An Assessment of Impediments to Competition in the Pharmaceutical Sector in Jamaica:

Supplementary Volume:

Comparative In Vitro Dissolution and Biopharmaceutical Properties of Some Multi-Source Antihypertensive Drug Products Marketed in Jamaica

by

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Summary

A study has been done on the biopharmaceutical properties of antihypertensive drug products marketed in Jamaica. Four pharmacological classes of antihypertensive drugs were selected: Beta blocker (Atenolol), Angiotensine Converting Enzyme inhibitors (ACEI), Diuretics and Central Alpha Blocker (Methyldopa).

Products were tested for uniformity of weight, content of active ingredients (assay) and dissolution rates, following the British Pharmacopoeia/USP procedures.

It was observed that products contained the required level of active ingredients. However, some products make the active ingredient available for absorption faster and to a greater extend than others.

Results generally suggest that more than company reputation and cost is required for making rational decisions on drug product selection.

1. Introduction

Hypertension is one of the major chronic illnesses in Jamaica, and is included in the top six reasons for visits to primary care facilities. In 2002, hypertension was the leading cause for medical visit to primary health care facilities. The high incidence these disease in Jamaica has lead to a continued demand for products used in its management [1]. However, inadequate patients' outcomes seem to have been fraught by problems arising from poor compliance, discontinuation and switching between therapies all of which may be economically motivated [2]. In addition, patients are often on multiple drug therapies for these conditions as they are sometimes not well controlled on monotherapy. Since a significant difference may sometimes exist between the prices of brand and their generic analogues, drug product selection which minimizes cost while maximizing safety and efficacy continues to be a primary and challenging responsibility of pharmacists [1]

In order for a drug to be interchangeable with the innovator's brand, it must be pharmaceutically equivalent and bioequivalent [1]

According to the United States Food and Drug Administration (FDA), drug products are considered to be pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration, and are identical in strength or concentration [3]

The term bioequivalence describes the bioavailability of two or more drug products (pharmaceutical equivalents) studied under similar experimental conditions.

The rate and extent of absorption of the test drug must not show significant difference from the rate and extent of absorption of the reference drug product when administered at the same molar dose of therapeutic ingredient, under similar experimental conditions in either single or multiple doses. However, the difference in bioavailability of drug from the test and reference products may be intentional as is the case with the modified and targeted release drug delivery systems. These differences should be reflected in labeling and should not impede the attainment of effective drug concentration in the body on chronic use [3]

Prior to the 1938 enactment of the Food Drug and Cosmetic Act (FDCA), regulatory barriers to generic drug competition did not exist. Generic drug companies could formulate, manufacture

and market their products without submitting bioequivalence or efficacy data to the FDA. In 1938, the Act required that document the safety of the product to the FDA. This general recognition of safety was based on a history of safe use of the innovator product. In 1962, the Act was amended to add requirement of "substantial evidence of both safety and efficacy in adequate and well-controlled studies" Pre-1962 drugs were also evaluated. In 1970, the FDA established the Abbreviated New Drug Application to review the approval of generic versions of drug products approved between 1938 and 1962 [4]. Potential generic drug manufacturers were notified of requirements for developing versions of approved drugs. This resulted in the Abbreviated New Drug Application (ANDA), for which approval by the FDA was based on active ingredients and bioequivalence, rather than safety and efficacy data [5]

The ANDA does not require generic manufacturers to perform pre-clinical or clinical tests in order to establish safety and efficacy of active drug as this would have already been done by the innovator brand. The major requirement of an Abbreviated New Drug Application (ANDA) is the inclusion of bioequivalence evaluation, chemistry, and microbiologic evaluation, inspection of manufacturing facility and review of the proposed drug label [5].

Bioavailability and bioequivalence problems are more likely to occur with solid oral dosage forms; therefore bioequivalence evaluation is a very important aspect of the ANDA review process [4]

Under the Drug Price Competition and Patent Term Restoration act of 1984, manufacturers seeking approval to market a generic product are required to submit data showing that the drug product is bioequivalent to the innovator product. A major premise underlying the 1984 law is that bioequivalent drug products are therapeutically equivalent and thus interchangeable [3]. The *Approved Drug Products with Therapeutic Equivalence Evaluations* guideline (the 'Orange Book') [6] identifies drug products approved by the FDA as safe and effective. The book includes therapeutic equivalents for approved multi-source prescription drug products and is updated monthly. It cites a letter code for every multi-source product. The code indicates the FDA's evaluation regarding the therapeutic equivalence of the product with respect to the innovator's brand [5].

The main substantive requirement for approval of an ANDA by regulatory authorities in most countries is that the manufacturer of the generic product submits data demonstrating the bioequivalence of his product to the brand. One approach in the establishment of bioequivalence is through the demonstration of a clinically significant effect. This is usually done in the initial stages of product development when proving the efficacy of a new chemical entity. Another approach is through quantification of pharmacologic effect by correlating the intensity of response with drug concentration at the site of action. However, it is difficult to monitor pharmacologic data as precision and reproducibility are difficult to establish. Moreover, only a limited number of pharmacologic effects (viz blood pressure, heart rate, body temperature) amenable to such measurement are available in practice.

The third and most commonly employed method involves measurement of drug concentration in the biological fluids. This study, which can adopt single of multiple dose assessment, require the administration of specified dosage amount to a group of normal healthy adults usually of ages 18 to 35 years. Blood and/or urine samples are then collected at specified time interval, samples are analyzed and used to make inferences on the rate and extent of absorption (bioavailability) of the product.

Currently, the Food and Drug Administration (FDA) requires that the innovator and test product differ in terms of their rate and extent of absorption by a value of not more than 20 to 25 %[7]. In Jamaica, there are regulations that govern the importation of drugs and pharmaceuticals. Drug approval for distribution is based on evidence of safety, efficacy and pharmaceutical quality submitted by the distributors as being representative of approval document at country of origin. The procedure involves the review of the scientific data that are submitted. In addition, for generic drug products, a scrutiny of the pharmacokinetic data that compare blood levels after absorption is done to verify their interchangeability with the brand-name product before approval [1]. The vulnerability of this approach to the whims and caprices of manufacturers of substandard, fake, counterfeit and adulterated products syndicates, who collude with local distributors to 'push' into the distribution systems drugs of standards other than those that have been registered, can not be taken for granted. Documentary evidence by the BBC has linked fake drug products

marketed in Nigeria to syndicates in China, Egypt, India, Indonesia and Pakistan with collaborators in Nigeria [8]

In 1977, US FDA bioequivalence regulations set forth some criteria for establishing bioequivalent requirement of a drug product including, among others [9],

- Evidence from controlled trials or observations that such products do not give comparable therapeutic effects.
- Evidence from well controlled bioequivalence studies that the products are not bioequivalent
- Evidence that the drug product exhibit a narrow therapeutic index
- Competent medical determination that a lack of bioequivalence can have serious adverse effects in treatment or prevention of a serious disease or condition. The presence of specific inactive ingredients (e.g. hydrophilic or hydrophobic excipients) that may be required for absorption of the active drug or may interfere with such absorption [10]

Historically there have been concerns regarding the bioequivalence of multi-source drug products. In 1974, concerns about bioinequivalence led to the establishment of the Drug Bioequivalence Study Panel of the Office of Technology Assessment (OTA). The objective of the panel was to ensure that drug products with similar chemical composition and physical properties produce similar therapeutic effects. It was observed that not all chemical equivalents were interchangeable [10]. This observation lead Koch-Weiser (1974) to conclude that bioinequivalence of different drug products appeared to be more common than bioequivalence[5]. Bioinequivalence has been reported for phenytoin, phenylbutazone, chloramphenicol, tobutamide. The clinical significance of these differences relate to the therapeutic index of the drug, the type of disease being treated and the dose of the drug [10].

In 1989, the US Federal investigators uncovered several issues concerning generic industry. Generic drug industry officials were implicated in the conduct of fraud, obstruction of justice and non-compliance with various manufacturing procedures. It was also found that several FDA employees accepted illegal compensations in exchange for information and assistance that gave certain firms an advantage in the approval process. In addition, about ten generic companies had

submitted fraudulent data related to bioequivalency, stability testing, and manufacturing protocols for some of their products.

There has been a growing concern in the scientific community about the bioavailability problems of drug products on the market [10]

1.1 Responsibility of the Health Care Practitioners

A major role and responsibility of pharmacists involves product selection among available brands of drug products from different manufacturers. The pharmacist ability to make decisions in this regard will call for knowledge of biopharmaceutics, in particular bioavailability and bioequivalence of products. The potential cost savings to patients may play an important role in this decision [11] but quality of the product should form the baseline [12]

The more pertinent the data available, the more comfortable is the practitioner in arriving at a dependable decision. In uncovering the bio-inequivalence among products, one solution is to clinically test for efficacy. The incidence of *in vivo* bioinequivalence among products or different batches of a product has called for increased demand for quantitative data on the therapeutic equivalence of certain drugs [11]

Data from the United States of America (USA) showed an increasing trend of pharmacist control in dispensing decision from 16% in 1983 to 41% in 1993. The selection of multi-source product has become a professional responsibility of pharmacists. In drug product selection, the pharmacist should consider therapeutic efficacy, safety and the patient specific condition. Therefore, the most important parameters for arriving at a decision point are patient's economy, reputation of the product manufacturer and product bioequivalence and conformity to official standards. High efficiency in this regard would imply selecting the most cost-effective product, thereby making the best use of the limited health care resources. Obviously, the third option would be most challenging to the pharmacist as it would require the application of the principles of biopharmaceutics and pharmacokinetics [10]. Hence, it has been observed that reputation and quality history of the company are the most common employed criteria in product selection. Thus, routine post marketing surveillance of product quality and conformity to the initial

standards on which market authorization was based can contribute significantly to the accuracy of drug product selection decision making by the dispensing pharmacists.

1.2 Applicability of *in vitro* Dissolution test to Product Selection

Instead of relying solely on company reputation and quality history, in vitro dissolution testing could provide additional and a more realistic approach to product selection. It could provide a useful index of bioavailability and bioequivalence. Following oral administration, drug absorption from a solid dosage form depends on the release of drug substance from the product, the dissolution or solubilization of the drug under physiologic conditions and the permeability of the therapeutic agent across the biomembrane of the gastrointestinal tract [7]. Because of the critical nature of drug dissolution from dosage form and solubility in physiologic fluids, *in vitro* dissolution may serve a useful guide in the prediction of *in vivo* performance. Thus, *in vitro* dissolution test for immediate release solid oral dosage, such as tablets and capsules is being used to:

- Assess the lot-to-lot quality of a drug product
- guide the development of new formulations
- Ensure sustenance of product quality on continuous basis
- Ascertain maintenance of product quality and performance after modification or changes to formulation, manufacturing process, site of manufacture and scale up of a manufacturing process.

