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Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications

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ABSTRACT

In view of the lack of suitable paediatric antiretroviral formulations on the market, a novel fixed dose combination (FDC) tablet containing 300 mg zidovudine (AZT) and 160 mg lamivudine (3TC) was developed to improve dosing accuracy and allow flexible drug dosing in function of the body weight of paediatric HIV patients as recommended by WHO.

Rectangular tablets with multiple fraction bars were designed and each tablet can be broken into 8 subunits, each subunit containing a drug dose corresponding to a body weight of 5 kg. These fast-disintegrating subunits can easily be administered to children after dispersion in a liquid or mixing with food. In vitro quality control of the FDC tablets was determined and a crossover bioavailability study using 18 adult volunteers was performed after oral administration of the novel FDC tablet and a Duovir tablet.

The results of the study showed that the novel tablets as well as its subunits disintegrated fast (<20 s). After 30 min dissolution, AZT and 3TC released from Duovir® and the novel tablets was above 95%, the similarity factors f2 were above 50 for both AZT and 3TC. A tablet breakability test showed low weight variability (125.1 ± 5 mg, R.S.D. = 4.4%), with limited weight loss (0.3%). There was no significant difference in pharmacokinetic parameters (C_{max}, t_{max} and $AUC_{0-12\,h}$ values) between Duovir and the novel tablets formulated for paediatric applications.

1. Introduction

By the end of 2005 an estimated 2.3 million children were living with HIV infection; of these children 2.0 million reside in sub-saharan Africa (World Health Organization, 2006b). The vast majority of them have contracted the virus by mother-to-child transmission during pregnancy or birth, or via HIV-positive breast-milk (World Health Organization, 2006b; Rouzioux et al., 1995) since it was estimated that only 23% of pregnant HIV-positive women were receiving antiretrovirals (ARV) to reduce the risk of transmitting the virus to their infants (Newell et al., 2004). Therefore, numerous HIV+ children are in need of antiretroviral treatment (ART), which must start as soon as possible after birth as in the absence of treatment the acquired HIV infection can rapidly progress to a severe symptomatic disease and death. However, the majority of these children are living in resource-limited settings (World Health Organization, 2006a), in which the availability of paediatric antiretroviral formulations is limited and where mortality by 2 years of age is above 50% due to late treatment (World Health Organization, 2006b; Newell et al., 2004). The epidemic is worst in developing countries, especially in sub-Saharan Africa where about 290,000 children under 15 died from AIDS in 2007 (Menson et al., 2006).

Among the ARV drugs currently recommended by WHO in its guideline on antiretroviral therapy for HIV infection in infants and children in resource-limited settings, the combination of two Nucleoside Transcriptase Reverse Inhibitor (NRTI) such as zidovudine (AZT) and lamivudine (3TC) is considered as preferred treatment and WHO strongly recommends to present them in a fixed dose combination (World Health Organization, 2006a). These ARVs are commercially available as tablets intended for adults containing 300 mg AZT and 150 mg 3TC (Duovir®, Cipla and Combivir®, GSK). However, these formulations are not appropriate for treatment of children as this group is treated with a dose based on body weight. Therefore, paediatric practice requires a range of dosage forms allowing administration of the correct weight-related dose. The caregivers try to overcome the challenge of adjusting the dose to the body weight and the lack of appropriate paediatric dosage forms by breaking or crushing tablets designed for adult use. However, the design of these tablets often does not allow to obtain the exact dose required for children (e.g. tablets without score line), resulting in inaccurate dosing with possible toxicity (in case of

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overdosing) or resistance (in case of underdosing) (Menson et al., 2006).

Alternatively, AZT and 3TC could be administered to children via syrups or suspensions. However, these liquids are also poorly available, the dose–volume ratio for older children is too large (Menson et al., 2006) and no fixed dose combination is available as a liquid formulation. Moreover, since these children have to be treated life-long with multiple drugs the administration of several formulations might lead to poor therapy adherence. Studies in adults on the adherence to combined AZT and 3TC therapy versus administration of individual components have shown that the compliance among patients on combination therapy was three times higher (Legorreta et al., 2005).

