefaction test and dissolution studies. Stability studies were also carried out on the formulated suppositories at storage temperatures of 27.0 ± 2.0 °C and 4.0 ± 0.5 °C.

Fattibase™ is an opaque, white solid that is odourless with a bland taste. It is a mixture of triglycerides from palm, palm kernel and coconut oil together with self-emulsifying glyceryl monostearate and polyoxyl stearate. Fattibase™ has advantages of cocoa butter, a popular base for suppositories, but without the difficulty caused by sensitive melting point range and polymorphism of cocoa butter (Coben *et al*, 2009). Fattibase™ has a melting point of 35 -37°C, and suppositories made from Fattibase™ are known to set quickly and release well from molds.

MATERIALS AND METHODS

Materials: Quinine Sulphate was obtained from BDH Chemicals Ltd, Poole, England. Fattibase™ was obtained from Perrigo®, Paddocks Laboratories, Minneapolis, Minnesota, USA. All other reagents were of analytical grade.

Methods

Formulation of quinine sulphate suppositories

Mold calibration

Sufficient quantity of Fattibase™ was melted over a hot water bath and poured into paediatric suppository molds (size 1.3 mL x 10) , filling each well completely (Coben *et al*, 2009). The base was then

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allowed to set. The solidified Fattibase™ was carefully removed from the mold and then weighed individually. The average weight was determined to calculate the mold capacity i.e the weight of pure base suppository (1.59 g).

Preparation of quinine sulphate suppositories

Suppositories containing quinine sulphate (10%w/w ∽ 0.167g) were prepared using Fattibase™. All suppositories were prepared by the fusion -pour molding method (Coben et al, 2009). The accurately weighed Fattibase™ were placed in porcelain dishes and heated on a water bath to melt. Quinine sulphate powder of accurate weight was incorporated into the melted mass with proper mixing. The melted mixture was then poured into the suppository mould. The mass was left to solidify at room tempeature. The congealed torpedo-shaped suppositories were weighed and packed in aluminum foil and stored in airtight containers. The average weight was determined for suppositories containing no medicament Then the average weight of the medicated suppositories with 10% w/w quinine sulphate was noted (1.678 ± 0.10g).

The displacement value, DV, was calculated as shown in Equation 1:

$$DV = \frac{d}{(a-c)} \qquad (1)$$

where d = weight of medicament in suppositories = 10/100 x 1.678g = 0.168g

; a = weight of pure base suppository = 1.59g

c = weight of base in medicated suppositories = 90/100 x 1.678 =.1.510g

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Evaluation of suppositories

Quinine sulphate suppositories were stored at 27.0±2.0 °C; relative humidity RH = 57 ± 2 % and 4.0 ± 0.5 °C. The following tests were carried on suppositories after storage at intervals of weeks 0 (immediately after preparation), 1, 4 and 8.

Physical Appearance

Twenty (20) suppositories from each batch were examined for uniformity in size and shape. Individual suppositories were examined for discoloration, cracks and pits that could have resulted from entrapment of air in the molten mass.

Weight Uniformity Test

Ten (10) suppositories were weighed individually. The average weight was determined and the standard deviation and standard error of mean were calculated (Fox, 2014).

Hardness Test

The tensile strength of the suppositories was determined at room temperature by diametral compression using DBK tablet hardness tester (Jannin and Rodier, 2013). The results were taken only from the suppositories which split cleanly into two halves. All measurements were made in triplicates for suppositories stored at 27.0 ± 2.0 °C and 4.0 ± 0.5 °C. The results given are the mean of several determinations.

Melting range

A flat stainless steel plate was placed on a water bath maintained at 37 ± 0.5°C, and was left to assume the temperature of the bath. Each suppository was placed on the plate and the time range from the moment it began to melt till complete melting occurred was determined. Determinations were done in triplicate.

Liquefaction test or softening time

The liquefaction or softening time of the suppositories stored at both temperatures was determined. Each suppository was introduced by its tip into a glass tube containing 10 mL of water and placed in a water bath equilibrated at 37.0 ± 0.5 °C. A rod was immediately introduced after the suppository introduction. After the cover was put on the tube (this being the start of the time measurements), the time that elapsed until the rod sank down to the bottom of the glass tube and the mark ring reached the upper level of the plastic cover was noted (European Pharmacopoeia, 2000).

