Formulation and bioequivalence of two Valsartan/Amlodipine Immediate release tablets after a single oral administration

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Abstract: The aim of this study was to formulate a film-coated Valsartan/Amlodipine (VS/AM) immediate release tablets and to evaluate their *in vivo* release profile. VS/AM core tablets were manufactured using dry granulation method. Opadry aqueous coating dispersion was used as film coating material. Dissolution of the film coated tablets was tested in 900 ml of 0.5% SLS media, bioequivalence of tablets was tested by comparisons against the refrence brand product. The ICH guidelines were used to evaluate the stability of the obtained tablets. The coated tablets were subjected to gastric pH, and drug release was analyzed using HPLC system to evaluate the efficiency of the film coat. The coated tablets had no defects. VS/AM release met the FDA guidelines for bioequivalence studies. Statistical comparison of the main pharmacokinetic parameters showed no significant difference between test and reference. These findings suggest that aqueous film coating with Opadry system is an easy and economical approach for preparing stable film coated VS/AM tablets without compromising their *in vivo* drugs release.

Keywords: Film coating, stability, aqueous dispersion, opadry, bioequivalence.

INTRODUCTION

Amlodipine (AM), chemically (RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (fig. 1,a) is a dihydropyridine calcium channel blocker (CCB) used in the treatment of hypertension. After oral administration, it is well-absorbed (bioavailability of 64-80%) with no food effect and reaches its maximum plasma level within 6-8 hours. Afterwards, it is subjected to elimination phase which occurs bi-exponentially with a long terminal half-life of 30-50 hours. AM is extensively bound to plasma proteins (94-98%) and is metabolized in the liver by CYP 3A4. Amlodipine based on Biopharmaceutical Classification System (BCS) is a class I drug (Domenech and Coca, 2010; Krzesinski and Cohen, 2010; Olusola *et al*., 2012; Plosker and Robinson, 2008).

Chemically, valsartan (VS) is (S)-3-methyl-2-(N-{[2'-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido) butanoic acid (figs. 1, b). It is an angiotensin II type 1 (AT_1) receptor antagonist, it is rapidly absorbed after oral administration and reaches its maximum level at 3 hours. It has an absolute bioavailability is 10-35% depending on the dosage form and this is not influenced by food ingestion. It belongs to the BCS class III drug classified as low permeability and high solubility drug. It has an elimination half-life of 6-9 hours and its plasma protein binding is more than 90%. The elimination of VS occurs mainly as unchanged drug in the bile (86%) and to a lesser extent in the urine by the renal excretion (13%) (Domenech and Coca, 2010; Krzesinski and Cohen, 2010; Siddiqui *et al*., 2011; Zaid *et al*., 2011).

The majority of hypertensive patients do not succeed to maintain their blood pressure (BP) within the normal range by a single medicine. Therefore, the application of combination therapy strategy is crucial to control BP with minimal side effects (Rubio-Guerra *et al*., 2009). Combining drugs from two different classes revealed greater therapeutic responses compared to doubling the dose of a single drug (Pimenta and Oparil, 2008; Wald *et al*., 2009). One of the most commonly prescribed antihypertensive drugs is a combination of a calcium channel blocker and an angiotensin II type 1 (AT_1) receptor antagonist. This drug combination was shown to provide a better control of BP along with simultaneous cardiovascular and renal risk reduction with minimal adverse effects. Exforge®, is the first commercially available combination of these drug classes as a fixed-dose regimen containing 5 or 10 mg AM and 160 or 320 mg VS (Krzesinski and Cohen, 2010; Rubio-Guerra *et al*., 2009).