The knowledge of solubility, permeability, dissolution and pharmacokinetics of drug products are considered in defining dissolution test specifications for drug approval processes and for ensuring product's sameness under scale-up and post approval changes.

The *in vitro* dissolution specifications for generic drug products are established based on a dissolution profile in relation to previously documented acceptable clinical, bioavailability and/or bioequivalence studies. Thus, the dissolution specifications for batch-to-batch quality assurance published by in the USP as compendia standard is the official specification for all subsequent immediate release (IR) products with the same active ingredients and, hence, could serve as a primary standard for product comparisons and selection.

1. 3. Problem Statement/Research Questions

According to the Jamaican Food and Drug Regulations (1975) Section 40 (1) (a), "A person shall not sell, manufacture, import or distribute a drug unless the drug has been registered with the Ministry of Health. Section 41 (1) states that "A person shall not manufacture a drug unless he has applied for and has been granted a permit to do so by the minister". In addition, section 43 (2) (b) stipulates that, before an imported drug is released for sale, the minister may request the importer to conduct tests in Jamaica by an acceptable method, on that drug in the form in which it is sought to be imported [13]. It is evident, therefore, that adequate measure is in place for the control of drug product quality. With the plethora of regulations and ordinances in various countries where incidences of fake drug, adulterated and counterfeit products have been reported, including the United States, is it certain that manufacturers are complying with the regulatory requirements for their products? Are batches of anti-hypertensive drug products being tested and found satisfactory before being admitted into the Island of Jamaica? Are products containing the same active ingredients in the same amount and in the same type of dosage form truly bioequivalent? Is there any justification for patients to insist on a particular brand or generic, refuse substitution even though Pharmacy Law in Jamaica promotes generic dispensing and actually mandates pharmacists to erect notices informing patients of availability of generics?

In light of the research problem, the results of the investigation should find relevance in guiding pharmacists and physicians in product selection for their patients, to influence the relevant authority to activate the mechanism for documentation and reporting by pharmacists and physicians of patients' complaints and sub-clinical responses to treatments, to improve patients' confidence in generic products, to influence policies on generic drug selection for government programs, to add to the body of knowledge on brand – generic bioequivalence investigations and suggest, based on dissolution studies, formulation considerations. With the availability of several generic drug alternatives on the market, bioequivalence data will assist health care agencies, pharmacists and physicians to make better product selections for the patients. The resulting feedback from this process will alert the manufacturers to the necessity of ensuring that their products will not fail the built in quality of design and performance in the market place.

1.4. Aims and Objectives of this Study

The primary aim of this study was to investigate the pharmacoeconomic and quality implications of anti-hypertensive drug product selection among brands and generic products available in Jamaica. It should be possible to correlate the biopharmaceutical and bioequivalence properties of these products with the current patient experiences when on the therapy.

Some of the specific objectives of the study are to:

- Assess the physical quality and presentation of some random selection of antihypertensive drug products containing atenolol, captopril, methyldopa and nifedipine
- Assess their uniformity of weight
- Assay the tablets content of active ingredients
- Conduct dissolution tests and determine the dissolution profiles of the products
- Determine the comparative amount of API released at specified time points
- Establish the substitutability of tested brand (innovator products) with the generics using the similarity factors of the amount dissolved at specified time points.

2. Methodology

2.1. Materials

2.2.1. Chemicals and Reagents

The following chemicals and reagents used in the study were sourced as follows: Potassium phosphate monobasic , Sodium Hydroxide Pellets, Potassium Bicarbonate and Sodium Bicarbonate (Mallinckrodt Baker Inc., Phillipsburg, NJ); di-sodium disulphide, trisodium citrate, iron (II) sulphate (BDH, Poole, England); Conc. HCl, Ammonium hydroxide, conc. sulphuric acid and methanol (HPLC/UV grade) were products of PHARMCO, Brookfield, CT). All reference standards (Atenolol US CRS, Captopril US CRS, Furosemide US CRS and Methyldopa US CRS) were obtained from

2.2.2. Methods

2.2.1. Drug Products

Commercial products in four pharmacological class of antihypertensive were selected randomly, using assigned random numbers from a statistical table (Jones, 2002). Samples (200 tablets each) were sourced from distributors in Kingston through the UTECH Pharmacy. No prior knowledge of the purpose of product collection was available to the distributors. Detailed information on products packages were recorded including Manufacturers, batch numbers, date of manufacture and expiry, dose size, type of packaging and size of package.

Table 1. Drug products selection protocols

Class of Drug	Brand/Generics	Comment
Diuretic	**F3**	**Innovator Brand**
	4 generic analogues were identified, only 2 could be sourced (**F1 & F2**)	
	Furosemide Standard Chemical (US *CRS*)	**Reference**
Beta-Adrenoceptor Blocker	**Atenolol A4**	**Innovator Brand**
	11 generic analogues were identified, three were randomly selected for study (**A1, A2 and A3**)	
	Atenolol Standard Chemical (*US CRS*)	**Reference**
Angiotensin Converting Enzyme Inhibitor (ACEI)	**Captopril C3**	**Innovator Brand**
	6 Generic analogues were identified, only 2 could be sourced (**C1 & C2**)	
	Captopril Standard Chemical (*US CRS*)	**Reference**
Central Alpha Blocker	**Methyldopa M1**	**Innovator Brand**
	Only one generic analogue exists in the market (**M2**)	
	• **Methyldopa Standard chemical (US *PCRS*)**	**Reference**

2.2.2. Assignment to treatments

Products in the same pharmacological class were listed alphabetically. The order of treatment was then assigned using random numbers from a statistical table (Jones, 2002)

2.2.3. Weight variation

At least twenty (20) randomly selected tablets from each batch or lot were weighed on an Adventurer electronic balance (OHAUS, Pine Brook, NJ). The average weight and coefficient of variation were computed on a Microsoft Excel spread sheet.

2.2.4. Assay of content of active ingredients

The British Pharmacopoeia procedures were followed. The procedures are summarized below.

2.2.4.1 Atenolol tablets

Twenty atenolol (50 mg) tablets were weighed on Adventurer electronic balance (OHAUS, Pine Brook, NJ) and ground in a glass mortar with pestle. The powder was transferred into a 500-ml flask using 300 ml of methanol. The resulting suspension was heated to 60°, shaken for 15 minutes, cooled and diluted to 500 ml with methanol. The mixture was filtered using Whatman Millipore 0.45 μm membrane filter. Half (0.5) ml of the filtrate was diluted to 10 ml with methanol and the absorbance was measured at 275 nm on a Unicam S10 Spectrophotometer (Pye Unicam, England). The content of $C_{14}H_{22}N_2O_3$ (Atenolol) was calculated, taking 53.7 as the value of A (1%, 1 cm) at the maximum at 275 nm [14]. Results represent average of three determinations.

2.2.4.2. Furosemide Tablets

Twenty Furosemide (40 mg) tablets were weighed and powdered in a glass mortar with pestles. A quantity of the powder containing 0.2 g of Furosemide was shaken with 300 ml of 0.1M *sodium hydroxide* for 10 minutes. The mixture was made up to 500 ml 0.1M *sodium hydroxide* and filtered through Whatman 0.45 μm Millipore filter. Five (5) ml sample was diluted to 250 ml

with 0.1M *sodium hydroxide* and the absorbance was measured at 271 nm (BP 2001) [14]. The content of $C_{12}H_{11}ClN_2O_5S$ (Furosemide) was calculated taking 580 as the value of A (1%, 1 cm) at the maximum at 271 nm. The procedure was replicated twice.

2.2.4.3. Methyldopa Tablets

Twenty 500 mg tablets of methyldopa were weighed on a Adventurer electronic balance (OHAUS, Pine Brook, NJ). A quantity of the powder containing the equivalent of 0.1 g of anhydrous methyldopa was dissolved as completely as possible in sufficient 0.05M *sulphuric acid* to produce 100 ml and filtered. To 5 ml of the filtrate was added 2 ml of *iron* (II) *sulphate-citrate solution*, 8 ml of *glycine buffer solution* and sufficient *water* to produce 100 ml. The *absorbance* of the resulting solution was measured on a Unicam spectrophotometer at the maximum at 545 nm (BP 2001) [14]. The procedure was repeated using 5 ml of a 0.10% w/v solution of *methyldopa BPCRS* in place of 5 ml of the filtrate. The content of $C_{10}H_{13}NO_4$ (methyldopa) was calculated using the declared content of $C_{10}H_{13}NO_4$ in *methyldopa BPCRS*. The procedure was repeated twice.

2.2.5. Dissolution rate tests

In each dissolution test, a randomly selected tablet was weighed on Adventurer electronic balance (OHAUS, Pine Brook, NJ) and placed in 900 ml of fluid specified in the product monograph (BP/USP) i.e. phosphate buffer pH 5.8 (for Furosemide tablets) and 0.1 N HCl for Atenolol, Captopril and Methyldopa tablets, in the hemispherical vessel of the Erweka DTZ dissolution chamber. Test temperature was maintained at 37 ± 0.5 °C and the stirrer speed at 50 rpm. Ten (10)-ml samples were taken at pre-determined time intervals and replaced with 10 ml of fresh medium maintained at the same temperature on a Thermostat hot Plate. Absorbance reading of solutions were taken on a Unicam Heλ 10S spectrophotometer (Pye Unicam, England)

at the absorption maximum specified in the BP/USP) i.e. of 275nm for Atenolol, 212 nm for Captopril, 274 nm for Furosemide and at 280 nm for Methyldopa. Amount of drug in solution was determined by converting absorbance readings to mg using the conversion factor obtained from a prepared calibration curves or using the value of $A_{1cm}^{1\%}$ specified in the monograph of the respective substance. Results represent average of several determinations

RESULTS AND DISCUSSION

1. Physical Characteristics of the Tablets

The physical features of the commercial anti-hypertensive tablets are shown in table 1 below. In the atenolol group, A1 and A4 are white while A3 is off-white and A2 is dark orange in colour. Scoring, film coating and markings on the tablet all serve additional benefits of attractiveness/elegance, protection and ease of swallowing, identification and facilitate administration of fractional doses. Type and size of packaging material are all important considerations on cost: A1 comes in 100 unit packs and with an average cost per tablet of ... A2 and A4 are calendar packs of 28 in two blister packs while A3 also comes in blister packs but with only 10 tablets per pack and average cost of ... per tablet. While high organoleptic qualities of tablets are desirable, they should not be such as to add too much to the overall cost of the products. Absence of these physical effects is one of the reasons why generic products are often cheaper than the brand.