In view of the Policy Statement of American Academy of Pediatrics that children have severely lagged behind adults in receiving the appropriate antiretroviral therapy (specifically in resource-limited settings), the manufacturing of fast-disintegrating, small-sized tablets (with uniform drug distribution, score lines and suitable shape to allow easy and accurate division of the tablet) has been suggested as a possible means to overcome the issues related with ARV therapy for HIV-infected infants, children and adolescents (American Academy of Pediatrics, 2007; UNICEF/WHO, 2004).

In this perspective, the aim of this study was to develop a novel FDC dosage form of AZT (300 mg) and 3TC (160 mg) for paediatric use, allowing easy oral administration to children and offering dose flexibility according to body weight. Rectangular tablets with multiple fraction bars on both sides were selected as dosage form. This tablet can easily be broken into 8 subunits, each subunit corresponding to an AZT and 3TC dose equivalent to 5 kg body weight. Since most children are infected with HIV from birth, this new FDC dosage form must be suitable for different age groups including infants (1 month–2 years), young children (2–12 years), children and adolescents (12–18 years) (National Prescribing Centre, 2000). Whereas older children can swallow the intact subunits as a solid dosage form, it is essential that the subunits of the tablet disintegrate rapidly in a limited liquid volume (to be administered via a spoon or mixed with food) since the average age of conversion from liquid antiretroviral to solid formulations was about 7 years (Yeung and Wong, 2005).

2. Materials and methods

2.1. Materials

The novel fixed dose combination (FDC) tablets were made with the following active pharmaceutical ingredients: zidovudine (USP29, batch HVZ0240206) and lamivudine (USP29, batch SV008306), both provided by UTAG (Amsterdam, Holland). Microcrystalline cellulose (Avicel® PH102, FMC, Ireland), sodium starch glycolate (Explotab®, JRS Pharma, Rosenberg, Germany), magnesium stearate (Fagron, Belgium) and colloidal silicium dioxide (Aerosil®, Alpha Pharma, Belgium) were used as excipients to prepare the tablets. Duovir tablets (batch G74799, Cipla, India) were donated by the University Hospital of Butare (Rwanda). Abacavir sulphate (batch ABV/0608010, UTAG, Amsterdam, Holland), acetonitrile (Biosolve, Valkenswaard, Holland), potassium dihydrogenphosphate (UCB, Pharma, Leuven, Belgium) and distilled water were used for analysis.

2.2. Tablet formulation

The tablet composition is listed in Table 1. After pre-mixing using mortar and pestle in order to break aggregates, all ingredients were mixed for 20 min using a tumbling mixer (Turbula, Switzerland). The flowability of the powder mixture was measured using a ring shear tester, type RST-XS (Dietmar Schulze, Schüttgutmesstechnik, Wolfenbüttel, Germany), considering the mean flowability index (ff_c) given by Eq. (1) (Gonnissen et al., 2008):

$$\mathrm{ffc} = \frac{\sigma_1}{\sigma_c} \quad (1)$$

where σ_1 is the consolidation stress and σ_c is the unconfined yield strength of bulk powder.

The powder mixture was directly compressed using a single punch tablet press (Korsch EK0, Berlin, Germany), at a compression force of 12 kN. The punches were specifically designed by Elizabeth Carbide (MacKeesport, USA) to manufacture the rectangular tablets with multiple score lines on both sides of the tablet to allow easy breaking. The surfaces were flat and the edges were slightly bevelled (Fig. 1).

Table 1
Composition of novel fixed dose combination tablets containing lamivudine and zidovudine.

Ingredient	Amount per tablet
Zidovudine	300 mg
Lamivudine	160 mg
Avicel® PH 102	470 mg
Explotab®	40 mg
Aerosil®	5 mg
Magnesium stearate	5 mg

2.3. Tablet evaluation

2.3.1. In vitro study

The following parameters of the FDC tablets were determined for quality control: mass uniformity, friability, breakability, drug content, disintegration and dissolution.

The mass uniformity was assessed according to European Pharmacopoeia on 20 randomly selected tablets. They were weighed individually and the average mass and relative standard deviation were calculated (European Pharmacopoeia, 1997).