In this research paper a bioequivalence study was performed, where a comparative study between two drug products (the reference brand Exforge® and the test generic Valsadipine®) was designed and the key pharmacokinetic (PK) parameters for both drugs were assessed. Besides, we examined the stability of the dosage form and then evaluated the influence of the formulation aging on the drug release and subsequently drug bioavailability. For this purpose, we developed and

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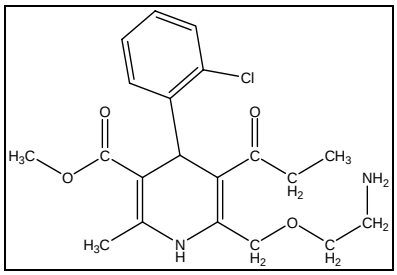
validated highly sensitive liquid chromatographic (LC) methods with mass spectrophotometric (MS) detection to determine the level of AM and VS in the plasma samples.

AM



VS

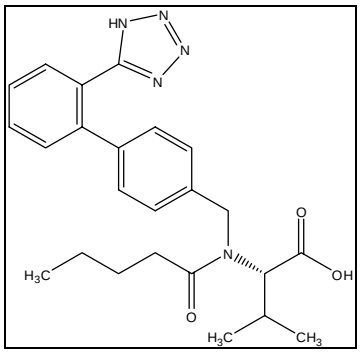


Fig. 1: Chemical structure of AM and VS.

METHODS AND MATERIALS

The study was a comparative randomized, single dose, two-way, crossover, open-label study to determine the bioequivalence of AM 10 mg/VS 160 mg Valsadipine® (Pharmacare PLC, Ramallah, Palestine) and Exforge® tablet (AM 10 mg/VS 160 mg) (Novartis Pharmaceuticals Corp. Suffen, NY, USA) after single oral dose administration of each product to healthy adults under fasting conditions.

Volunteers and clinical protocol

The study protocol and the informed consent forms were approved by the Institutional Review Board (IRB) at the Genuine Research Center-Egypt. The study was conducted in accordance with the requirements of the declarations of Helsinki (World Medical Association 2008), the current Good Clinical Practice (GPC) Guidelines [EME 1997] and the International Conference Harmonization (ICH) [ICH 1996] Guidelines. Thirty six adult male volunteers were recruited to participate in the study. The volunteers aged between 18-36 years, weighing between 58 and 107 Kg with an average weight of 73.68±13.88 Kg. The volunteers were subjected to a full medical and physical exam to confirm their healthy status and were not on any medication during the study period. A written informed consent, which explained the nature of the study, was given to the volunteers. The volunteers were instructed to abstain from taking drugs, caffeine and alcohol-containing beverages for at least two days prior to the study and throughout the study period and to fast for at least 10 hours before drug administration.

The study used an open-label, randomized two-period crossover design with a seven-day washout period between doses. The volunteers were randomly divided into two groups each of 18 subjects. The first group was given the reference brand and the second group was given the test formulation with a crossover after the washout period. On the morning of the study, each volunteer gave a blood sample to serve as a blank for the drug assay. Each volunteer received an oral dose of the assigned formulation given with 240 ml of water. Blood samples for plasma drug measurements were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 24, 48 and 72 hours after drug administration. Blood samples were collected in tubes containing EDTA, and centrifuged to separate the plasma fraction of the blood. The resulting plasma was immediately stored at -70C° until analyzed. Two hours after drug administration, a standard breakfast of bread and cheese was allowed. The second meal (standard lunch containing fried chicken, rice and bread) was 4 hours later and allowed free access to water.

Medicines and chemicals

HPLC-grade acetonitrile (ACN) and formic acid (FA) were from Lab Scan®. HPLC grade water was supplied by ELGA® system. Control human plasma was harvested from donors. All other solvents and reagents were analytical grade. AM and VS (batch number RD-03110, expiration date 9/2012) and clarithromycin (batch number CAS 1938 internal standard for AM and atomoxetine internal standard for VS were supplied by Pharmacare PLC, Ramallah, Palestine. All experiments were prepared before March 2011.

Formulations AND evaluation of core tablets

Several trials were carried out to develop AM/VS core tablets in order to find the most suitable formulation that meets the pharmacopeial specifications such as hardness, friability, weight and content uniformity and show acceptable appearance. Tablet core were prepared using a dry granulation method to obtain suitable granules for compaction. The tablet core was composed of the following excipients: Avicel PH 101, Crospovidone, Aerosil® 200 and Magnesium stearate.