Table 1 Physical characteristics, packaging and cost of commercial antihypertensive drug products marketed in Jamaica

Chemical Name	Pharmacological Class	Brand/Generic Code	Physical Characteristics	Primary Packaging Material	# of Units/ Pack)	Average Cost/Tablet ($)
Atenolol (50 mg)	Beta Adrenoceptor Blocking Agent (B-Blocker)	A1	White, flat bevel edge, scored, with markings on both faces	Plastic Bottle; tamper evident	100	5.29
		A2	Dark Orange, biconvex, film coated, not scored	Blister pack (2)	28 (2 x 14 tablets)	4.46
		A3	Off-white, convex/concave faces, film coated, scored with marking on one face	Blister pack (1)	10	-
		A4	White, uncoated, biconvex with marking on one face, not scored	Blister pack (2)	28 (2 x 14 tablets)	7.32
Captopril (25 mg)	Angiotensine Converting Enzyme Inhibitor	C1	White, uncoated, rectangular double-scored tablets with markings on one face only	Plastic bottle, tamper evident	100	9.37
		C2	White concave/convex round tablet, double-scored on one face only	Blister pack	10	-
		C3	White, flat with bevel edge, double-scored on one face only	30 (3 x10) tablets		21.43
Furosemide	Diuretic	F1	Yellow, flat face with bevel edge, scored and markings on one face only	Plastic bottle, tamper evident sealing	500	1.58
		F2	White, flat face with bevel edge, scored and markings on one face only	Blister pack	28 (2 x14) tablets, calendar pack	6.02
		F3	White, flat face with bevel edge, markings on both faces, scored on one face only	Blister pack in cardboard box	10 x 25 blisters	13.06
Methyldopa	Central Alpha Blocker (α-Blocker)	M1	Dark yellow, biconvex, film coated tablets, marking on one face only	Blister pack (3)	30 (3 x 10 tablets)	11.30
		M2	Cream, biconvex, film coated, no markings			6.12

1. Tablet weight variation

Average weight of tablets and the standard deviations are shown in Table 2 below. In the Atenolol group, the order of increasing weight variation is A2 < A4 < A1 < A3. Thus, Atenolol group A3 has the poorest consistency in tablet weight while group A2 has the highest consistency. Tablet weight variation influences the content of active ingredient variation and as such, a limit has been set in the BP. Deviation of individual tablet weight from the average group weight is shown in Table 3 below. Values of the range are shown in Table 3. However, all group of products passed the BP limit test for weight variation. Since different manufacturers have their specific % of basic formulation which comprised of active drug, the absolute weights can not be compared. However, weight variation, which assesses the consistency of unit dosage, is a good parameter for comparative evaluation of the respective products. According to the British Pharmacopoeia (2001)[14], for uncoated and film coated tablets weighing 80 mg or less, no individual tablet weight should deviate from average weight by more than 10 %, while for tablets weighing more than 80 mg but less than 250 mg, deviation should not be more than 7.5 %. Captopril group C3 has the best consistency in tablet weight uniformity (Appendix 5) with range of ± 1.22, followed by C1 (±2.03 % deviation) and C2 with a deviation of ± 4.88 % respectively. BP requires a deviation of ≤ 10% for captopril tablet size. In the Furosemide group, rank order of weight uniformity was F2 < F3 < F1, with deviations of ± 0.72 %, ± 1.44 % and 5.05 % respectively. Methyldopa M1 was more consistent than M2 with deviations of ± 1.03 % and 1.67 % respectively. BP requires a deviation of less than 5 % for methyldopa tablets. On the basis of weight uniformity, which ascertains the ability of the tablet to retain tablet constituents from manufacturer to the patient, products within each pharmacologic class can be interchanged.

Table 2 Tablet weight variation (mg)

Brand/Generic (A,C,F & M	Atenolol (mg) ± SD	Captopril (mg) ± SD	Furosemide (mg) ± SD	Methyldopa (mg) ± SD
Group 1	120.57 ± 2.64	95.52 ± 1.04	161.56 ± 0.53	**711.09 ± 4.38**
Group 2	225.86 ± 1.33	101.97 ± 1.66	158.32 ± 4.01	714.86 ± 6.01
Group 3	214.19 ± 3.42	**140.60 ± 0.70**	**159.56 ± 1.27**	-
Group 4	**212.69 ± 2.51**	-	-	-

*Brand product is highlighted in bold.

Table 3 Percent Deviations in tablets weights of commercial antihypertensive drug products

Brand/Generic (A,C,F & M)	Range of weight deviations			
	Atenolol (mg %) Official limit: ≤ 10 %	Captopril (mg %) Official limit: ≤ 10 %	Furosemide (mg %) Official limit: ≤ 10 %	Methyldopa (mg %) Official limit: ≤ 5 %
Group 1	-7.65 - +3.85	-1.94 - +2.04	-0.72 - +0.46	**-1.88 - +1.59**
Group 2	-1.46 - +1.16	-1.66 - +4.88	-5.05 - + 4.69	-1.67 - + 1.98
Group 3	-3.57 - + 3.35	**-1.22 - +0.78**	**-1.05 - + 1.45**	
Group 4	**-3.30 - + 2.21**	-	-	

*Brand product is highlighted in bold.

3. Assay of drug content

The per cent content of active ingredients among the four different group of antihypertensive drug products are shown in Table 4. The rank ordering of the content of active ingredients are atenolol group A3 > A4 > A2 > A1 ($p > 0.05$); Furosemide group F3 > F 1 ($p > 0.05$), F2 > F3 ($p > 0.05$), F2 > F3 ($p < 0.05$). Thus, the difference in drug content of F2 and F3 is significant and they may not be substituted one for the other. Drug content of methyldopa tablets are not significantly different and they may be interchanged one with the other on the assurance of equivalent amount of drug content.

Table 4 Assay of Drug Content

Brand/Generic	**Atenolol** % LC (BP Limit: 92.5 – 107.5 %)**	**Captopril** % LC (BP Limit: 95 – 105 %)**	**Furosemide** % LC (BP Limit: 95 – 105 %)**	**Methyldopa** % LC (BP Limit: 95 – 105 %)**
Group 1	96.03 ± 0.47	-	97.56 ± 0.50	115.17 ± 2.03†
Group 2	96.40 ± 1.68	-	95.11 ± 1.53	113.73 ± 1.18†
Group 3	99.32 ± 1.13	-	95.76 ± 2.16	-
Group 4	98.08 ± 0.89	-	-	-

% LC is the percent of label content **British Pharmacopoeia (2001). †The two methyldopa products were outside the upper limit

Table 5 Pair wise comparison of % of label content of different atenolol tablet products marketed in Jamaica

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Atenolol A1 (% label content) - Atenolol A4 (% label content)	-1.67598	3.73834	2.15833	-10.96252	7.61056	-.777	2	.519
Pair 2	Atenolol A2 (% label content) - Atenolol A4 (% label content)	-2.04842	2.37750	1.37265	-7.95444	3.85761	-1.492	2	.274
Pair 3	Atenolol A3 (% label content) - Atenolol A4 (% label content)	1.24147	2.79537	1.61390	-5.70261	8.18554	.769	2	.522
Pair 4	Atenolol A1 (% label content) - Atenolol A3 (% label content)	-2.91744	5.60003	3.23318	-16.82868	10.99379	-.902	2	.462
Pair 5	Atenolol A2 (% label content) - Atenolol A3 (% label content)	-3.28988	3.12901	1.80653	-11.06277	4.48301	-1.821	2	.210
Pair 6	Atenolol A1 (% label content) - Atenolol A2 (% label content)	.37244	2.58705	1.49363	-6.05414	6.79902	.249	2	.826

Table 6 Pair wise comparison of % of label content of different Furosemide tablet products marketed in Jamaica

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Furosemide F1 % label content - Furosemide F3 % label content	-.64655	3.67641	2.12258	-9.779	8.48616	-.305	2	.789
Pair 2	Furosemide F2 % label content - Furosemide F3 % label content	1.79596	2.51639	1.45284	-4.455	8.04703	1.236	2	.342
Pair 3	Furosemide F1 % label content - Furosemide F2 % label content	-2.44250	1.18696	.68529	-5.391	.50608	-3.564	2	.070**

****Statistically significant difference**

Table 7 Pair wise comparison of % of label content of different Methyldopa tablet products marketed in Jamaica

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Methyldopa M1 % label content - Methyldopa M2 % label content	1.44256	2.77371	.98065	-.87632	3.76144	1.471	7	.185

4. Rate of Drug Dissolution from Tablets

Results of Beer-Lambert (calibration) curves for standard atenolol, captopril, furosemide and methyldopa US Chemical Reference Substances (US CRS) are shown in Figs. 1, 3, 5 and 7 respectively. An almost perfect linearity was obtained in the regression of absorbance values on concentrations of drugs in solution. This high degree of linearity is confirmed by the variance of the equations. The variances (R^2) for atenolol, captopril, furosemide and methyldopa were 0.9963, 0.9854, 0.9950 and 0.9999 respectively. This indicates that the equations of the respective line can be used to convert absorbance values to concentrations in the relevant range.

The dissolution profiles of atenolol tablets are shown in Fig. 2. Atenolol A1 and A3 started dissolving earlier (at 5 min.) than the brand (A4)($p = 0.000$) while A2 was slower dissolving (Table 9). By 10 minutes, the brand was significantly higher in amount dissolved relative to the generic A2 ($p = 0.003$). The maximum amount of drug released (Qpeak) was significantly higher with brand (A4) than with the generic A2 ($p = 0.005$) while values were comparable among other generics and the brand ($p > 0.05$). In addition, time for maximum drug release (Tpeak) was significantly longer with generic A2 than with brand ($p = 0.006$) whereas it was significantly shorter with generic A1. The results suggest that generic A2 requires caution in its substitution for the brand (A4). A1 and A3 can be interchanged and or substituted for the brand without fear of delay in patient time to benefit from the drug action.