Uniformity of drug content

Ten randomly selected suppositories were dissolved in 100 mL of 0.1M Phosphate buffer (pH 6.8). The amount of quinine sulphate in the suppository was determined using a UV/Visible spectrophotometer at wavelength of 325nm. Determinations were done in triplicate.

***In vitro* dissolution studies**

Drug release from the suppositories was carried out using the USP XX III basket method rotated at 50 rpm in 900 mL Phosphate buffer (pH 6.8), maintained at 37.0 ± 0.5°C. Samples (5 mL) were withdrawn and replaced with equal amounts of fresh medium. The amount of quinine sulphate released was determined using UV/Visible Spectrophotometer at wavelength of 325nm. Calibration curve data were generated using phosphate buffer (pH 6.8), in the concentration range of 0.2 – 2.0 µg/ml (r^2=0.999).

Determinations were done in triplicate.

Stability Studies

Stability tests were performed for the Quinine sulphate in suppositories of all batches using thin layer chromatography (TLC).. Suppositories were kept at room temperature 27.0±2.0 °C; (relative humidity RH = 57 ± 2 %) and refrigerated temperature 4.0 ± 0.5 °C The samples were withdrawn after intervals of one week and the drug was extracted with dilute ethanol (USP, 2020). The sample drug

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in ethanol solution was spotted on a silica-coated TLC plate against the standard drug solution in the same solvent mixture and was allowed to run with a mobile phase which was a mixture of chloroform, acetone and diethylamine (50:40:10). After development of the chromatogram, the plate was taken out of the tank, dried, sprayed with glacial acetic acid and observed under UV light at 254nm. The presence of any degradation products of quinine sulphate as secondary spots were checked. The physical appearance of the suppositories were also evaluated.

Statistical Analysis

Statistical analysis was done using the two-way analysis of variance (ANOVA) on a computer software GraphPad Prism© 8 (GraphPad Software Inc. San Diego, CA, USA). At 95% confidence interval, probability, p values less than or equal to 0.05 were considered significant.

RESULTS AND DISCUSSION

Stable quinine sulphate suppositories were formulated for paediatric use to meet the conditions of adequate release properties, affordability and ease of administration. Furthermore, presenting the drug as suppositories does not pose any choking risks, and does not require taste-masking, unlike oral dosage forms. Suppositories containing 10%w/w of quinine sulphate were prepared using Fattibase™ by the fusion method, a convenient and reproducible technique. The suppositories did not contain any additives. The suppositories were white in colour, uniform in shape (torpedo), with no cracks, pits or air bubble. In this study, the displacement value was 2.1. The suppositories obtained were not melted nor disfigured under ambient temperature (27.0 ± 2.0°C) nor in the refrigerator (4.0 ± 0.5°C). The results for the uniformity of weight, hardness, melting range and liquefaction time of the suppositories at the different storage conditions for the period of study are also presented in Table 1. The weights of the suppositories remained relatively constant throughout the study period. Each suppository contained 167 mg of quinine sulphate. In previous studies, rectal administration of doses of 16 or 20 mg/kg of body weight led to similar concentration profiles to those made for 12 mg/kg intramuscular (IM) administration (Barenness *et al*, 2006). Children aged between 1 – 5 years have a body weight of ≥10kg to <19kg; the 167mg suppository can therefore be recommended for a child with 10kg body weight (< 18 months old) and suffering from complicated malaria.

Table 1: Test on properties of Quinine Sulphate Suppositories (mean ± standard deviation; n = 3)

Properties	Temperature of storage °C	Week 0	Week 1	Week 4	Week 8
Weight uniformity	27.00 ± 2.00	1.68 ± 0.00	1.67 ± 0.01	1.67 ± 0.01	1.67 ± 0.02
(g)	4.00 ± 0.50	1.68 ± 0.01	1.67 ± 0.01	1.67 ±0.02	1.67 ±0.01
Liquefaction time	27.00 ± 2.00	1.45 ± 0.03	1.46 ± 0,03	2.69 ± 0.24	3.22 ±0.07
(min)	4.00 ± 0.50	2.03 ± 0.02	2.38± 0.38	2.30 ± 0.05	3.09 ±0.03
Melting range (min)	27.00 ± 2.00	0.90 ± 0.30 – 19.59 ± 1.78	0.89 ± 0.27 – 20.95 ± 0.35	0.94 ± 0.33 – 16.36 ± 0.73	0.96 ± 0.14 – 25.08 ±1.96
	4.00 ± 0.50	1.35 ± 0.04 – 20.02 ± 0.68	0.92 ± 0.25 – 13.44 ± 0.91	0.34 ± 0.05 – 12.64 ± 0.34	1.15 ± 0.02 – 22.66 ± 2.32
Hardness (N)	27.00 ± 2.00	5.20 ± 0.00	8.70 ± 0.16	5.60 ± 0.00	6.13 ± 0.19
	4.00 ± 0.50	6.00 ± 0.00	6.40 ± 0.00	4.00 ± 0.33	6.87 ± 0.09
Uniformity of	27.00 ± 2.00	117.02 ± 0.05	105.04 ± 0.05	122.04 ± 0.07	125.06 ± 0.07
Content (%w/w)	4.00 ± 0.50	114.20 ± 0.08	108.21± 0.01	110.84 ± 0.04	113.17 ± 0.06
Q_{120} (%)	27.00 ± 2.00	52.16± 3.50	49.18± 2.75	36.11± 2.51	41.24± 3.65
	4.00 ± 0.50	71.16± 4.00	72.84± 5.80	57.98± 5.50	70.30± 6.10