All the ingredients were accurately weighed and sieved through a 24-mesh sieve. Tablet core ingredients were mixed and were dry granulated thereafter. The obtained granules were lubricated by magnesium stearate, and then compressed using a Manesty compression machine (type D3B). The resulting core tablets were assessed for physical appearance, thickness, hardness, friability, weight variation, identification, assay, disintegration and

dissolution (United States Pharmacopeia 2007). Weight uniformity was assessed using an electronic balance (Precisa 205 ASCS). Thickness was evaluated using a Vernier caliper. Hardness was determined using (Pharma test PTB311E), while friability was evaluated using a TA-100 Erweka friabilator. Disintegration testing was carried out using Erweka apparatus (type ZT 221). Dissolution was also carried out according to the FDA guidelines procedure using Erweka apparatus (Erweka ZT-2, Husenstamn, Germany). The vessel has a capacity of 1000 ml volume and 900 ml of a 6.8 pH buffer solution was used and maintained at 37°C. The apparatus was set at 75 rpm for 45 minutes (www.fda.gov). After passing all the above tests, the decision to coat the core AM/VS tablets was taken.

Film coating of AM/VS (10 mg AM/160 mgVS/tablet)

Preparation of Opadry white dispersion for film coating

Opadry white (300 gm) was mixed with 2000 ml distilled water using a mixing pan for about 25 minutes. The aqueous dispersion was passed through a 250 µm sieve in order to achieve homogenous dispersion. The dispersion was continuously and slowly stirred during the entire time of the coating process.

Coating methodology

Tablet coating was performed in a coating pan of 5 kg capacity using one spraying gun. The core tablets (3.5 kg) were placed into the coating pan and were pre-heated to about 40°C by a dryer of a high pressure air spray gun. Heated air at 55-60°C was then introduced into the coating pan. The pan temperature was kept around 35 to 40°C during the entire coating process. The spray gun was filled with Opadry aqueous dispersion and positioned at distance of 15 cm from the tablet bed. The aqueous coating dispersion was sprayed at an appropriate flow rate. The motion of the pan was adjusted and the opadry dispersion was sprayed onto the falling cores using a suitable air pressure (1.7 bars). The air heater was switched off and tablets blow dried for about 25 minutes in the coating pan.

Characterization of AM/VS film coated tablets

The properties of the film coated tablets, such as physical appearance, thickness, and weight uniformity, content uniformity, hardness, disintegration, dissolution, and assay were determined. Weight uniformity of coated tablets was evaluated according to the USP 30 method (USP 2007). The average weight obtained was 410±5% mg, which means 2.5% increase in tablet weight due to the film coat. Diameter and thickness of 10 tablets were determined using a Vernier caliper. Hardness of the coated tablets was also examined according to procedures of USP 30 (USP 2007). The dissolution of coated tablets was determined according to the recommended dissolution method suggested by USP 30 (USP 2007). Assay for AM/VS tablets content was performed according to the reported validated assay method in order to evaluate content uniformity. The hardness of the coated tablets was tested by randomly selecting 20 tablets from each three study batches at different time intervals of the study. The disintegration test of film coated tablets was performed according to USP 30 (USP 2007). Six coated tablets of atorvastatin were placed in pH 6.8 buffer solutions in a USP basket rack assembly and the time of complete disintegration was recorded.

The dissolution test for film coated tablets was according to Food and Drug Administration (FDA) method for dissolution of AM/VS (www.fda.gov). The dissolution of six tablets was determined after 45 minutes run; an aliquot of the fluid was drawn and assayed by the LC methods at time 0, 5, 10, 15, 30, and 45 minutes.

Selected samples of the film coated tablets packaged in a blister of aluminum foil and PVC was subjected to both long term and accelerated stability study in accordance with the ICH guidelines (EMA 2003). The long term stability study samples kept at room temperature (25±2°C) and 65±5% relative humidity conditions (RH). The samples were collected for testing at a time interval of 0, 3, 6, 9 and 12 months. The accelerated stability study were kept at 40±2°C and RH 75±5% and were tested at time interval of 0, 3 and 6 months. Samples in both studies were tested for their appearance, disintegration, dissolution, hardness and assay using the above described procedures to evaluate the stability of the coated tablets.