Among the captopril group, dissolution profiles were generally comparable. However, drug dissolution started earlier with the brand (A3) than the two generics and the difference was statistically significant for generic C2 ($p = 0.000$). By the 10 and 15 minute sample points, the dissolution rates were comparable ($p > 0.05$) (Tables 14 & 15). Although Qpeak appeared to be significantly higher from C2, Tpeak was also significantly longer than with the brand (C3). Generally, it appears that the generic captopril can be substituted for the brand without any delay in patient therapeutic experience.

The generic Furosemide F1 and F2 showed higher dissolution at 5 and 10 minutes sample points than the brand and the difference between F2 and F3 was significant at 10 min ($P= 0.057$ and 0.002 respectively at 5 and 10 minutes). By 30 minutes, however, dissolution rates were comparable ($p >0.05$). The peak amounts and the time to peak were comparable ($p > 0.05$).

With the methyldopa products, the brand started dissolving earlier ($p = 0.000$, at 5 min.)(Table 24), but the eventual dissolution profiles were comparable ($p > 0.05$ at 10 min.) (Table 25). Although the maximum amounts of drug released were comparable, the time for peak release was significantly shorter for brand than for generic. Thus, patient may experience faster response to brand than to generic methyldopa.

Fig. 1. Absorbance-concentration curve for Atenolol USP CRS

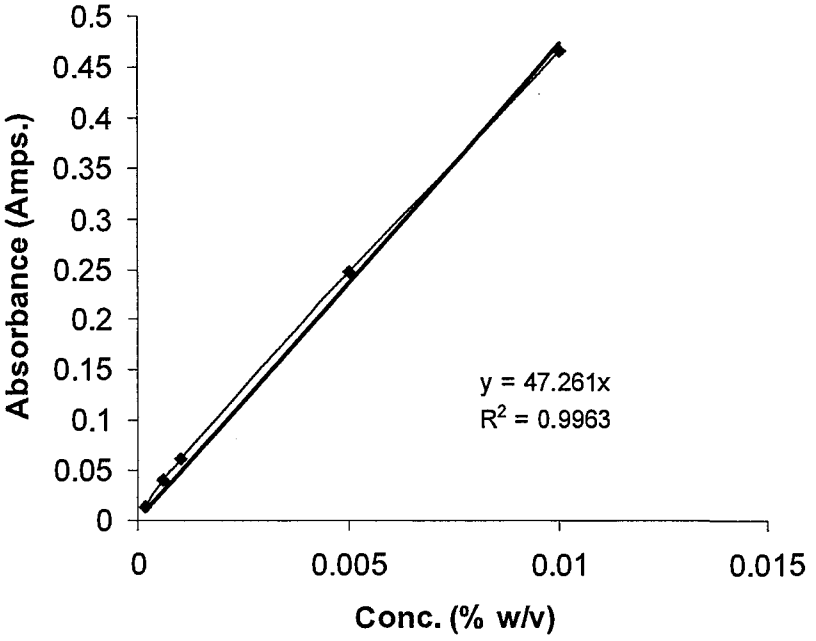

Fig. 2. Dissolution profiles of commercial Atenolol tablets marketted in Jamaica

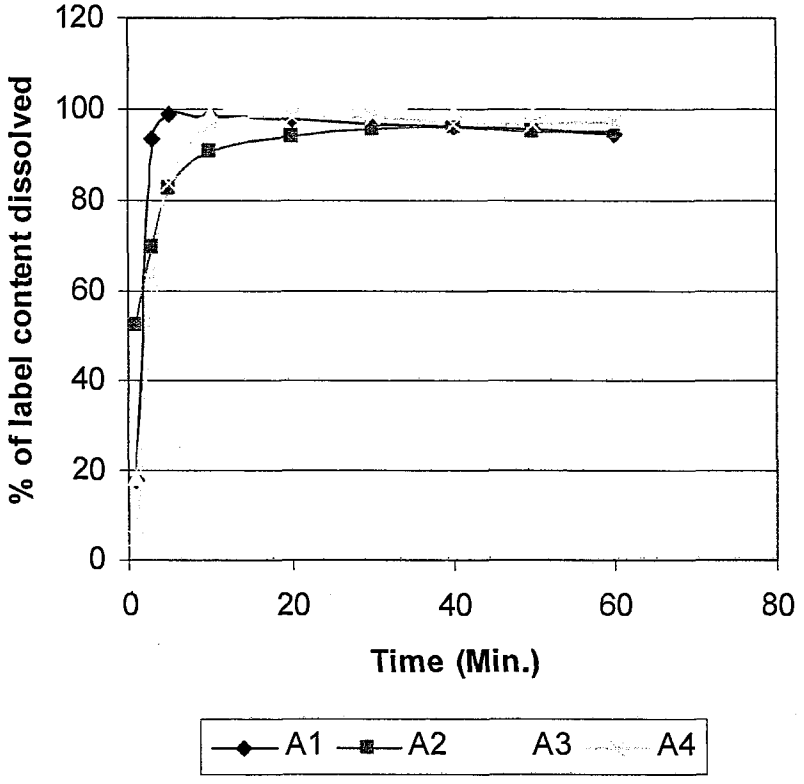

Table 9 Atenolol generic versus brand comparisons of amount dissolved in 5 minutes

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ATENOLOL A1 (5 MIN) - ATENOLOL A4 (5 MIN)	15.0667	8.46864	2.44468	9.686	20.4474	6.163	11	.000**
Pair 2	ATENOLOL A2 (5 MIN) - ATENOLOL A4 (5 MIN)	-1.1600	10.82501	3.12491	-8.037	5.7179	-.371	11	.718
Pair 3	ATENOLOL A3 (5 MIN) - ATENOLOL A4 (5 MIN)	5.7542	12.20553	3.52343	-2.001	13.5092	1.633	11	.131

Table 10 Atenolol generic versus brand comparisons of amount dissolved in 5 minutes

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ATENOLOL A1 (5 MIN) - ATENOLOL A4 (5 MIN)	15.0667	8.46864	2.44468	9.686	20.4474	6.163	11	.000**
Pair 2	ATENOLOL A2 (5 MIN) - ATENOLOL A4 (5 MIN)	-1.1600	10.82501	3.12491	-8.038	5.7179	-.371	11	.718
Pair 3	ATENOLOL A3 (5 MIN) - ATENOLOL A4 (5 MIN)	5.7542	12.20553	3.52343	-2.001	13.5092	1.633	11	.131

Table 11 Atenolol generic versus brand comparisons of amount dissolved in 10 minutes

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ATENOLOL A1 (10 MIN) - ATENOLOL A4 (10 MIN)	1.4583	3.14376	.90752	-.5391	3.4558	1.607	11	.136
Pair 2	ATENOLOL A2 (10 MIN) - ATENOLOL A4 (10 MIN)	-6.1492	5.71372	1.64941	-9.780	-2.519	-3.728	11	.003**
Pair 3	ATENOLOL A3 (10 MIN) - ATENOLOL A4 (10 MIN)	2.3317	5.97943	1.72611	-1.468	6.1308	1.351	11	.204

Table 12 Atenolol generic versus brand comparisons of maximum amount of drug released (Qpeak)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ATENOLOL A1 Qpeak - ATENOLOL A4 Qpeak	-.7275	3.63185	1.04843	-3.035	1.5801	-.694	11	.502
Pair 2	ATENOLOL A2 Qpeak - ATENOLOL A4 Qpeak	-3.209	3.20109	.92407	-5.243	-1.175	-3.473	11	.005**
Pair 3	ATENOLOL A3 Qpeak - ATENOLOL A4 Qpeak	.6708	3.76357	1.08645	-1.720	3.0621	.617	11	.550

****Statistically significant**

Table 13 Atenolol generic versus brand comparisons of time required for release of maximum amount of drug (Tpeak)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ATENOLOL A1 Tpeak - ATENOLOL A4 Tpeak	-14.3333	9.57585	2.76431	-20.4175	-8.2491	-5.185	11	.000**
Pair 2	ATENOLOL A2 Tpeak - ATENOLOL A4 Tpeak	13.3333	13.70689	3.95684	4.6244	22.0423	3.370	11	.006**
Pair 3	ATENOLOL A3 Tpeak - ATENOLOL A4 Tpeak	7.5000	19.59824	5.65752	-4.9521	19.9521	1.326	11	.212

****Statistically significant**

Fig. 3 Calibration curve for Captopril US CRS

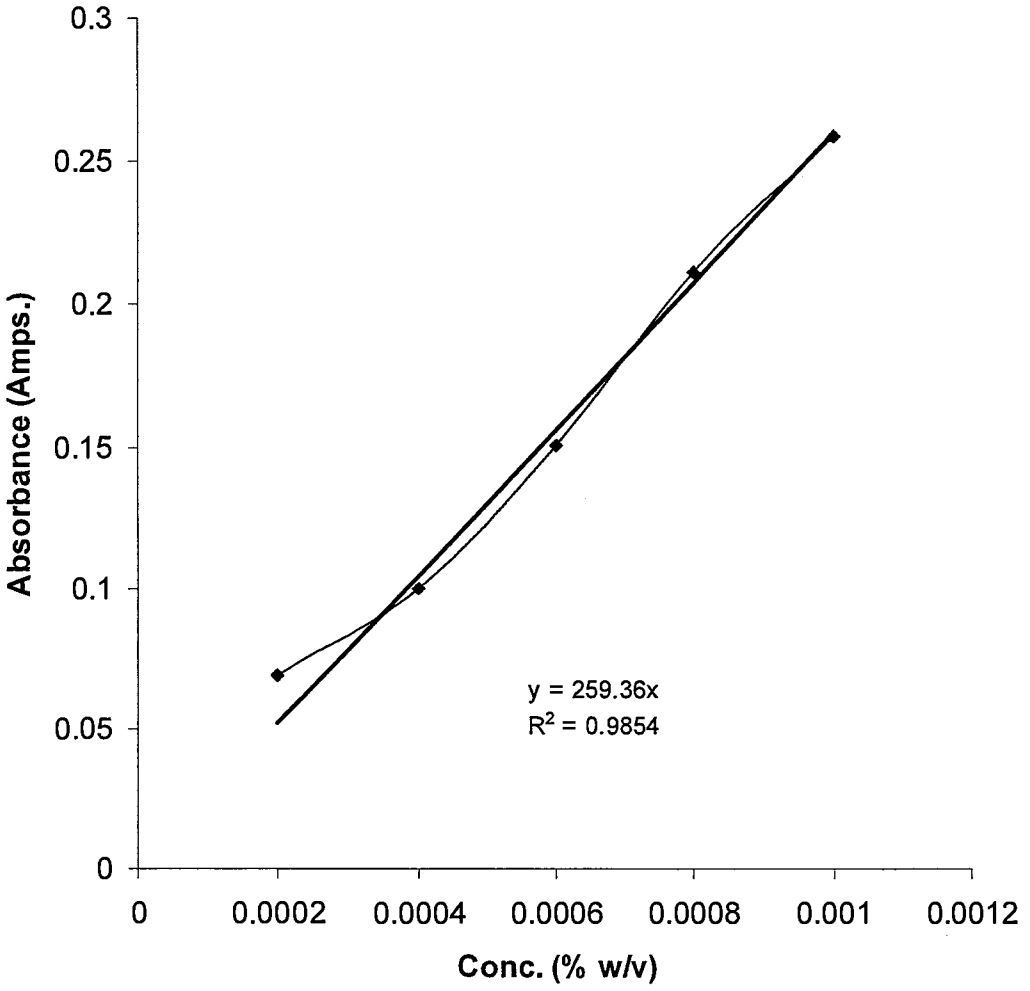

Fig. 4. Dissolution Profiles of some Commercial Captopril Tablets Marketed in Jamaica