The breakability of the novel FDC tablets was evaluated by independent persons (i.e. nurses working in the paediatric ward of the University Hospital of Butare (Rwanda). Three volunteer nurses (after expressing their interest to participate) received 10 tablets and divided these tablets along the score lines into 1/2 (along shortest axis of the tablet), 1/4 (along shortest axis), 3/4 (along shortest axis) and 1/8 tablet. In addition, the weight loss due to tablet breaking was calculated (i.e. the difference between the weight of an intact tablet and the total weight of its different subunits). Statistical analysis (one-way ANOVA) with post hoc analysis using least significance difference (LSD) at a level of signification below 0.05 was performed on the smallest pieces which were considered as the best reflection of the effects of manual tablet breaking on variability of mass, drug content and weight loss. The analysis was extended to an assay of the zidovudine and lamivudine content in the smallest pieces obtained.

The tablet friability was determined in accordance with US Pharmacopoeia (USP): a sample of 10 tablets was weighed and placed in the drum of the friabilator (type PTZ, Pharma Test, Hainburg, Germany). After 100 times rotations they were removed from the drum and accurately weighed (The United State Pharmacopoeia, 2004). The friability was expressed the percentage weight loss.

Tablet disintegration was determined on the entire tablets using the Pharma-Test PTZ-E tablet disintegration tester (Pharmatest, Hainburg, Germany) via the USP method (The United State Pharmacopoeia, 2004). In addition, the disintegration on the subunits of the tablet was performed by measuring the time required for disintegration of 1/8, 1/4 and 1/2 tablets in 4 ml of distilled water on a teaspoon.

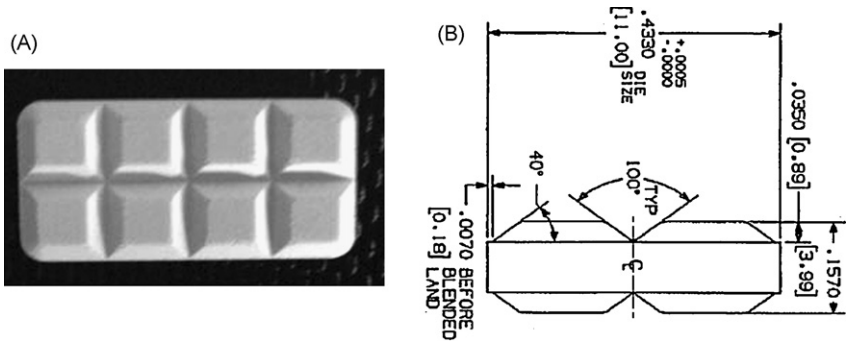

Fig. 1. Design of rectangular tablets: topview (A) and sideview along shortest axis (B).

The drug content was assessed on the entire tablets and the smallest subunits (1/8) of the tablets. They were individually dissolved in 100 ml-distilled water, the solutions were filtered and diluted with mobile phase and analysed by HPLC validated method (Pai and Desai, 2007) at 265 nm to determine the zidovudine and lamivudine content. The mobile phase was composed of phosphate buffer (20 mM sodium diphosphate adjusted to pH 7.2 with NaOH 0.1N) and acetonitrile (86:14, v/v). Abacavir (75 μg/ml) was used as internal standard. The concentration of both AZT and 3TC was calculated using a calibration curve constructed using standard solutions containing AZT in the range of 30–450 μg/ml and 3TC in the range of 16–200 μg/ml. The curve was obtained by plotting the ratio of the peak area drug/internal standard against drug concentration. The HPLC system (Hitachi, Tokyo, Japan) consisted of a pump (L-7100), an autosampler (L-7200), a UV detector (L-7400) and an automatic sample integrator (D-7000). The separation of AZT and 3TC was performed using a RP18 column (Lichrospher®, particle size 5 μm, Merck, Darmstadt, Germany). The volume of injection loop and the injection volume were 100 and 20 μl, respectively.