Instruments and chromatographic separations

The analysis was performed using an HPLC system (Shimadzu autosampler model SIL-20a) coupled with MS detector. For AM the mobile phase consisted of ACN, MeOH, de-ionized water and FA (60:30:10:0.1 v/v/v/v). The stationary phase was a Luna C_{18} (phenomenex) (50 x 4.6) mm, 5µ particle size. For VS the mobile phase consisted of ACN, 0.02 M ammonium acetate and FA (80:20:0.1 v/v/v) respectively. The stationary phase was C_{18} (kinetex) (50x4.6) mm, 5µ particle size. Samples were pumped at a flow rate of 1 ml/minute. The analysis was done by analyst software version 1.4.3, applied biosystems MDS, SCIEX, Canada.

Preparation of Standard solutions

Stock solutions of AM were prepared by dissolving the drug in 1:1 v/v acetonitrile and distilled water. Working standard solutions were prepared from the stock solution by sequential dilution to prepare working solutions of AM with concentrations of 200 µg/ml, 1000 ng/ml, 250 ng/ml and 100 ng/ml. Stock solutions of VS were prepared by dissolving the drug in co-solvent system. Working standard solutions were prepared from the stock solution by sequential dilution to prepare working solutions of VS with concentrations of 400 µg/ml, 200 µg/ml, 50 µg/ml, 10 and 1 µg/ml. Stock solutions of clarithromycin (internal standard for AM) were prepared by dissolving

clarithromycin in 1:1 v/v ACN and water to give concentrations of 200 µg/ml, 1 µg/ml and 20 ng/ml. Stock solutions of atomoxetine (internal standard for VS) were prepared by dissolving atomoxetine in 1:1 v/v ACN and distilled water also to give concentrations of 272 µg/ml and13.6 µg/ml. The calibration standards were prepared to form a set of calibration standards with concentrations from 0.2 ng/ml to 16 ng/ml for AM and from 10ng/ml to 10000 ng/ml for VS.

Sample preparations for HPLC injection

For AM: Aliquot of 0.5 ml plasma was pipette into 4 ml centrifuge tubes, 50 µl of 200 ng/ml clarithromycin as IS was added and extraction was done using tertiary butyl methyl ether, then it was loaded to equilibrated HPLC system. For VS: Aliquot of 1 ml plasma was pipette into 4 ml centrifuge tubes, 100 µl of 13.6 ng/ml atomoxetine as IS was added and extraction was done using ACN, then it was loaded to equilibrated HPLC system.

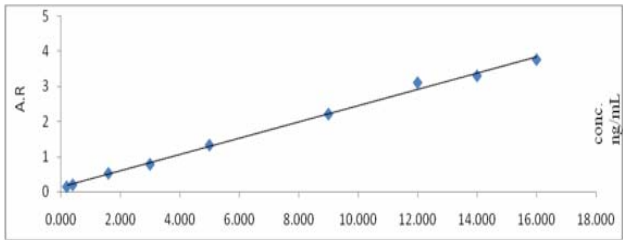
Validation procedures

Validation of the analytical method was performed in order to evaluate its linearity, selectivity, stability, precision and accuracy. Calibration curves were constructed from the peak area ratio (drug/internal standard) and the corresponding drug concentration in each calibration standard. For AM the linearity study was carried out in the range of concentrations from 0.2-16 ng/ml. For VS the linearity study was carried out in the range of concentrations from 10-10000 ng/ml. The lower limit of quantitation (LLOQ) is the lowest concentration of analyte that can be determined with acceptable precision and accuracy under the stated experimental conditions. It was estimated by analyzing known samples of AM and VS at progressively lower concentrations, starting at the lower end of the calibration curves.