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Stability considerations for suppositories also include observations on excessive softening and oil stains on packaging. Faulty packages have been shown to be capable of causing damage to well-formulated products (Noordin, 2014).
The quinine sulphate suppositories passed the weight uniformity test according to the British Pharmacopoeia (2010) the permissible variation in individual weights of suppositories from the average weight of 20 suppositories is ±5%.

At day 0, the liquefaction time of suppositories stored at room temperature was lower than that stored in the refrigerator. But with ageing (weeks 1 to 8), the liquefaction time of suppositories stored at room temperature became higher than that stored in the refrigerator. This implies that the suppositories were relatively more stable in the refrigerator than at room temperature. In general, liquefaction should not take more than 30 minutes and all the suppositories passed the test for liquefaction time (Setnikar and Fantelli, 1962).

The results of the two-way ANOVA indicated a significant main effect for storage time on displacement value, F (3, 16) = 8.16, p = 0.002; on hardness, F (3, 14) = 74.33, p < 0.001; on melting range, F (3, 16) = 16.63, p < 0.001; on liquefaction time, F (3, 16) = 92.16, p < 0.001; on Q_{120}, F (3, 16) = 14.22, p < 0.001and on drug content, F (3, 16) = 51096, p < 0.001. The results further revealed a significant main effect for storage temperature on hardness, F (1, 14) = 70.13, p < 0.001; ; on melting range, , F (1, 16) = 8.06, p = 0.012; on liquefaction time, , F (1, 16) = 13.56, p = 0.002; on Q_{120}, F (1, 16) = 168.80, p < 0.001 and on drug content, F (1, 16) = 56172, p < 0.001. On the other hand, the two-way ANOVA results showed there was non-significant effect of both storage time and storage temperature on weight uniformity (F (3, 16) = 1.03, p = 0.405 and F (1, 16) = 0.13, p = 0.724, respectively).
The interaction between storage time and storage temperature was found to be significant on hardness, F (2, 14) = 46.33, p < 0.001; on liquefaction time, F (3, 16) = 20.93, p < 0.001 and on drug content, F (3, 16) = 22497, p < 0.001. However, interaction effect between storage time and storage temperature on weight uniformity, melting range and Q_{120} were non-significant.

Increase in melting range was observed in the suppositories stored at room temperature as storage time increased. This could be related to the enhancement of hardness with aging. On aging, further conversion from liquid phase to solid phase causes increase in the duration of time required to melt the suppositories. On the other hand, there was a decrease in the melting range of suppositories stored at 4.0±0.5 °C between week one and four. This justifies the report of Bouwman *et al* .that aging of suppositories may be limited by cool storage, after sufficient initial hardening. However, increase in melting range was observed at week eight for suppositories stored at 4.0 ± 0.5°C. Generally, fatty bases may harden for several months after molding and this rise in melting range could affect absorption (Coben *et al*, 2009).

From the results in Table 1, it was observed that the hardness of the suppositories increased after one week of formulation, particularly for those suppositories stored at 27.0 ± 2.0°C. The hardness values then decreased after week four. By the eighth week of storage, the hardness increased again, Aging of suppository base, caused by further conversion from liquid phase to solid phase and a slow transition into formulations with a higher melting point, usually causes increase in hardness which may be minimized by cool storage, after sufficient initial hardening (Bowman *et al*, 2015). Statistical analysis revealed there was significant interactive effect of storage time and temperature on hardness.