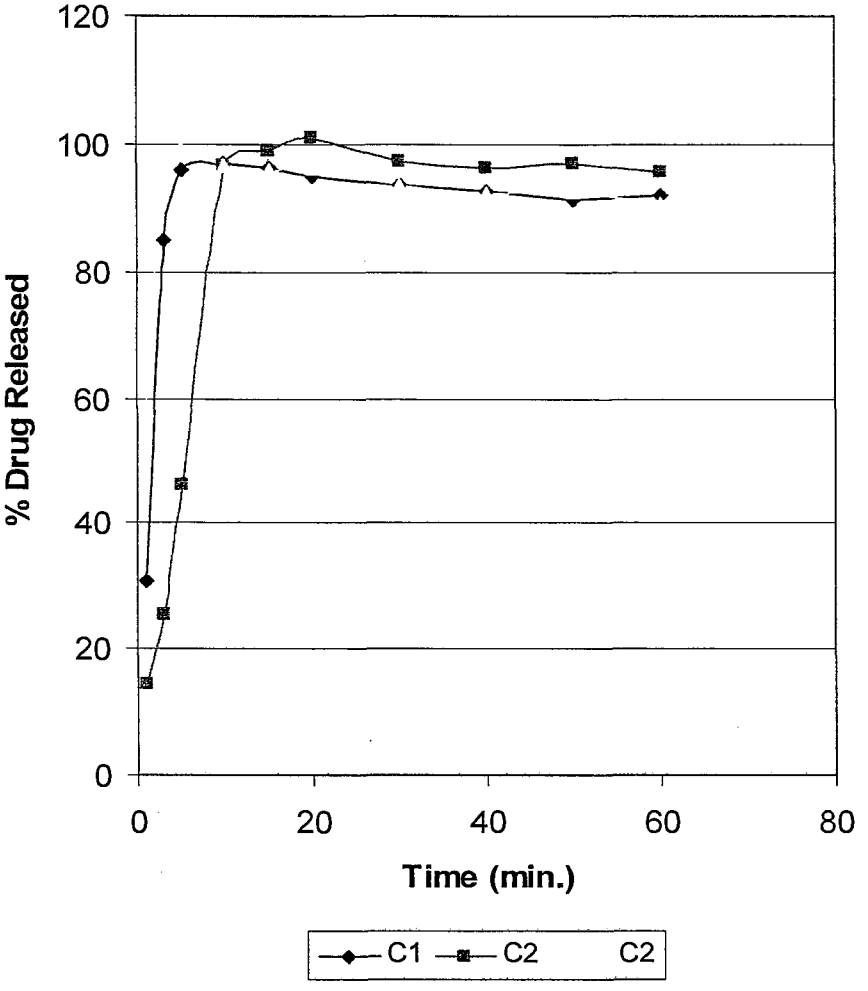

Table 14 Comparisons of amount of captopril dissolved in 5 minutes from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	CAPTOPRIL C1 5 MIN DISSOL - CAPTOPRIL C3 5 MIN DISSOL	-1.0750	9.37295	4.68647	-15.99	13.8395	-.229	3	.833
Pair 2	CAPTOPRIL C2 5 MIN DISSOL - CAPTOPRIL C3 5 MIN DISSOL	-50.8700	5.82658	2.91329	-60.14	-41.599	-17.46	3	.000**

Table 15 Comparisons of amount of captopril dissolved in 10 minutes from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	CAPTOPRIL C1 10 MIN DISSOL - CAPTOPRIL C3 10 MIN	1.1200	5.64715	2.82358	-7.866	10.1059	.397	3	.718
Pair 2	CAPTOPRIL C2 10 MIN - CAPTOPRIL C3 10 MIN	.4950	5.78523	2.89261	-8.711	9.7006	.171	3	.875

Table 16 Comparisons of amount of Captopril dissolved in 15 minutes from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	CAPTOPRIL C1 15 MIN DISSOL - CAPTOPRIL C3 15 MIN DISSOL	.6600	5.03469	2.51734	-7.351	8.6713	.262	3	.810
Pair 2	CAPTOPRIL C2 15 MIN DISSOL - CAPTOPRIL C3 15 MIN DISSOL	3.3675	3.83299	1.91650	-2.732	9.4666	1.757	3	.177

Table 17 Comparison of maximum amount of captopril dissolved (Qpeak) from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	CAPTOPRIL C1 Qpeak - CAPTOPRIL C3 Qpeak	-.1025	5.24315	2.62158	-8.446	8.2405	-.039	3	.971
Pair 2	CAPTOPRIL C2 Qpeak - CAPTOPRIL C3 Qpeak	3.1900	1.32471	.66236	1.0821	5.2979	4.816	3	.017**

Table 18 Comparison of time for maximum amount of captopril dissolved (Tpeak) from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	CAPTOPRIL C1 Tpeak - CAPTOPRIL C3 Tpeak	3.0000	4.76095	2.38048	-4.576	10.5757	1.260	3	.297
Pair 2	CAPTOPRIL C2 Tpeak - CAPTOPRIL C3 Tpeak	13.0000	2.44949	1.22474	9.1023	16.8977	10.614	3	.002**

**Highly statistically significant

Fig.5. Calibration curve for Furosemide US CRS

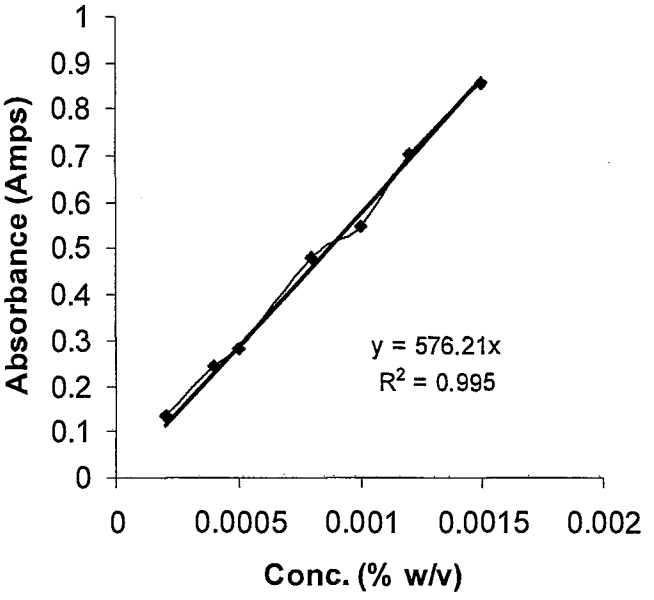

Fig. 6 Dissolution Profiles of Commercial Furosemide Tablets Marketted in Jamaica

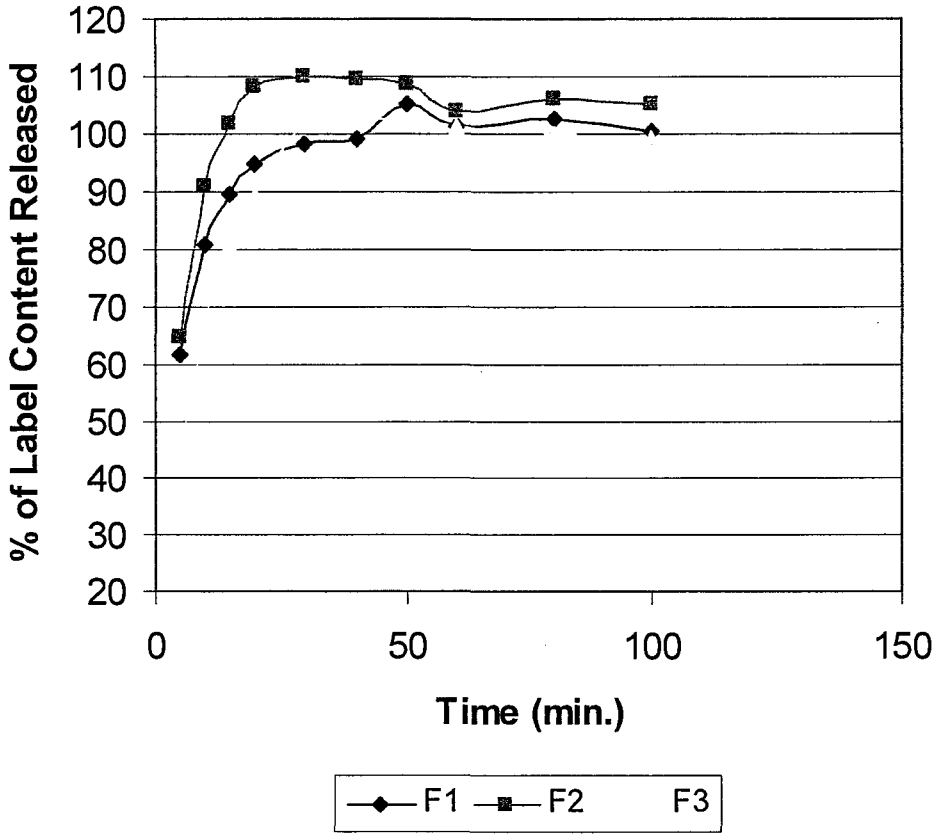

Table 19 Comparisons of amount of Furosemide dissolved in 5 minutes from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	FUROSEMIDE F1 5 MIN DISSOL - FUROSEMIDE F3 5 MIN DISSOL	18.4675	27.57435	13.78718	-25.409	62.344	1.339	3	.273
Pair 2	FUROSEMIDE F2 5 MIN DISSOL - FUROSEMIDE F3 5 MIN DISSOL	21.8150	14.50515	7.25258	-1.2659	44.896	3.008	3	.057*
Pair 3	FUROSEMIDE F1 5 MIN DISSOL - FUROSEMIDE F2 5 MIN DISSOL	-3.3475	29.11717	14.55858	-49.679	42.984	-.230	3	.833