Percentage relative error (RE) of a series of measurements was used to determine accuracy and coefficient of variation (CV) was used to determine assay precision. Aliquots of five spiked plasma at low, middle and high concentration levels of AM and VS were analyzed for this purpose. Three replicates of calibration curves were analyzed on the same day, for intraday repeatability and six different calibration curves on different days were analyzed for inter-day precision.

Three different plasma samples for each drug concentration were prepared and injected immediately into the LC system. They were kept at room temperature and were injected again after 6 hours. The concentrations measured at time zero and after 6 hours were compared to determine the stability of the drug in plasma and at room temperature. The study samples obtained from seven volunteers were analyzed at the beginning of the study and at the end of the study. The samples were stored at -70ºC between the analyses to determine the stability of the drug in frozen plasma.

AM



VS

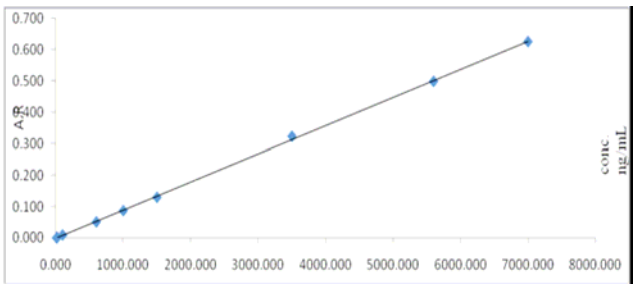


Fig. 2: Calibration curves of AM and VS

The quality control (QC) samples were used to evaluate the performance of the assay. They were prepared by spiking blank plasma with AM or VS. The QC samples were prepared to have low, medium and high concentrations (AM: 0.6, 8 and 13.5 ng/ml and VS: 30, 5000 and 8000 ng/ml). Three QC samples were incorporated with each analysis run as unknown samples. The concentration in each QC sample was determined from the calibration curve and it was compared with the nominal concentration. The analysis run was accepted if at least 2 out of 3 QC samples were within 15% of nominal concentration (Shah *et al*., 1991).

Pharmacokinetic and statistical analysis

The pharmacokinetics parameters were estimated using standard non compartmental methods. The peak plasma concentration (C_{max}) and the corresponding time of peak plasma concentration (T_{max}) were taken directly from the data. The elimination rate constant (ke) was calculated from the slope of the semi-logarithmic plot of the terminal phase of the plasma concentration-time curve calculated by linear regression. The elimination half-life time ($T_{1/2}$) was calculated using the formula $t_{1/2}$=ln2/ke. The areas under the drugs plasma concentrations time curves from (AUC_{0-72}) and the area to the infinity ($AUC_{0-\infty}$) were calculated by using the linear trapezoidal method. Extrapolation to the infinity was done by adding the value Ct/ke to the calculated AUC_{0-72} (where Ct is the last detectable concentration). For the purpose of bioequivalence analysis, one way analysis of variance (ANOVA) was used to assess the effect of formulations, periods, sequences and subjects on AUC_{0-72}, $AUC_{0-\infty}$, and C_{max} using Kinetica 2000 statistical software (FDA 2001).

RESULTS

Results of validation procedures

Under the chromatographic conditions described above, there were no peaks for endogenous compounds that appeared at the same retention time for AM and VS in the chromatograms for six different blank plasma samples obtained from different subjects (data not shown). A summary of the validation parameters for the assay is provided in table 1. Briefly, the relationship between concentration and peak area ratio was found to be linear within the range 0.2-16 ng/ml for AM and 10-10000 ng/ml for VS. The correlation coefficient (r) was always greater than 0.995 during the course of the validation (fig. 2). The LLOQs were 0.2 and 10 ng/ml for AM and VS respectively. For precision, the intra-day and inter-day CV values for AM and VS were within the acceptable limits and were all less than 15%. For accuracy, the intra-day and inter-day accuracy were between 90%-110% for both analytes during the entire range of the calibration curves. There was no change in the drug concentration when the samples were kept at room temperature, indicating sufficient stability of AM and VS in the plasma samples at room temperature. Similarly, there was no change in the drug concentration in frozen plasma stored at -70°C, indicating the stability of the medications in frozen plasma. table 1 summarizes the data obtained during method validation.

