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Quality Assessment of Solid Pharmaceuticals and Intravenous Fluid Manufacturing in Sub-Saharan Africa

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1. Introduction

The quality of pharmaceuticals cannot be compromised as these constitute a group of products ingested into the human and animal systems by routes such as oral, parenteral, topical etc. These groups of products therefore have direct bearings on our well being and there is therefore an absolute need to guarantee their quality, safety and efficacy. Drugs therefore have to be designed and produced such that when patients receive them for management of their ailments, they do not produce any adverse side reactions on such patients or their unborn babies.

The sub-Saharan Africa countries market are flooded with fake and adulterated drugs to such an extent that only 30 % of drugs available in these countries can be said to be genuine in terms of contents and efficacy. The side effect of fake and adulterated drugs is so serious that therapeutically, if administered, can give rise to treatment failure which at times may be serious enough to result to death. Assurance of the quality, safety and efficacy of pharmaceutical products is a continuing concern of World Health Organization. It is now recognized that stability of active components of preparations poses serious problems for many manufactured products, especially those entering international commerce and/or distributed in territories with harsh climatic conditions. These problems may arise as a consequence of

a. Improper storage (in heat, moisture, sunlight). This might lead to degradation or loss in potency. The manufacturer will always indicate the best possible storage conditions on the product, but it has been found that retailers and wholesalers do not have required facilities to achieve these conditions or some do not give regard to these warning consequently this leads to product quality deterioration before expiry dates.

In most sub-saharan Africa countries, manufacturers, retailers, wholesalers and general public persistently flout most storage instructions and thereby jeopardize the quality of the product.

b. Poor quality assessment. Due to local sourcing of raw material in a developing nation, lack of current high-tech analytical instrument or even unavailability of certain reagents used in official procedure may force the quality control analyst to develop alternative methods.

Despite efforts made around the world to ensure a supply of right quality and effective drugs, substandard, spurious and counterfeit products still compromise health care delivery in some countries especially in Sub-Saharan Africa.

Every government allocates a substantial proportion of its total health budget to drugs. This proportion tends, to be greatest in developing countries, where it may exceed 40%.

Without assurance that these drugs are relevant to priority health needs and that they meet acceptable standards of quality, safety and efficacy, any health service is evidently compromised. In Sub-Saharan Africa, drug manufacturing faces various challenges in assessment of quality of solid pharmaceuticals and intravenous fluid.

The first challenge is the deterioration of solid pharmaceuticals during distribution and storage as a result of sunny and humid climate..

The second challenge is non-availability of equipments specified in official references books (British Pharmacopeaia and United States Pharmacopeaia) in monographs for analysis of drugs. The third challenge is insufficiency of personnel with adequate technical know-how to man the quality control unit of the pharmaceutical company.

Intravenuos fluids, otherwise called infusions are fluids used in medical delivery by intravenous administration.

The most challenging quality control aspect of infusion manufacturing are sterilty and pyrogen level determination of the final product. Most intravenuous fluid product failures in Nigeria involve sterility failures and high pyrogen contents. The challenges of quality control of infusion manufacturing in Nigeria is compounded by lack of infrastructures (epileptic electric power supply) and high cost of useful test kits for sterilty and pyrogen. There is challenge of finding a more affordable and reliable test materials (kit) for pyrogen test. Most companies use the rabbit test method for pyrogen tests which has limitations in false results, delayed decision making. Since rabbit test for pyrogen is done after the terminal sterilization of products, failed product cannot be re-processed. The Limulus Amebocyte Lysate (LAL) test kits are expensive and not affordable though reliable. Nigerian infusion manufacturers require a cheaper and locally sourced test kit for in-vitro determination of pyrogen in addition to good infrastuctures for smooth operation.

It is therefore reasonable to assure that the analytical procedures involving the use of simple instruments will find greater application in Sub-Saharan Africa. Taking into consideration the aforementioned challenges, the main objectives of this paper is to carry out a review of degradation studies of common antibiotics in Sub-Saharan Africa by investigating the effect of heat, sunlight, moisture and U.V radiation on the potency of the drugs. The paper will also review some of the alternative analytical methods developed for assessment of quality of selected solid pharmaceuticals. A cheaper and locally sourced test kit for in-vitro determinations of pyrogen in intravenous fluids will be described. The chapter will also review some of the previous work done on this subject.