The dissolution properties of the tablets ($n = 6$) were determined according to USP 27 using a Vankel dissolution tester, type VK7000 (Edison, NJ, USA) at a paddle speed of 50 rpm and using distilled water (37 °C) as dissolution medium. An aliquot (5 ml) was withdrawn at different time points and the zidovudine and lamivudine concentrations in each sample were determined using a validated HPLC method as defined above for drug content. The release profiles of AZT and 3TC from the novel FDC tablets were compared to those from commercially available AZT/3TC tablets (Duovir®, Cipla, India) using the f2 similarity factor calculated via Eq. (2):

$$f2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{1}\left|Rt - Tt\right|^2\right]^{-0.5}\right\} \times 100 \quad (2)$$

where n is the number of dissolution time points and Rt and Tt are the dissolution values (mean of the percentage drug release) of the reference and trial tablets, respectively. In this case Duovir® tablets were considered as reference and the novel FDC tablets as the trial formulation.

2.4. In vivo study

The study was conducted in healthy adult volunteers at the University Hospital of Butare (Rwanda) and the plasma samples were analysed at the Laboratory of Pharmaceutical Technology (Ghent University, Belgium).

This study was performed according to the revised Declaration of Helsinki for Biomedical Research involving human subjects and the rules of Good Clinical Practice. The protocol of this study was reviewed by the Ethics Committee of Ghent University Hospital (Belgium) and the National AIDS Control Commission (Rwanda), and approved by the Rwandan National Ethics Committee.

The study was an open randomized, two-period crossover study in 18 Rwandan adult volunteers (males and females, aged 21–55 years, HIV seronegative, no pregnancy for women). The mean age was 28 ± 7 years and the mean weight was 61.9 ± 7.3 kg. They were in good health based on medical history, physical examination and laboratory screening. Each subject was competent and voluntarily signed the informed consent form after receiving the detailed information about the study. Per period each volunteer received a single tablet of the novel FDC tablet (300 mg AZT/160 mg 3TC) or a Duovir® tablet (300 mg AZT/150 mg 3TC). Tablets were given together with 200 ml of water. The subjects were fasted for at least 8 h before entering the test facility. Drinking of water was allowed up to 2 h before drug administration. A standard breakfast and lunch were served 4 and 10 h post-drug intake, respectively. A 14-day washout period was respected between both sessions. Venous blood samples were collected from an antecubital vein 0.5 h pre-dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h after drug administration. The heparinised blood samples were immediately centrifuged at 2600 g and plasma was stored at −21 °C until analysis.

The plasma samples were analysed using a validated HPLC method previously described (Kano et al., 2005). In a glass tube containing 1 ml plasma sample and 500 μl internal standard 2 ml acetonitrile was added to precipitate proteins, followed by mixing and centrifugation at 1450 g. The clear supernatant was transferred to a new glass tube and dried at 40 °C using a nitrogen flow. The residue was reconstituted in 500 μl mobile phase and filtered through a 0.2 μm cellulose acetate filter (Whatman, Dassel, Germany). 20 μl sample was injected into the chromatographic system. The AZT and 3TC concentrations in the plasma samples were determined as defined for drug content using calibration curves constructed in the range of 0.75–30 μg/ml for AZT and 0.4–16 μg/ml for 3TC.

The following pharmacokinetic parameters were determined for both drugs: maximum plasma concentration (C_{max}), time at which C_{max} was reached (T_{max}) and area under the plasma concentration versus time curve ($AUC_{0-12\,h}$ and $AUC_{0-\infty}$). C_{max} and T_{max} values were read directly from the individual plasma concentration–time profiles, while $AUC_{0-12\,h}$ and $AUC_{0-\infty}$ were determined using the MW Pharm software, version 3.15E. The average and relative standard deviations of these parameters were then calculated.

The relative bioavailability (F_{rel}) was calculated using the following equation:

$$F_{rel} = \frac{AUC_{0-\infty}T}{AUC_{0-\infty}D} \times 100 \quad (3)$$

where T represents the novel FDC tablet and D is the Duovir tablets.

Table 2
Average weight (R.S.D.) and weight loss obtained by manual breaking of the rectangular tablets.