Table 1: Summary of validation parameters for amlodpine and valsartan.

	Amlodipine	Valsartan
Linear Range	0.2-16 ng/ml	10-10000 ng/ml
(LOQ)	0.2 ng/ml	10 ng/ml
R	0.995	0.998
Precision		
Intra-day Variation	2.3-11.9%	3.4-11.5%
Inter-day Variation	7.0-10.0%	4.6-9.5%
Accuracy		
Intra-day Variation	97.6-105.3%	93.7-106.6%
Inter-day Variation	95.8-100.8%	98.3-103.6%

Results of tablet formulation and coating

Regarding the manufacturing of core tablets, the used excipients were selected in order to produce optimum cores. Accordingly, avicel PH101 was selected as a filler to improve the compressibility of the obtained granules. Whereas, crospovidone and aerosil® 200 were chosen to function as a disintegrant and as glidant/adsorbant against moisture respectively. The obtained tablets had an average weight of 400±5% mg. They had a proper strength of hardness, and their friability was less than 1% when tested by the friability tester. Physical appearance, weight variation and drug content evaluation of the cores were found to be satisfactory under pharmacopoeial standards of tablet evaluation (USP 2007). These cores were coated without having any visual defects such as roughness, yellow or orange peel appearance, chipping, tacking or other unacceptable defects. Tablets were found to be hard enough and had no visual defects or signs of peeling or chipping and all their specifications were within the acceptable limits. The average weight of the final coated tablets was about 410±5% mg which main an average weight gain due to film coat of about 2.5%. The immediate release characteristics of the obtained film coated tablets were determined by placing them into simulated gastric solution, and drug release was analyzed using HPLC system. tablets also showed satisfactory release of both AM and VS. In fact, AM/VS release met the criteria outlined in this study i.e. not less than 80% dissolved after 45 minutes according to the FDA dissolution method (www.fda.gov).

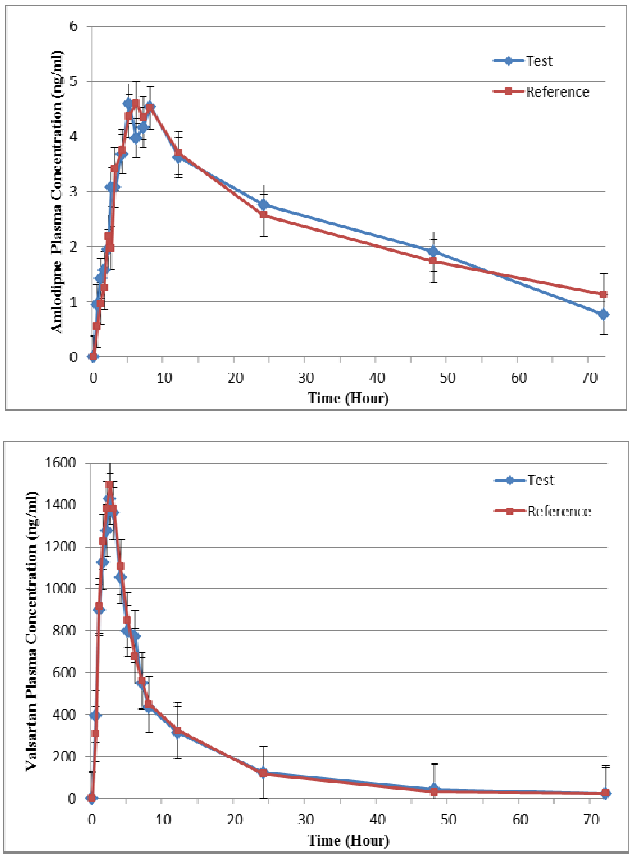


Fig. 3: Mean plasma concentration of AM and VS of 36 volunteers versus time after the administration of a single oral dose of AM 10 mg/VS 160 mg FCT from (Pharmacare PLC) and Exforge® tablet.