2. Degradation of drugs

Some of the drugs that are marketed in tropical countries are vulnerable subjected to degradation processes that can result into loss in the active component of these drugs. These problems may arise as a consequence of improper or inadequate storage and distribution of

the products which can lead to physical deterioration and chemical decomposition resulting in reduced bioactivity, formation of toxic degradation products or the formation of an unstable product especially under tropical conditions of high ambient temperature and humidity. Many pharmaceutical substances are known to deteriorate during distribution and storage particularly in hot, sunny and humid climate. Tropical and subtropical climatic conditions are therefore expected to pose serious problems with respect to stability of drug.
Many drugs are thermosensitive, when they are exposed to high temperature, degradation tends to occur.Many workers have investigated the effect of heat on the degradation rate profile of many pharmaceuticals.
In 1982, Kabela studied the influence of temperature on the stability of solid tetracycline HC1 measured by High Performance Liquid Chromatography in pure drug and capsules. The tetracycline hydrochloride were stored for about two years at temperature of 37°C, 50°C, and 70°C. It was found that at 37°C and 50°C, no decomposition was observed for tetracycline nor for its related substance. At 70°C, a distinct decrease in tetracycline HC1 was observed as well as a small increase in degradation products (Anhydrotetracyclinavaie HC1, 4-epitetracycline HC1 and 4-epianhydrotetracycline HC1). The degradation products are shown in figure 1.

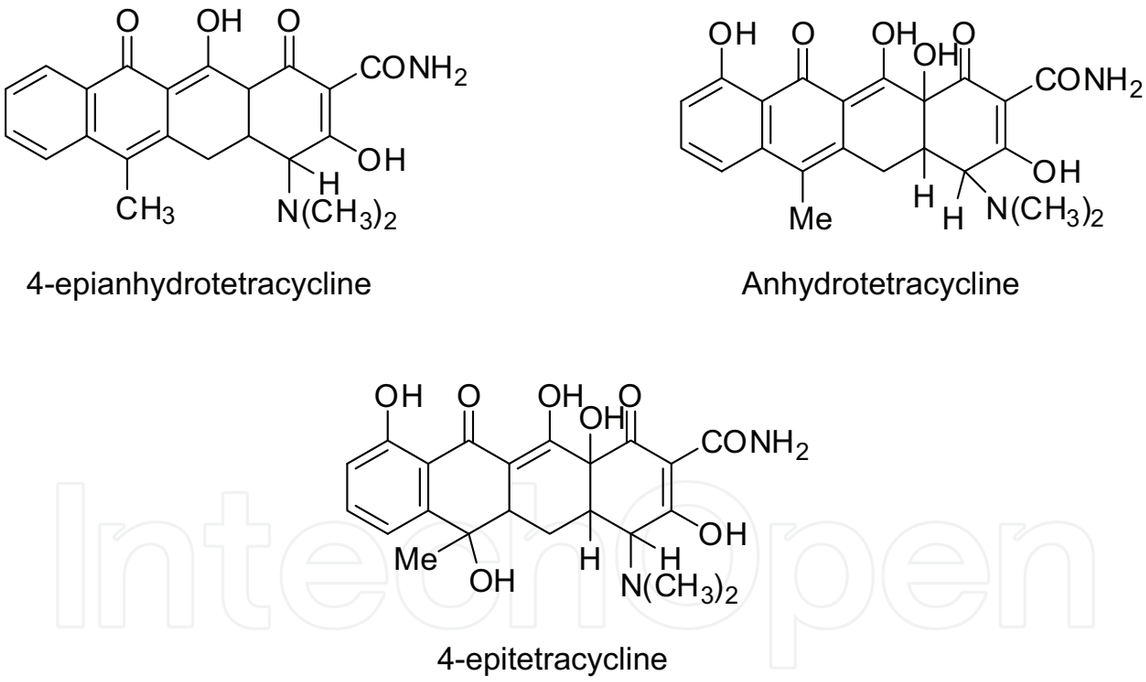
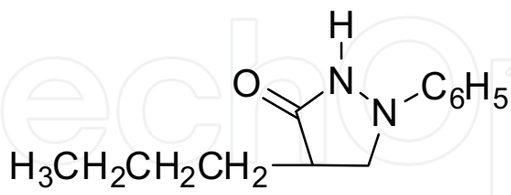