*Statistically significant difference

Table 20 Comparisons of amount of Furosemide dissolved in 15 minutes from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	FUROSEMIDE F1 15 MIN DISSOL - FUROSEMIDE F3 15 MIN DISSOL	8.9700	25.66992	12.83496	-31.876	49.8166	.699	3	.535
Pair 2	FUROSEMIDE F2 15 MIN DISSOL - FUROSEMIDE F3 15 MIN DISSOL	21.0850	4.24883	2.12442	14.3242	27.8458	9.925	3	.002**
Pair 3	FUROSEMIDE F1 15 MIN DISSOL - FUROSEMIDE F2 15 MIN DISSOL	-12.1150	25.52321	12.76160	-52.728	28.4981	-.949	3	.412

****Highly statistically significant difference**

Table 21 Comparisons of amount of Furosemide dissolved in 30 minutes from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	FUROSEMIDE F1 30 MIN DISSOL - FUROSEMIDE F3 30 MIN DISSOL	-3.7350	8.44120	4.2206	-17.167	9.6968	-.885	3	.441
Pair 2	FUROSEMIDE F2 30 MIN DISSOL - FUROSEMIDE F3 30 MIN DISSOL	7.9700	7.70539	3.8527	-4.2910	20.231	2.069	3	.130
Pair 3	FUROSEMIDE F1 30 MIN DISSOL - FUROSEMIDE F2 30 MIN DISSOL	-11.705	13.75717	6.8786	-33.596	10.186	-1.702	3	.187

Table 22 Comparison of maximum amount of Furosemide dissolved (Qpeak) from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	FUROSEMIDE F1 Qpeak - FUROSEMIDE F3 Qpeak	3.0525	7.07821	3.53910	-8.211	14.3155	.863	3	.452
Pair 2	FUROSEMIDE F2 Qpeak - FUROSEMIDE F3 Qpeak	7.6975	7.34981	3.67490	-3.998	19.3927	2.095	3	.127
Pair 3	FUROSEMIDE F1 Qpeak - FUROSEMIDE F2 Qpeak	-4.645	13.65335	6.82667	-26.37	17.0805	-.680	3	.545

Table 23 Comparison of time for maximum amount of Furosemide dissolution (Tpeak) from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	FUROSEMIDE F1 Tpeak - FUROSEMIDE F3 Tpeak	12.500	28.72281	14.36141	-33.204	58.2044	.870	3	.448
Pair 2	FUROSEMIDE F2 Tpeak - FUROSEMIDE F3 Tpeak	-7.5000	9.57427	4.78714	-22.735	7.7348	-1.57	3	.215
Pair 3	FUROSEMIDE F1 Tpeak - FUROSEMIDE F2 Tpeak	20.000	25.81989	12.90994	-21.085	61.0852	1.549	3	.219

Fig. 7 Calibration curve for methyldopa USP CRS

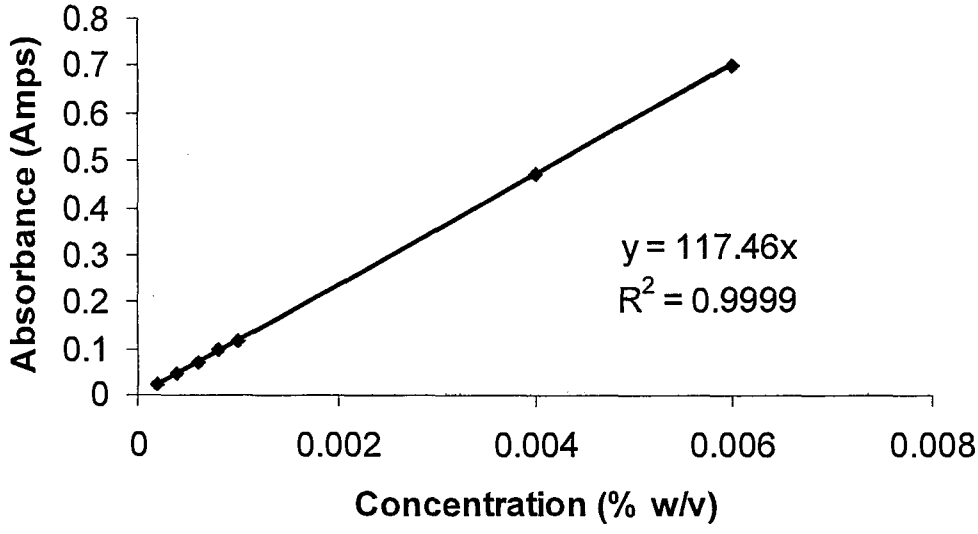

Fig. 8. Dissolution profiles of Methyldopa tablets

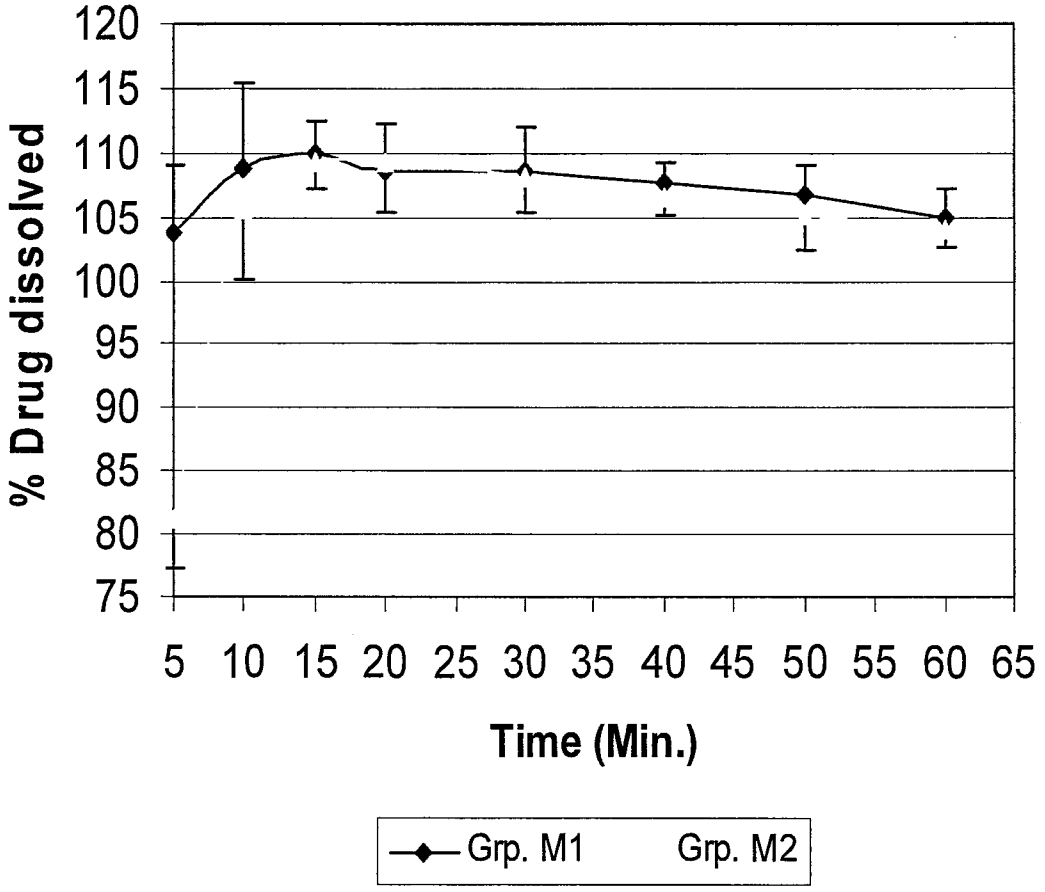

Table 24 Comparison of amount of Methyldopa dissolved in 5 minutes from brand and generic tablets

		Paired Differences					T	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	METHYLDOPA M1 (5 min.) - METHYLDOPA M2 (5min)	22.5175	5.19444	1.49951	19.2171	25.8179	15.017	11	.000**

Table 25 Comparison of amount of Methyldopa dissolved in 10 minutes from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	METHYLDOPA M1 (10 min.) - METHYLDOPA M2 (10 min.)	3.0042	10.72788	3.09687	-3.8120	9.8203	.970	11	.353

Table 26 Comparison of maximum amount of Methyldopa dissolved (Qpeak) from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	METHYLDOPA M1 Qpeak - METHYLDOPA M2 Qpeak	.8442	4.20636	1.21427	-1.828	3.5168	.695	11	.501

Table 27 Comparison of time for maximum amount of Methyldopa dissolution (Tpeak) from brand and generic tablets

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	METHYLDOPA M1 Tpeak DISSOL - METHYLDOPA M2 Tpeak DISSOL	-3.75	4.82654	1.39330	-6.816	-.6834	-2.691	11	.021*

5. Conclusions

Drug products containing nominally equal amount of active drug substances and present in the same type of dosage form should make the substance available for absorption as soon as possible after administration. Results of this study have shown that antihypertensive drug products in four different pharmacologic classes contain very similar levels of the active drug substances. They generally contain prescribed levels as specified in the British Pharmacopoeia (BP) 2001. An important exception is the methyldopa group which contain slightly higher levels of drug than is recommended in the BP. However, the two products marketed in Jamaica showed comparable levels of active ingredient. Hence, the tested generics can be fairly substituted for the brand and selected with other considerations of cost, availability and accessibility, elegance and patient personal preferences with the assurance of equivalent amount of drug substance in each brand/generic.

Using the dissolution profiles, however, some differences were noticed on the rate and extent at which some generic/brand make the drug available for absorption. Atenolol brand (A4) showed faster rate and higher peak amount than one of the generics (A2). While A1 and A3 can be substituted for A4 with assurance of similar patient experience, this may be difficult to guarantee with the generic A2.

Captopril and furosemide product categories are generally comparable and can be interchanged without any hindrance to drug absorption. However, with the methyldopa group, the shorter time for maximum drug release may make patients show response to therapy faster than with the generic.

Results have shown that, generally, more than cost consideration and company reputation is required for day-to-day rational decision making in drug products sourcing.