The data of the long term and accelerated stability studies showed reliable and satisfactory results, indicating no significant variation in physical characteristics, color, assay, dissolution profiles, friability, hardness and disintegration time of the coated tablet as reported in tables 2 and 3.

Table 2: Long term stability study of film coated Valsartan/Amlodipine tablets

Tests	Time (months)				
	0	3	6	9	12
% Assay Amlodipine Valsartan mean±standard deviation	101.4±2.3 99.7±3.1	101.6±1.4 99.4±2.8	101.0±2.9 98.9±2.4	100.7±3.1 99.4±2.5	100.7±2.2 99.1±2.8
% Dissolution Amlodipine Valsartan mean±standard deviation	96.4±2.2 98.4±2.8	97.1±3.1 98.1±2.9	95.4±2.8 94.1±2.1	94.8±2.5 94.6±3.2	95.2±3.1 93.2±2.4
Disintegration (minutes)	3.5	2.9	3.2	3.2	2.8
Appearance test	Complies	Complies	Complies	Complies	Complies
% Friability	0.02	0.1	0.1	0.2	0.2
Hardness (kN) mean±standard deviation	12.2±1.1	12.7±3.0	13.4±2.3	12.3±2.8	11.6±3.2

Table 3: Accelerated Stability Study of film coated Valsartan/Amlodipine Tablets

Tests	Time (months)		
	0	3	6
% Assay Amlodipine Valsartan mean ± standard deviation	101.4±2.0 99.7+1.1	100.8±1.8 99.2±1.4	100.4±1.4 99.1±1.0
% Dissolution Amlodipine Valsartan mean±standard deviation	96.4±2.2 98.4±2.8	94.3±2.0 98.8±2.6	95.8±2.4 98.7±2.1
Disintegration (minutes)	3.5	2.4	2.8
Appearance test	complies	Complies	complies
% Friability	0.02	0.2	0.4
Hardness (kN) mean±standard deviation	12.2±1.1	11.4.0±3.0	12.2±1.8

Results of pharmacokinetic study

Both AM 10 mg/VS 160 mg film coated tablet from (Pharmacare PLC) and reference tablet were well tolerated by all the subjects and they were discharged in good health. fig. 3 shows mean AM and VS plasma concentrations of both brands over the 72 hours indicating that the two brands are superimposable.

All estimated PK parameters were in agreement with reported values. table 4 shows a summary of the PK parameters for the two formulations of AM 10mg/VS 160 mg. For AM the confidence interval (CI) of log-transformed test/reference ratio were 100.09%, 100.60%, and 97.95% for AUC_{0-72}, $AUC_{0-\infty}$, and C_{max} respectively. For VS these values were 105.86%, 103.36% and 110.03%. No statistically significant difference between the two formulations was found. The 90% CIs for these PK parameters values lie within the FDA specified bioequivalence limit (80-125%) (FDA 2001). Our results in this part of the study suggest equivalent clinical efficacy of the two brands of AM 10mg / VS 160 mg.

DISCUSSION

The validated analytical methods described above were utilized for quantification of AM/VS. Both LC methods were successfully applied for measuring of both AM and VS in tablets without interference with the used excipients in the tablet formulation. They provided the appropriate accuracy, sensitivity, and selectivity with high sample throughput and economically convenient procedure required for PK studies. Indeed, our methods have LLOQs of 0.2 and 10 ng/ml for AM and VS respectively which make it more suitable for the routine chromatographic analysis of AM/VS combination in human plasma samples encountered in PK studies.