The criteria proposed in USP 26-NF 21 of <905> Uniformity of Dosage Units, mandate that each of the dosage units must lie between 85.0 and 115.0% of the label claim and that RSD of 10 dosage units be less than or equal to 6.0% for the product to pass specification (Ahuja and Dong, 2005). From the results obtained, the suppositories stored at refrigeration temperature fell within this limit but those kept at room temperature did not. It was also observed that the values obtained for the uniformity of content of the suppositories stored at refrigeration temperature tend to be more constant throughout the study period than those stored at room temperature. The variation in content of the suppositories can be attributed not only to the storage condition but also to the method of formulation. Due to sedimentation of drug that could have occurred when pouring into the mold, the mass meant for the last few suppositories may often contain more active substance (Bowman *et al*, 2015). Continuous stirring prior to pouring was used to enhance homogeneity and minimize such sedimentation.

The dissolution profiles of the various batches are presented in Figure 4. From the plots of percentage drug released vs time, the values of Q_{120} (amount of quinine released after 120 minutes) were determined and these are also presented in Table 1. The results of release profile generally showed consistent release throughout the 8 weeks of study for samples stored in the refrigerator. The quantity of drug released after 120 min was generally ≥ 70 % except for week 4. The

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refrigeration at low temperature appeared to preserve the integrity of the suppositories over the period of study. The release of quinine from samples stored at room temperature appeared to be more prolonged, with reduced quantities of drug released as period of storage increased. There was significant difference ($p<0.05$) between the quantity of drug released from suppositories stored at room temperature and those refrigerated.

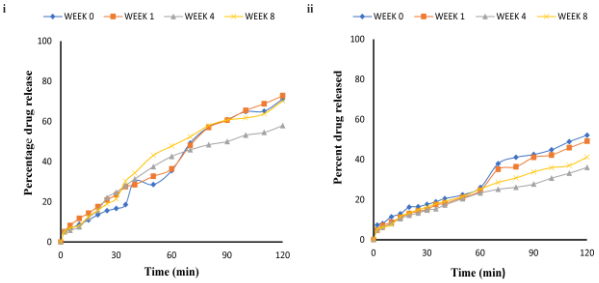

Fig. 1: Plot of percent of quinine sulphate released versus time at (i) 4°C and (ii) 27°C.

The release rate of a drug substance from suppositories, either in lipophilic or hydrophilic excipients depends greatly on the water solubility of the drug. A drug with high water solubility leaves the lipophilic excipient quickly, thus producing a high concentration in the intra-rectal phase, which supports a high diffusion rate across the barrier (Soremekun *et al*, 2012; Akinjo *et al*, 2018). Quinine sulphate salt is relatively soluble in water and it is thus expected that a good release profile would be obtained from lipophilic bases such as Fattibase™. Generally, it took a longer time (2 hours) before a significant quantity of quinine sulphate (≥ 50%) was released from the suppositories irrespective of their storage temperature. This percentage of quinine sulphate released would provide a therapeutic dose if completely absorbed in a child with body weight of 10 kg at a targeted dose of 10 - 16mg/kg. The dissolution rate could be further enhanced by the addition of a suitable surfactant into the formulations of the suppositories.

For the stability studies, the R_f value for the spots of the sample solution were similar (0.242 ± 0.04) to the standard quinine sulphate solution (0.24). This indicates detection of quinine sulphate and the absence of any other secondary spot proved the absence of any degradation product of quinine sulphate in the suppositories. Physical appearance of the suppositories was also evaluated for four weeks but no appreciable change was noticed. Indicating the compatibility of the drug with Fattibase™ in the preparation of quinine sulphate suppositories

CONCLUSIONS

Quinine sulphate suppositories were prepared with Fattibase™ using the fusion method. The physical appearance of the suppositories remained the same all through the study period. Storage time showed significant influence on all the tested parameters while storage temperature had significant influence on melting range, liquefaction time, hardness, Q_{120} and drug content. Release of quinine from the Fattibase™ was constant, with suppositories stored at refrigeration temperature releasing higher quantities of quinine than those stored at room temperature. The Fattibase-based quinine sulphate suppositories could therefore be suitable alternatives in the treatment of malaria in pediatric care. From the melting range FattiBase™ suppository will be stable in the tropic region and should not require special storage conditions Limitations of this study include the relatively expensive cost of Fattibase. Also, addition of a surfactant such as polysorbate 80 to the formulations of suppositories would have enhanced their wetting properties and therefore improved the rate of drug release.

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