Fig. 1. Degradation products of tetracycline

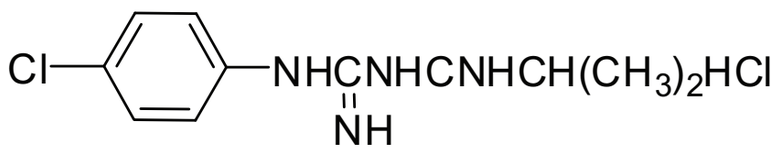
Another work on influence of temperature on drugs was reported by Matsui *et al*., (1978) . It was observed that phenylbutazone (figure 3) formulations showed no evidence of chemical instability when stored at ambient temperature of 37°C. At temperature above 37°C measurable chemical degradation occurred with several formulations showing more than 50% degradation.
Even at temperature below 37°C , degradation can take place as shown by work carried out by Kaplan *et al*, 1976. They reported that Amikacin exposed to 25°C for 24 months showed

an average of 3.9% degradation. But when the drugs were subjected to 56°C for 4 month an average of 7.2% degradation was observed. Owoyale and Elmarkby, (1989) found out that proguanil (Figure 4) which appeared not to undergo photochemical reaction was thermally degraded when subjected to heat at 45°C. The same drug when stored at room temperature of 25°C for six years was found not to undergo any decomposition.



Phenylbutazone

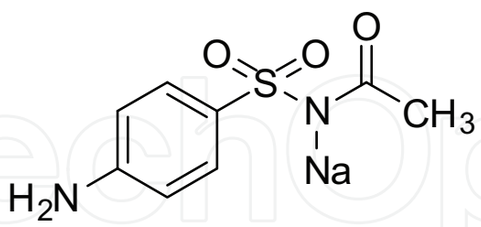
Fig. 2. Structure of Phenylbutazone



Proguanil

Fig. 3. Structure of Proguanil

Low temperature can sometimes have a negative effect on the stability of some drugs, for instance sulfacetamide sodium (Figure 3) in aqueous medium may be recystallized if stored at low temperature.



Sulphacetamide Sodium

Fig. 4. Structure of Sulfacetamide Sodium

Many drugs have been discovered to be photosensitive, hence they undergo photochemical reactions when exposed to sunlight, due to absorption of U.V light (wavelength of 190 - 320mn). It is therefore not surprising to find many pharmaceutical preparation being destroyed or degraded when exposed to sunlight.

Fadiran and Grudzinski, (1987) studied photostability of chloramphenicol using TLC to detect the number of degradation products. It was shown that chloramphenicol in solid

crystalline state (pure drug) and capsule on exposure to U.V light and sunlight developed a yellow colour, the intensity of which increased with increasing exposure time. During photolysis of chloramphenicol, the Beta-bond to the aromatic ring undergoes cleavage to yield one aromatic and one alkyl radical. Irradiation of drugs in solution produces a reaction that is faster than in solid state. Earlier worker preferred to study degradation of drugs in solution.

Chloramphenicol was degraded by light in 0.25% w/v aqueous solution and the solution became yellow and acid to form 2-amino-1 -(4-nitrophenyl) propane-1, 3-diol. and dichloroacetic Acid. (*Shih,1971*). Similarly, Hvalka, (1989) reported that the potency of tetracycline HC1 reduced to 50% when the solution was irradiated with U.V. light for 3 hours. The Degradation products are 4-epitetracycline, Anhydrotetracycline and 4-epianhydrotetracycline.

Drugs which contain multiple unsaturation are particularly prone to photolysis. Drugs with more double bonds are more susceptible to degradation. This assumption was proved by Hamlin *et al*. (1960), they investigated the photolytic degradation of alcoholic solution of hydrocortisone, prednisolone, and methylprednisolone exposed to Ordinary Fluorescent light. It was discovered that the degradation follows 1st order kinetics and that prednisolone and methylprednisolone showed the same rate of degradation, whereas hydrocortisone degrades 1/7th the rate of the two steroids. Hence the two double bonds present in prednisolone and methylprednisolone make these steroids more susceptible to light catalyzed degradation than the one double bond in the ring of hydrocortisone.