Aqueous based film coating materials for oral solid dosage forms contain mainly water soluble polymers and other additives with the objective of improving the quality and performance of the resultant film coat. The results of this study showed a high stability of the coated tablets without the use of a sub-coating layer. So there are significant savings in both time and material cost, and the coating obtained maintained its properties. Tablet coating was carried out using a traditional coating pan. During coating, different parameters such as temperature of coating pan and spray rate of coating dispersion were kept under control in order to obtain the desired smoothness and uniformity of film coat. In fact, the most important process parameters, such as temperature of coating pan and the spray rate of the coating dispersion were assessed

by other researchers (Sauer *et al*., 2007). According to these studies, the temperature of the coating pan had no effect on the smoothness of the obtained coat when a low spray rate was used. However, higher spray rates and higher temperatures should give smoother films. In another study, content uniformity was significantly influenced by pan speed and time of coating (Rege *et al*., 2003). Moreover, the use of high inlet-air temperature and low spray rate of the film coating dispersion during coating should decrease the rates of drug release from the obtained coated tablets (Frisbee *et al*., 2002).

Table 4: Summary of calculated pharmacokinetic parameters of amlodipine and valsartan in the bioequivalence study (n=24)

	Test Formulation mean±standard deviation	Exforge® mean±standard deviation
Amlodipine		
AUC_{0-t} (ng.h/mL)	149.1±99.5	147.3±104.2
$AUC_{0-\infty}$ (ng.h/mL)	199.4±123.6	198.9±133.1
C_{max} (ng/mL)	6.11±3.88	6.23±3.87
t_{max} (h)	5.69±1.75	6.56±2.81
$t_{1/2}$ (h)	29.7±15.9	30.6±17.3
k_e (hr^{-1})	0.06±0.16	0.03±0.03
Valsartan		
AUC_{0-t} (ng.h/mL)	13130.7±7213.6	13098.5±8602.1
$AUC_{0-\infty}$ (ng.h/mL)	13638.0±7096.4	13744.5±8368.8
C_{max} (ng/mL)	1630.61±888.56	1553.67±939.49
t_{max} (h)	2.44±0.47	2.5±0.82
$t_{1/2}$ (h)	10.46±5.78	13.07±8.75
k_e (hr^{-1})	0.08±0.04	0.07±0.04

The obtained film-coated tablets were considered of high quality since they were compared to Exforge® tablets, and the results of *in vitro* dissolution profile and *in vivo* drug absorption showed that both formulations were well-tolerated at the administered dose by all the subjects. Unexpected side effects that could have impact on the outcome of the study did not occur, and all volunteers left the hospital in a good health condition. Statistical comparison of the main PK parameters, AUC_{0-72}, $AUC_{0-\infty}$, C_{max} and T_{max} clearly indicated no significant difference between test and reference tablets, in any of the calculated PK parameters. The obtained values were compliant with the FDA and EMEA requirements for bioequivalence of generic drugs since the $AUC_{0-\infty}$ and C_{max} mean ratios are within the 80-125% interval (EMA 2001, FDA 2001). It was concluded that the test tablets (AM 10 mg/VS 160 mg) film-coated tablet manufactured by Pharmacare PLC, Ramallah, Palestine is bioequivalent for both extent and rate of absorption to the commercial Exforge® tablet (AM 10 mg/VS 160 mg) (Novartis Pharmaceuticals Corp. Suffen, NY, USA) after single oral dose administration of each to healthy male adults under fasting conditions.

CONCLUSION

The validated analytical method employed in this study proved to be simple, fast, reliable, selective and sensitive enough. This encouraged us to use it in clinical PK studies of AM/VS. Aqueous film coating was successfully conducted and provides acceptable performance in terms of appearance characteristics and drug availability. The statistical analysis of the results which performed on AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} using the ANOVA method showed that both test tablets, (10 mg AM/160 mg VS, Pharmacare) and reference tablets Exforge® (10 mg AM/160 mg VS, Novartis Pharmaceuticals Corp.) are bioequivalent, since they deliver equivalent quantities of both AM and VS to the systemic circulation at equivalent rates for both AUC_{0-72} h and C_{max} ratios within the 80-125% interval proposed by FDA. These results show the good formulation of this new generic tablet, which is important to achieve good therapeutic benefits and avoid any potential problems which may arise due to poor formulation.

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DISCLOSERS

The authors report no conflicts of interest in this manuscript.

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