Size of subunit		Nurse 1	Nurse 2	Nurse 3
3/4	Average weight (mg)	749.8 (1.1%)	757.3 (1.2%)	753.2 (1.1%)
	Weight loss (%)	0.2	0.04	0.2
1/2	Average weight (mg)	501.5 (2.0%)	503.7 (1.3%)	502.5 (1.6%)
	Weight loss (%)	0.2	0.1	0.2
1/4	Average weight (mg)	250.5 (3.9%)	251.1 (2.5%)	250.4 (3.1%)
	Weight loss (%)	0.3	0.2	0.4
1/8	Average weight (mg)	124.8 (4.8%)	125.5 (4.5%)	125.1 (5.3%)
	Weight loss (%)	0.3	0.2	0.4

2.4.1. Statistical data analysis

The pharmacokinetic data of zidovudine and lamivudine were statistically analyzed using SPSS, version 15.0 (SPSS, Chicago, USA). The normal distribution of the data was evaluated via the Kolmogorov–Smirnov test, followed by a parametric *t*-test ($p < 0.05$) for C_{max} and $AUC_{0-12\,h}$ and a non-parametric analysis for T_{max}.

3. Results

3.1. In vitro study

The novel FDC tablets containing AZT and 3TC were designed as having a rectangular shape (22.4 mm long, 11.2 mm wide) with multiple score lines (depth 0.89 mm, angle 100°) to allow easy breaking in up to 8 subunits (Fig. 1). The tablets were formulated using commonly used excipients for tabletting purposes (Table 1). The powder mixture could be processed via direct compression without adhesion to the punches and due to its good flowability (mean flowability index ff_c of 10.2 ± 1.5) a reproducible tablet weight (1002.6 ± 4.3 mg, R.S.D. 0.4%, $n = 20$) was obtained.

These tablets were easily broken along the score lines into pieces having a reproducible weight, independent of their size (Table 2). Statistical analysis (one-way ANOVA) showed no significant difference ($p > 0.05$) between the average weights of the smallest pieces (1/8 of a tablet) of the novel FDC tablets broken by the three nurses. The mass of each piece was within the 85–115% range of the average mass limits as required by Pharmaeuropa (Pharmaeuropa, 2004). The weight loss was low, independent of the subunit size (Table 2).

Analysis of drug content by HPLC showed that the average amount of zidovudine and lamivudine in the tablets was 100.3% (R.S.D. = 2.1%) and 100.2% (R.S.D. = 3.2%) of the theoretical amount, respectively. The average amount of AZT and 3TC contained in the smallest subunit of the tablets (1/8) were 97.4% (R.S.D. = 4.9%) and 99.8% (R.S.D. = 5.4%), respectively. This complied with USP27 requirements stipulating a content ranging from 85.0 to 115.0% of the label claim with a relative standard deviation less than or equal to 6.0%. These drug contents corresponded to the zidovudine and lamivudine dose prescribed for 5 kg body weight (i.e. 7.5 and 4 mg, respectively per kg body weight). The appearance was satisfactory at the end of the friability test.

The average disintegration time of the novel FDC tablets was 19 ± 2 s for the entire tablets, while 1/2, 1/4 and 1/8 tablets disintegrated in 4 ml of water within 15, 20 and 26 s, respectively.

The in vitro drug release profiles, summarized in Fig. 2, showed that the drug release was fast: 98.4 and 97.5% of AZT and 3TC, respectively, was released from the novel FDC tablets after 30 min versus 98.3 and 95.9% of AZT and 3TC from Duovir tablets. USP27 states that at least 80% of the drug content must be released from AZT tablets within 30 min. All products dissolved greater than 85% in 15 min.

3.2. In vivo study

All volunteers ($n = 18$) completed the study and no adverse drug reactions were reported. The HPLC method used for plasma sample analysis allowed the separation of lamivudine, zidovudine and abacavir (internal standard) with a good resolution, the retention times were 1.8, 3.7, and 6.1 min, respectively. No peaks were interfering with the drug signals.

The pharmacokinetic parameters of both drugs expressed as mean with relative standard deviation are presented in Table 3 and the average plasma concentration–time profiles are illustrated in Fig. 3.