Solid pure drugs with ester, amide linkages deteriorate with moisture via hydrolysis pathways. The effect of moisture on degradation of drugs, are many, when deposited on drugs, especially the solid dosage forms, it provides a suitable medium for micro-organism to thrive which may eventually lead to biological degradation of the drugs. Moisture may also cause some physical changes such as swelling, dissolution, cracking and adhesion of coated tablets. Ordinarily, one expects hydrolysis to occur frequently in drugs in aqueous solution and suspension.

Leeson and Mattocks (1958) reported that a thin layer of moisture deposited on aspirin was all it needed for hydrolytic degradation to commence.

There is no restriction to the use of additives and excipient but they should be chosen in a way so as not to affect the stability of the drugs. Incompatibilities of active ingredient with additives can lead to degradation. Kornblum and Zoglio, (1967) studied the potency degradation of Aspirin suspension with lubricant-namely, Aluminum stearate, magnesium stearate, calcium stearate. It was found out that the extent of degradation was more with magnesium stearate.

From the review of the previous works done on degradation of drugs, it can be observed that few works have been reported in degradation of antibiotics, especially in solid state. The few reports that are available are not comprehensive enough especially exposure of the drugs to environmental conditions. Hence there is need to investigate and carry out extensive studies on the degradation of drugs.

Antibiotics like any other drugs show loss in potency when subjected to some environmental conditions.

In continuation of an effort on stability studies of drug, effects of moisture, sunlight, heat and UV radiation on the potency of some antibiotics (Ampicillin, Tetracycline and Chloramphenicol) were investigated by our research group (Adediran and Tella, 2000; Adediran *et al*, 2003; Tella *et al*, 2008). The pure drug of antibiotics and capsules were

exposed to moisture, sunlight, temperature (37°C), (70°C) and UV (254nm) for 60 days. Percentage potency or Percentage residual amount of active ingredient were determined before and after exposure.

The three drugs showed evidence of stability with no loss of potency at 37°C, but exhibited loss in potency when exposed to moisture and heat at 70°C.

Exposure of the three drugs to sunlight and UV resulted in loss of potency except Ampicilin which showed loss in potency only at UV radiation.

Peak (cm^{-1})	**Assignments**
3789	Free OH
3475	N-H (str)
2920	C-H (Str)
1895	C=O (str)
1684	C=C aromatic System
1352, 1527	NO_2 vibration
1569	C-N (str)
1069	C-O (str)
978	O-H (def)
701	Presence of free adjacent protons in aromatic

Table 1. Infrared spectrum of unirradiated Chloramphenicol pure drug and its assignment

Peak (cm^{-1})	**Assignment**
3475	N-H (str)
1647	C=O (str) or C=C (str)
1521	presence of NO_2 vibration
1418	C-H (def) in methyl)
1069, 1105	C-O (str)
972	OH (def)
701, 815	Presence of hydrogen or Proton in aromatic

Table 2. Infrared spectrum of sunlight irradiated Chloramphenicol pure drug

The infrared spectral assignments of samples of the Chloramphenicol exposed to sunlight and unexposed chloramphenicol are shown in tables 1 and 2

Peaks such as 3789 cm^{-1} due to free OH, 2920cm^{-1} for C-H (str) in unexposed pure drug disappeared in the drug exposed to sunlight. This is in agreement with the finding of Fadiran and Grudzinki(1987) who reported that β–bond to aromatic ring present in Chloramphenicol molecule in solid state undergoes cleavage to form one aromatic and one alkyl radical when the drug was exposed to sunlight.

Also 1894cm^{-1} due to C=O (str), 978cm^{-1} due to O-H (def) in pure drug shifted to 1647cm^{-1} and 972cm^{-1} respectively in exposed drug. There is one C-O (str) peak at 1069cm^{-1} in pure drug whereas there are two in the exposed drug, one at 1069cm^{-1} and another 1105cm^{-1}. All these changes arise from peak destruction and spectra shift are indications of drug degradation.