6. Recommendations

Routine analysis of drug products that are being distributed in the market would provide additional guidance on drug product selection decision making by health care professionals, care providers and sponsors. Sole reliance on company reputation would leave the distribution channel vulnerable to possible assault from substandard, fake, counterfeit and adulterated products. Although this assault does not seem to happen frequently, if and when it eventually happens, the effect is usually "one too many". In order to proactively forestall any possibility of "worm" in the distribution channel, routine analysis of drug content and *in vitro* dissolution testing should be instituted. Just as it assures the manufacturers of the quality of their product within the factory, it can also assure the public of the quality of what they are taking from the market.

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APPENDICES

Appendix 3 SAMPLE RANDOMIZATION SCHEME FOR ASSIGNMENT OF PRODUCT/SAMPLE TO TREATMENTS

SORTED RANDOM NUMBERS	CODE
10	A1
30	A2
36	A3
61	A4
77	A5
86	A6
111	A7
124	A8
134	A9
158	A10
169	A11
180	A12
214	A13
257	A14
300	A15
341	A16
382	A17
422	A18
461	A19
500	A20
537	A21

574	A22
610	A23
645	A24
679	A25
713	A26
725	A27
745	A28
778	A29
809	A30
831	A31
840	A32
870	A33
882	A34
899	A35
918	A36
921	A37
924	A38
926	A39
928	A40
929	A41
931	A42
932	A43
934	A44
936	A45
956	A46
982	A47
983	A48

APPENDIX 4 UNIFROMITY OF WEIGHT OF ATENOLOL TABLETS

A1		A2		A3		A4	
Weight (g)	%DEV	Weight (g)	% DEV	Weight (g)	%DEV	Weight (g)	% DEV
0.1208	0.192881	0.2258	-0.02657	0.2095	-2.23723	0.2117	-0.46859
0.12	-0.4725	0.2227	-1.41895	0.2162	0.931082	0.2129	0.097698
0.1186	-1.65852	0.226	0.061947	0.2196	2.464936	0.2131	0.191459
0.1224	1.497549	0.2273	0.633524	0.2169	1.250807	0.2134	0.331771
0.1237	2.532741	0.2274	0.677221	0.2193	2.331509	0.2175	2.210575
0.119	-1.31681	0.2261	0.106148	0.2101	-1.94526	0.2147	0.935259
0.1126	-7.07549	0.224	-0.83036	0.21	-1.99381	0.2114	-0.61116
0.1198	-0.64023	0.2254	-0.20408	0.2144	0.099347	0.2111	-0.75414
0.1197	-0.72431	0.2282	1.025416	0.2139	-0.13417	0.2131	0.191459
0.1191	-1.23174	0.2247	-0.51624	0.2181	1.794131	0.2067	-2.89889
0.1177	-2.43585	0.2251	-0.33763	0.2086	-2.67833	0.2138	0.518241
0.1189	-1.40202	0.2267	0.370534	0.2148	0.285382	0.2153	1.211333
0.1216	0.849507	0.2257	-0.07089	0.213	-0.55728	0.2108	-0.89753

0.1153	-4.56808	0.2253	-0.24856	0.2102	-1.89676	0.2102	-1.18554
0.1218	1.012315	0.2241	-0.78536	0.2147	0.238938	0.2104	-1.08935
0.1206	0.027363	0.2242	-0.74041	0.2146	0.192451	0.2099	-1.33016
0.1174	-2.69761	0.2248	-0.47153	0.2206	2.907072	0.2133	0.285045
0.1208	0.192881	0.226	0.061947	0.2171	1.341778	0.2079	-2.30495
0.1206	0.027363	0.2251	-0.33763	0.2164	1.022643	0.213	0.144601
0.1227	1.738386	0.2231	-1.23711	0.2086	-2.67833	0.2151	1.119479
0.1185	-1.7443	0.226	0.061947	0.2125	-0.79388	0.2111	-0.75414
0.112	-7.64911	0.2254	-0.20408	0.2104	-1.7999	0.2156	1.348794
0.1213	0.604287	0.2255	-0.15965	0.2096	-2.18845	0.2117	-0.46859
0.1254	3.854067	0.2255	-0.15965	0.2068	-3.57205	0.212	-0.32642
0.1205	-0.0556	0.2249	-0.42686	0.2173	1.432582	0.2133	0.285045
0.1213	0.604287	0.2257	-0.07089	0.2105	-1.75154	0.2147	0.935259
0.1184	-1.83024	0.2259	0.017707	0.2142	0.006069	0.2127	0.003761
0.119	-1.31681	0.2275	0.720879	0.2207	2.951065	0.2123	-0.18464
0.118	-2.17542	0.2266	0.326567	0.2128	-0.65179	0.2119	-0.37376
0.1206	0.027363	0.2271	0.546015	0.2147	0.238938	0.2136	0.425094
0.1236	2.453883	0.226	0.061947	0.211	-1.51043	0.2149	1.027455
0.12	-0.4725	0.2238	-0.92046	0.2089	-2.53088	0.2122	-0.23186
0.1213	0.604287	0.2255	-0.15965	0.2132	-0.46295	0.2143	0.75035
0.1218	1.012315	0.227	0.502203	0.2102	-1.89676	0.2083	-2.1085
0.1202	-0.30532	0.2257	-0.07089	0.2139	-0.13417	0.216	1.531481
0.1235	2.374899	0.2269	0.458352	0.2148	0.285382	0.2059	-3.29869
0.1195	-0.89289	0.2282	1.025416	0.2188	2.108318	0.2133	0.285045
0.1239	2.690073	0.2226	-1.46451	0.2132	-0.46295	0.217	1.985253
0.1223	1.417007	0.226	0.061947	0.2132	-0.46295	0.2163	1.668054
0.1193	-1.06203	0.2263	0.194432	0.2137	-0.22789	0.2079	-2.30495
0.122	1.17459	0.2282	1.025416	0.2119	-1.07928	0.2107	-0.94542
0.1191	-1.23174	0.2246	-0.561	0.2201	2.686506	0.2124	-0.13748
0.1202	-0.30532	0.2259	0.017707	0.2123	-0.88884	0.2118	-0.42115
0.1214	0.686161	0.2259	0.017707	0.2163	0.976884	0.2149	1.027455
0.1234	2.295786	0.226	0.061947	0.213	-0.55728	0.2087	-1.91279
0.12	-0.4725	0.225	-0.38222	0.2122	-0.93638	0.2107	-0.94542
0.1236	2.453883	0.2267	0.370534	0.2216	3.345217	0.2104	-1.08935
0.1191	-1.23174	0.2242	-0.74041	0.2173	1.432582	0.2133	0.285045
0.1211	0.440132	0.2276	0.764499	0.2126	-0.74647	0.2132	0.238274
0.1188	-1.48737	0.2264	0.238516	0.2151	0.424454	0.2174	2.165593
0.1251	3.623501	0.225	-0.38222	0.2125	-0.79388	0.2145	0.84289
0.124	2.768548	0.2273	0.633524	0.2176	1.568474	0.2107	-0.94542
0.1193	-1.06203	0.2278	0.851624	0.2131	-0.51009	0.2132	0.238274
0.1252	3.700479	0.2274	0.677221	0.2139	-0.13417	0.2139	0.56475
0.1238	2.61147	0.226	0.061947	0.2195	2.420501	0.2154	1.257196
0.1206	0.027363	0.2257	-0.07089	0.2147	0.238938	0.2136	0.425094
0.1172	-2.87287	0.2266	0.326567	0.2133	-0.41585	0.2138	0.518241
0.1213	0.604287	0.2247	-0.51624	0.2149	0.331782	0.2129	0.097698

0.1226	1.658238	0.2285	1.155361	0.2151	0.424454	0.2142	0.704015
0.1227	1.738386	0.2263	0.194432	0.2172	1.387201	0.2155	1.303016
0.120567		0.22586		0.214187		0.212692	
0.002637		0.001326		0.00342		0.002514	

APPENDIX 5WEIGHT UNIFORMITY OF WEIGHT OF CAPTOPRIL ABLETS

	C1	% DEV	C2	%DEV	C3	% DEV
1	0.0975	2.035897	0.1046	2.51912	0.1409	0.216466
2	0.0951	-0.43638	0.1005	-1.45771	0.1402	-0.28174
3	0.0947	-0.86061	0.1011	-0.85559	0.1407	0.074627
4	0.0959	0.40146	0.101	-0.95545	0.1413	0.498938
5	0.0949	-0.64805	0.1029	0.908649	0.1399	-0.49678
6	0.0962	0.712058	0.1016	-0.35925	0.1389	-1.2203
7	0.0967	1.22544	0.1005	-1.45771	0.1416	0.709746
8	0.0945	-1.07407	0.1018	-0.16208	0.1403	-0.21026
9	0.0948	-0.75422	0.1011	-0.85559	0.14	-0.425
10	0.0952	-0.33088	0.1014	-0.5572	0.1399	-0.49678
11	0.0949	-0.64805	0.1003	-1.66002	0.1409	0.216466
12	0.097	1.530928	0.1018	-0.16208	0.1409	0.216466
13	0.0968	1.327479	0.101	-0.95545	0.1409	0.216466
14	0.0958	0.297495	0.1008	-1.15575	0.1399	-0.49678
15	0.0946	-0.96723	0.1035	1.483092	0.1417	0.779817
16	0.097	1.530928	0.1072	4.883396	0.1401	-0.35332
17	0.0937	-1.93703	0.1021	0.132223	0.1414	0.569307
18	0.0952	-0.33088	0.1022	0.229941	0.1412	0.42847
19	0.0948	-0.75422	0.1009	-1.0555	0.1406	0.003556
20	0.095	-0.54211	0.103	1.004854	0.1406	0.003556
SUM	1.9103		2.0393		2.8119	
AVE	0.095515		0.101965		0.140595	
STDEV	0.001035		0.001657		0.000699	