Statistical analysis of these pharmacokinetic parameters (parametric *t*-test ($p < 0.05$) for C_{max} and AUC, and non-parametric analysis for T_{max}) showed that they were within the 95% confidence interval complying with the FDA limits (85–125%) (Food and Drug Administration, 2003). There were no significant differences ($p > 0.005$, *t*-test) between the in vivo behaviour of the novel FDC tablets and Duovir tablets. The relative bioavailability of zidovudine and lamivudine was 101.8 and 101.4%, respectively, using Duovir tablets as reference formulation.

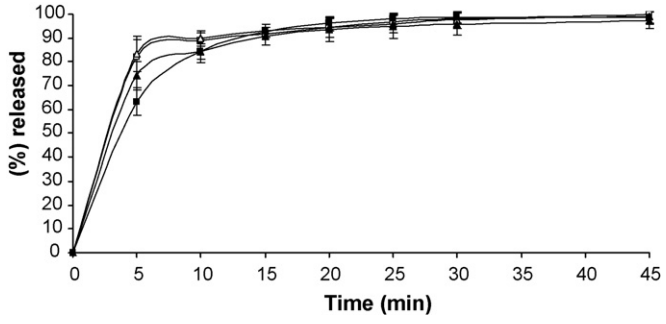

Fig. 2. Release profile of zidovudine (□) and lamivudine (△) from the novel FDC tablets and zidovudine (■) and lamivudine (▲) from Duovir® tablets.

Table 3
Mean pharmacokinetic parameters (R.S.D.) of AZT and 3TC after oral administration of a novel FDC tablet and Duovir® tablet to healthy volunteers ($n = 18$).

	Novel FDC tablet	Duovir tablet
Zidovudine		
C_{max} (μg/ml)	3.1 (12.8%)	3.0 (27.6%)
T_{max} (h)	0.6 (28.6%)	0.7 (35.8%)
$AUC_{0-12\,h}$ (μg/ml h)	4.4 (16.5%)	4.2 (21.4%)
$AUC_{0-\infty}$ (μg/ml h)	5.4 (13.6%)	5.1 (17.5%)
Lamivudine		
C_{max} (μg/ml)	1.5 (20.7%)	1.4 (21.0%)
T_{max} (h)	1.0 (12.4%)	1.0 (12.4%)
$AUC_{0-12\,h}$ (μg/ml h)	3.9 (15.0%)	3.7 (17.3%)
$AUC_{0-\infty}$ (μg/ml h)	5.9 (6%)	5.6 (12.8%)

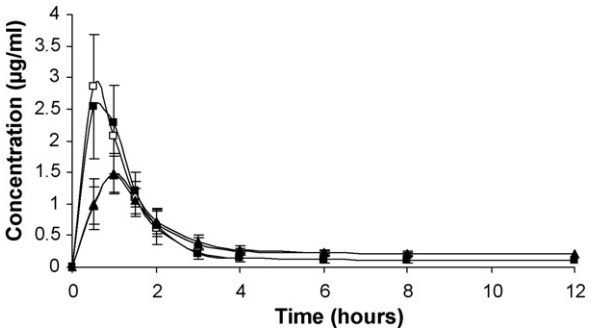

Fig. 3. Mean (±standard deviation) concentration–time profiles of zidovudine (□) and lamivudine (△) released from the novel FDC tablets and zidovudine (■) and lamivudine (▲) released from Duovir® tablets.

4. Discussion

The use of Nucleoside Reverse Transcriptase Inhibitors (NRTI) in treatment of patients infected by HIV has been successful in reducing virus load and boosting the immune system. The combination of two NRTI (zidovudine and lamivudine) in a fixed dose provided the best results, in combination with a high patient compliance compared to the administration of individual drug formulations (Legorreta et al., 2005). However, on the market there is a remarkable lack of suitable paediatric ARV drug formulations, emphasised in developing countries. Although the first paediatric cases of AIDS were reported in 1982 (Rogers et al., 1987), different HIV/AIDS treatment programs of UNICEF and WHO consider children as a largely neglected patient group by drug manufacturing companies based on the lack of suitable paediatric dosage forms (UNICEF/WHO, 2004).