Infra red spectroscopic analyses were carried out on ampicillin and Tetracycline before and after exposure to heat and moisture (Tables 3, 4 , 5 and 6). Ampicillin drug was exposed to

heat at 70°C and moisture for 60 days. Ampicillin pure drug exposed to temperature 70°C exhibited loss in potency and degradation as evidenced by disappearance of absorption band at 1785cm^{-1} of the C=O (Str) in the Beta-lactam ring. This led to the appearance of new band at 2932cm^{-1} due to C-H (str) and 2510cm^{-1} due to S-H (str) and C=N (str) at 1563cm^{-1} in Ampicillin exposed to 70°C to form pencillenic acid as shown in Figure 5.

Peak (cm^{-1})	**Assignment**
3700	OH in carboxylic acid
3442	Free N-H (str)
1782	C=O (str) in β–lactam ring
1697	C=O (str) in the amide
1266	C-N (def)
1168	C-O (str)
651, 700,931	Presence of free adjacent protons in aromatics or C-S (str).

Table 3. Infrared spectrum of ampicillin pure drug (unexposed) and its assignment

Peak (cm^{-1})	**Assignment**
3700	OH in carboxylic acid
3451	Free N-H (str)
2931	C-H (str)
2510	S-H (str)
1660	C=O or C=C (str)
1576	C=N (str)
1508	Presence of aromatic system
1400	C-H deformation in CH_3 or CH_2
1243	C-O (str)
701	Presence of free adjacent protons in aromatics.

Table 4. Infra-red spectrum of ampicillin pure drug exposed to 70°C (assignments)

Peak (cm^{-1})	**Assignments**
3500	N-H (str)
2360	H-X (str) in salt of hydrohalides)
1715	C=O (str)
1636	C=O/CO-NH_2 (str)
1500, 1526	C=C Stretching in Aromatic system.
1236, 1183	Presence of C-O/C-N (str)

Table 5. Infrared spectrum of tetracycline pure drug unexposed (assignments)

It can be observed from Figure 5 that the peaks due to 1715cm^{-1} and one (2360) due to H-X (str), in unexposed drug disappeared in spectrum of exposed drug. Also, new peaks at 2926cm^{-1} due C-H (str) and 3700cm^{-1} due to free OH appeared in the exposed drug, which is an indication that hydrolysis of tetracycline may have taken place.

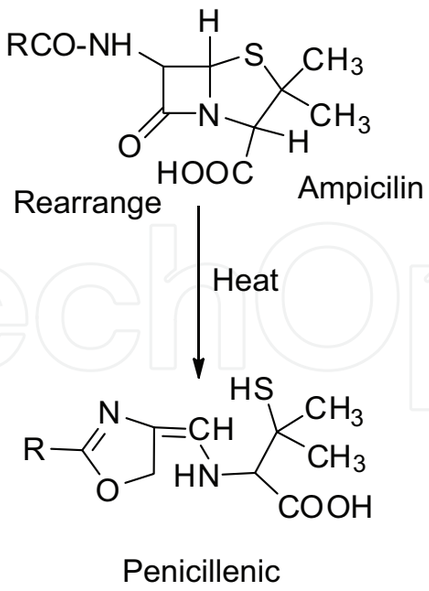


Fig. 5. Rearrangement of Ampicillin after exposure to heat

Peak (cm^{-1})	**Assignments**
3700	Free O-H
3500	N-H (str)/ OH in carboxylic acid.
2926	C-H (str)in Aromatic system
1623	C=O (str)
1521	C=O in aromatic system
1038, 1128, 1261	C-O/C-N (str)

Table 6. Infra-red spectrum of tetracycline capsule exposed to moisture

The infrared spectra of all the three drugs showed evidence of degradation when they are exposed to different environmental conditions.

3. Development of alternative analytical procedure

The awareness of populace as regards drug toxicity and effectiveness in relation to drug quality, requires stricter control of qualitative and quantitative nature of governmental agencies. It is however not possible to enforce a quality standard when there is no analytical method to determine the level of compliance with such standard.

New analytical procedure development is required due to advancement of pharmaceutical practice but problems peculiar to an environment may bring about adaptation of even old methods.

In any case, such new method has to be checked to be at least of equal performance, if not superior, to an already accepted official compendia method.