APPENDIX 6 WEIGHT UNIFORMITY OF FUROSEMIDE TABLETS

	F3			F1			F2	
	Weight (g)	%dev		Weight (g)	% dev		Weight (g)	% dev
	0.16	0.275		0.1567	-1.03063		0.1614	-0.09603
	0.1579	-1.0513		0.1624	2.515394		0.1619	0.213095
	0.158	-0.98734		0.1535	-3.13681		0.1619	0.213095
	0.16	0.275		0.1587	0.242596		0.1618	0.151422
	0.1582	-0.85967		0.1576	-0.45368		0.161	-0.34472
	0.1619	1.445337		0.1611	1.72874		0.1612	-0.22022
	0.1611	0.955928		0.1583	-0.00948		0.1611	-0.28243
	0.1592	-0.22613		0.157	-0.83758		0.1616	0.027847
	0.1587	-0.5419		0.16	1.053125		0.1617	0.089672
	0.158	-0.98734		0.1584	0.053662		0.1617	0.089672
	0.1599	0.212633		0.1645	3.759878		0.1616	0.027847
	0.158	-0.98734		0.1609	1.606588		0.162	0.274691
	0.1599	0.212633		0.1578	-0.32636		0.1604	-0.72007
	0.1598	0.150188		0.1566	-1.09515		0.162	0.274691
	0.161	0.89441		0.1541	-2.73524		0.1623	0.459026
	0.1597	0.087664		0.1507	-5.05309		0.1621	0.336212
	0.1606	0.647572		0.1635	3.171254		0.1613	-0.15809
	0.1618	1.384425		0.1557	-1.67951		0.1606	-0.59465
	0.1589	-0.41536		0.1527	-3.67714		0.1612	-0.22022
SUM	0.1586	-0.6053		0.1661	4.686936		0.1623	0.459026
AVE	0.15956	1.445337		0.158315	4.686936		0.161555	0.459026
STDEV	0.001274197	-1.0513		0.004008	-5.05309		0.000526	-0.72007

APPENDIX 7 WEIGHT UNIFORMITY OF WEIGHT OF CAPTOPRIL ABLETS

	M1			M2	
S/N		% dev			% dev
1	0.7074	-0.52205259		0.7163	0.201312299
2	0.7105	-0.08346235		0.7186	0.520734762
3	0.7097	-0.19628012		0.7162	0.187377827
4	0.705	-0.86425532		0.7132	-0.23247336
5	0.7136	0.35131726		0.7114	-0.486083778
6	0.7099	-0.16805184		0.7217	0.948039352
7	0.7049	-0.87856434		0.7253	1.439680132
8	0.7112	0.01504499		0.7147	-0.022107178
9	0.7116	0.07124789		0.7179	0.423735896
10	0.7104	-0.09755068		0.7124	-0.345030882
11	0.7107	-0.05529759		0.7238	1.23542415
12	0.7094	-0.23865238		0.7069	-1.125760362
13	0.7153	0.58814483		0.7074	-1.054283291
14	0.7094	-0.23865238		0.7152	0.047818792
15	0.7161	0.69920402		0.7156	0.103689212
16	0.7084	-0.38015246		0.7098	-0.712595097
17	0.7105	-0.08346235		0.7156	0.103689212
18	0.7116	0.07124789		0.7177	0.395987181
19	0.705	-0.86425532		0.7211	0.865621966
20	0.7057	-0.76420575		0.7157	0.117647059
21	0.7154	0.60204082		0.7093	-0.783589454
22	0.7133	0.30940698		0.716	0.159497207
23	0.7118	0.09932565		0.7221	1.002908184
24	0.7103	-0.11164297		0.7031	-1.672308349

25	0.7144	0.46290594		0.7136	-0.176289238
26	0.7114	0.04315434		0.7194	0.631359466
27	0.7099	-0.16805184		0.7246	1.344465912
28	0.7039	-1.02187811		0.7154	0.075761812
29	0.708	-0.43686441		0.7189	0.562247879
30	0.714	0.40714286		0.7092	-0.797800338
31	0.7054	-0.80705982		0.7179	0.423735896
32	0.712	0.12738764		0.715	0.01986014
33	0.7103	-0.11164297		0.7124	-0.345030882
34	0.7157	0.64370546		0.7125	-0.330947368
35	0.7185	1.0308977		0.7171	0.312648166
36	0.7072	-0.55048077		0.722	0.989196676
37	0.7122	0.15543387		0.7161	0.173439464
38	0.7105	-0.08346235		0.7154	0.075761812
39	0.7148	0.5186066		0.7213	0.893109663
40	0.709	-0.29520451		0.7228	1.098782512
41	0.7114	0.04315434		0.7188	0.548414023
42	0.7096	-0.21040023		0.72	0.714166667
43	0.7171	0.83767954		0.7175	0.368222997
44	0.7166	0.76849009		0.7199	0.700375052
45	0.7034	-1.0936878		0.7189	0.562247879
46	0.7132	0.29542905		0.7172	0.326547685
47	0.7137	0.36527953		0.7293	1.980255039
48	0.7226	1.59244395		0.7143	-0.078118438
49	0.7203	1.27821741		0.7061	-1.24033423
50	0.7103	-0.11164297		0.7059	-1.269018275
51	0.7122	0.15543387		0.7142	-0.092131056
52	0.7078	-0.46524442		0.7206	0.79683597
53	0.7078	-0.46524442		0.72	0.714166667
54	0.7099	-0.16805184		0.7086	-0.883149873
55	0.698	-1.87578797		0.7112	-0.514341957
56	0.7107	-0.05529759		0.716	0.159497207
57	0.705	-0.86425532		0.7233	1.16715056
58	0.7092	-0.26692047		0.7081	-0.954384974
59	0.7083	-0.39432444		0.7113	-0.500210881
60	0.7089	-0.30935252		0.7288	1.913007684
61	0.7219	1.49702175		0.7111	-0.528477007
62	0.7124	0.18346435		0.711	-0.542616034
63	0.7123	0.16945107		0.7031	-1.672308349
64	0.7146	0.49076406		0.7042	-1.513490486
65	0.7192	1.12722469		0.7124	-0.345030882
66	0.7054	-0.80705982		0.7106	-0.599211934
67	0.7153	0.58814483		0.7044	-1.484667802
68	0.711	-0.01308017		0.7095	-0.755179704
69	0.7094	-0.23865238		0.7065	-1.183014862

70	0.7068	-0.6073854		0.7059	-1.269018275
71	0.7157	0.64370546		0.7133	-0.218421422
72	0.7144	0.46290594		0.7072	-1.082861991
	51.1987			51.4698	
Av. Wt.	0.711093			0.714858	
S.D	0.004412			0.006055	

APPENDIX 8 STANDARD OPERATING PROCEDURES FOR ASSAY OF THE ANTIHYPERTENSIVE DRUG PRODUCTS (The British Pharmacopoeia 2001 Procedures)

A. ATENOLOL

1. Powder 20 tablets.
2. Transfer the powder to a 500-ml flask using 300 ml of *methanol*
3. Heat the resulting suspension to 60° and shake for 15 minutes.
4. Cool, dilute to 500 ml with *methanol*
5. Filter through a fine glass micro-fibre filter paper (Whatman GF/C is suitable)
6. Dilute a suitable volume of the filtrate with sufficient *methanol* to produce a solution containing 0.01% w/v of Atenolol.
7. Measure the *absorbance* of the resulting solution at the maximum at 275 nm, Appendix II B.
8. Calculate the content of $C_{14}H_{22}N_2O_3$ taking 53.7 as the value of A (1%, 1 cm) at the maximum at 275 nm.
9. Repeat the procedures in 1 to 8 twice
10. Calculate the average and standard deviation of the determination

B. FUROSEMIDE

1. Weigh and powder 20 tablets.

2. Shake a quantity of the powder containing 0.2 g of Furosemide with 300 ml of 0.1M *sodium hydroxide* for 10 minutes
3. Add sufficient 0.1M *sodium hydroxide* to produce 500 ml and filter
4. Dilute 5 ml to 250 ml with 0.1M *sodium hydroxide*
5. Measure the *absorbance* of the resulting solution at the maximum at 271 nm, Appendix II B.(BP 2001)
6. Calculate the content of $C_{12}H_{11}ClN_2O_5S$ taking 580 as the value of A(1%, 1 cm) at the maximum at 271 nm.
7. Repeat the procedures in 1 to 8 twice
8. Calculate the average and standard deviation of the determination

C. METHYLDOPA TABLETS

1. Weigh and powder 20 tablets.
2. Dissolve a quantity of the powder containing the equivalent of 0.1 g of anhydrous methyldopa as completely as possible in sufficient 0.05M *sulphuric acid* to produce 100 ml and filter.
2. To 5 ml of the filtrate add 2 ml of *iron* (II) *sulphate-citrate solution*, 8 ml of *glycine buffer solution* and sufficient *water* to produce 100 ml.
3. Measure the *absorbance* of the resulting solution at the maximum at 545 nm, Appendix II B.
4. Repeat the procedure using 5 ml of a 0.10% w/v solution of *methyldopa BPCRS* in place of 5 ml of the filtrate, beginning at the words 'add 2 ml of...'
5. Calculate the content of $C_{10}H_{13}NO_4$ using the declared content of $C_{10}H_{13}NO_4$ in *methyldopa BPCRS*.
6. Repeat the procedures in 1 to 8 twice
7. Calculate the average and standard deviation of the determination

** **IRON(II) SULPHATE-CITRATE SOLUTION** (Prepare immediately before use)

1. **Dissolve 1 g of *sodium metabisulphite* in 200 ml of *water***
1. **Add:**
   a. **0.5 ml of 2M *hydrochloric acid***
   b. **1.5 g of *iron*(II) *sulphate* and**
   c. **10 g of *sodium citrate.***

****GLYCINE BUFFER SOLUTION**

1. **Mix 42 g of sodium hydrogen carbonate and 50 g of potassium hydrogen carbonate with 180 mL of water**
2. **Add a solution containing 37.5 g of Glycine and 15 mL of 13.5 M ammonia in 180 mL of water**
3. **Dilute to 500 mL with water and stir until solution is complete.**

D. ASSAY OF CAPTOPRIL TABLETS

1. Weigh and powder 20 tablets.
2. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.
   a. For solution (1) transfer a quantity of the powdered tablets containing 25 mg of Captopril to a centrifuge tube
   b. Add 25 ml of the mobile phase
   c. Mix with the aid of ultrasound for 15 minutes and centrifuge.
   d. Dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase. Solution (2) contains 0.01% w/v of *captopril BPCRS* and 0.0005% w/v of *captopril disulphide BPCRS* in the mobile phase.
3. For chromatographic procedure, use:
4. (a) a stainless steel column (25 cm×4.6 mm) packed with *stationary phase C* (10 μm) (Nucleosil C18 is suitable)
5. (b) a mixture of 0.5 volume of *orthophosphoric acid*, 450 volumes of *water* and 550 volumes of *methanol* as the mobile phase

   (c) a flow rate of 1 ml per minute and

   (d) a detection wavelength of 220 nm.

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to captopril and captopril disulphide is at least 2.0.

Calculate the content of $C_9H_{15}NO_3S$ using the declared content of $C_9H_{15}NO_3S$ in *captopril BPCRS*.