Paediatric practice requires dosage forms that are acceptable for different age groups and that allow administration of the correct age-related dose. Whereas only liquids are appropriate for oral use in the youngest age groups, solid dosage forms (tablets, capsule) are also convenient for adolescents (Nunn and Williams, 2005). Since liquids (solution, suspension, possibly obtained after reconstitution of a powder formulation) are less suitable in resource-limited settings due to the specific dosing devices (syringes, spoons) required for accurate dosing in function of body weight, to the higher risk of physical, chemical and microbiological instability (Standing and Tuleu, 2005) and to the large bulk volume, this study focuses on solid dosage forms for paediatric drug dosing. Pellets have been identified to allow drug dosing in function of body weight (Kayumba et al., 2007a), but must be packed into capsules of different sizes (Kayumba et al., 2007b) to obtain doses covering the weight range from infants to adolescents. Since a tablet can be designed to cover the entire dose range in a single dosage form, fast-disintegrating tablets consisting of multiple subunits were selected as dosage form to formulate the combination of AZT and 3TC. The entire tablets or its subunits can be administered as a liquid after dispersion in a limited volume of water or as solid dosage forms depending on the child's age (Yeung and Wong, 2005; Nunn and Williams, 2005).

The novel tablet with a fixed dose combination of zidovudine and lamivudine possessed three essential features required from a paediatric HIV formulation: flexibility in dosing, fast disintegration and high bioavailability.

The rectangular-shaped tablets (22.4 mm long/11.2 mm wide) with multiple score lines at both sides was designed taking into account the following parameters required from tablets allowing dose adjustment via tablet breaking: ease of breaking, mass uniformity of subdivided tablets and limited weight loss after subdivision (Van Santen et al., 2002). Since the tablets of this study were intended to be used in resource-limited settings where commercial tablet cutters are unavailable; their design focused on the successful manual breakability. The specific tablet design was selected based on results obtained in previous studies performed on tablet breakability considering the following aspects: size and shape of the tablets, and impact of score lines (Polli et al., 2003; Marriot and Nation, 2002).

The size of the novel FDC tablets was sufficiently large to allow easy breaking into multiple units (even the quarter tablets could be further broken into subunits of uniform weight). The correlation between tablet size and accuracy of division in favour of larger tablets was already identified in previous studies: Gupta and Gupta (1988) reported that elongated tablets broke cleanly with low weight deviation whereas smaller tablets were more difficult to break accurately (Gupta and Gupta, 1988), a larger weight variability of small tablets was also reported by Mc Devitt using 6 mm tablets containing 25 mg hydrothiazide (MacDevitt et al., 1998) and Marriott and Nation considered a small tablet size as one of the factors contributing to increased inaccuracy of tablet splitting (Marriot and Nation, 2002).

Rectangular FDC tablets (Fig. 1) were designed as splitting of cylindrical-shaped tablets is limited to a maximum of 4 parts (using score lines intersecting at a 90° angle). Manual splitting of cylindrical-shaped tablets (even large one) beyond 4 parts with sufficient weight accuracy is impossible due to the pie-shaped structure of the subunits. Polli et al. (2003) reported that all tablets failing the weight uniformity test (even using a tablet splitter) had an unusual shape (trapezoid, octagon, spherical or convex) and they concluded that the tablet shape was more important for the weight uniformity than scoring (Polli et al., 2003).

Although splitting of scored tablets was already FDA-approved as safe and efficacious, literature data showed that not all scored tablets allow easy splitting and/or result in a homogeneous weight distribution of the subunits (Polli et al., 2003; Kristensen et al., 1995) due to the position of the score lines (e.g. only on one tablet face) or technical quality of score lines (e.g. limited depth) (Rodenhuis et al., 2004). Therefore, to assure the functionality of the score line and obtain accurate manual breaking the tablets were designed with multiple and deep score lines (0.75 mm) on both sides of the tablet (Makino et al., 1993).

The ease and reproducibility of breaking of these rectangular tablets was assessed via manual breaking. As suggested by Wilson et al. (1996), a short instruction on how to divide the tablets was given to the nurses, who participated in this study, in order to harmonize the procedure: keep the tablet on the index finger, apply the breaking force by thumbs positioned along the score lines and break like opening the score. This method previously showed the best results in relation to weight loss and variability after tablet breaking (Thonissen et al., 2002). Our study showed that after a short demonstration the caregivers could break the tablets into 8 subunits having a reproducible weight (125.1 ± 5.5 mg), independent of the user ($p > 0.05$, one-way ANOVA) and with minimal weight loss (0.3%).

The drug assay showed that both AZT and 3TC were homogeneously distributed over the different subunits. Such dosing accuracy cannot be expected when the currently commercially available single drug tablets (Retrovir or Zidovir tablets for AZT and Epivir tablets for 3TC) or FDC tablets (Combivir and Duovir) are broken beyond halves because of the limited number of score lines and/or the tablet size and shape. Hence the use of the novel tablets will offer sufficient dosing flexibility to the caregivers with excellent dosing accuracy (dose adjustment possible for every 5 kg body weight).

Due to the incorporation of a super-disintegrant in the formulation and the use of a low compression force (12 kN) the novel tablets and its subunits disintegrated rapidly, even in a limited volume of liquid, and the rapid dissolution was expected because AZT and 3TC are qualified by Biopharmaceutical classification system

(BCS) as Class III drugs (Therapeutic systems research laboratories). Therefore, these dosage forms can be used in the treatment of children living with HIV, independently of their ability to swallow since the subunits can be easily dispersed in a small volume of water on a spoon or mixed with food before administration (Mizumoto et al., 2005). The fast disintegration facilitated the dissolution of both drugs from the novel FDC tablets, ensuring similar release profiles compared to Duovir® tablets (similarity factor $f2 > 50$).

According to the Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH Guideline E11: Clinical investigation of Medicinal Products in the Paediatric Population) when a medical product is to be used in the paediatric population for the same indications as those approved in adults (and the disease process is similar in adults and paediatric patients), adult pharmacokinetic data should be available before a paediatric study is planned (ICH Topic E11, 2003). Therefore, a bioavailability study in adult volunteers was conducted as a pre-study to provide information on zidovudine and lamivudine pharmacokinetics after oral administration of the newly developed formulation. These were compared to the commercially available Duovir® tablets. This information was indispensable for safety when planning a future efficacy study in the children with HIV/AIDS.

This study showed that the pharmacokinetic parameters of the new FDC tablets were not significantly different compared to those obtained from Duovir tablets currently used in treatment of HIV (Table 3 and Fig. 3). These values were comparable to a study assessing the pharmacokinetics of AZT and 3TC after oral administration to HIV-negative Indian women in 2006 (Vezina et al., 2006) and to a study where both drugs were administered in separate formulations (Lamivir and Epivir) to healthy adult Indian volunteers in 2005 (Narang et al., 2005).

Therefore, the novel FDC tablets containing 300 mg AZT and 160 mg 3TC are suitable for future studies in children because they comply with the essential features required of a paediatric HIV formulation: flexibility in dosing, fast disintegration and high bioavailability. The results of this study showed that there were no significant difference between the in vitro and in vivo release of AZT and 3TC from the novel FDC and Duovir tablets.

5. Conclusions

Due to their specific size and shape (large rectangular tablets with multiple score lines) the in vitro quality parameters (mass uniformity, friability, breakability, drug content, disintegration and dissolution) of the novel fixed dose combination tablets containing 300 mg zidovudine and 160 mg lamivudine were acceptable to provide flexibility for drug dosing based on the body weight of children. The bioavailability of zidovudine and lamivudine administered via the novel FDC tablets was similar to that observed following administration of marketed Duovir tablets. Based on this study, an evaluation of the pharmacokinetics and dosing requirements of the novel tablet formulation in HIV-infected children can be initiated.

This approach using the multiple scored and fast disintegrating tablets can be used for paediatric applications for other drugs which require dosing in function of the body weight.

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