The first scientist to develop analytical method for the assay of penicillin was Alicino[24] in 1946. He reported the first general iodometric method for the assay of most penicillin. He discovered that most chemical methods of assay for the benzyl penicillin salts depend upon hydrolytic cleavage of the Beta-lactam ring to give penicilloic Acid. The cleavage can be

brought about either by alkali or by the enzyme penicillinase. If the cleavage is brought by penicillase in a previously neutral and unbuffered solution the resulting acid may be titrated with alkali to give a measure of the penicillin present. Alternatively, most commonly, the liberated penicilloic acid is determined through the ability to take up iodine, a property not possessed by the parent molecule. This method has undergone various modifications and revisions from time to time.

The modification of Alicino was done by Beckett and Stenlake (1976) using benzyl penicillin for the modification. After primary hydrolysis with sodium hydroxide solution to convert the antibiotics to the corresponding penicilloic acid, treatment with acid yield D-penicillamine (and benzylpenillic Acid) which is oxidized almost quantitatively by iodine to the corresponding disulphide, excess iodine is back-titrated with 0.02M sodium thiosulfate solution. The equation of reaction is shown figure 6.

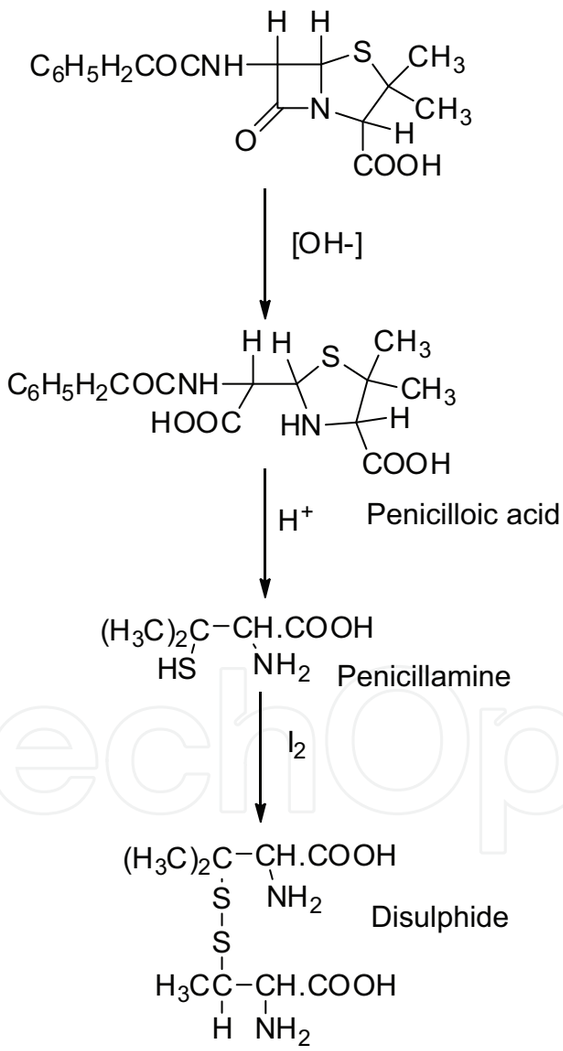


Fig. 6. Back -titration of Ampicillin by iodiometry

Benzyl penicillin sodium is standardized against a chemical reference substance of known potency.

The above method has two principal advantages over spectrophotometric method. First, it has a high degree specificity since non-penicillin impurities are to a large extent allowed for in the blank determination and secondly the relatively large iodine absorption makes the method highly sensitive.

Apart from the titrimetric methods of assay reported above, an attempt was made to assay penicillin by spectrophotornetric method. Beckett and Stenlake,1976 described the spectrophotometric method by the use of imidazole mercury reagent. Mercuric chloride is known to attack the sulphur atom of the penicillin leading to a rearrangement involving penicillin side chain. The rearrangement is catalyzed by imidazole. The product III formed is a penicillenic acid mercuric mercaptide which absorbs between 325 - 345nm. The equation of reaction is shown in figure 7.

By using a reference and test samples, the absorbance given by the penicillenic acid mercuric mercaptide formed from a known weight of the reference is compared with that of the test. From the comparison of the absorbance given by a reference as compared to that of the test sample, the actual penicillin content can be computed. The method is official in British Pharmacopoeia (1993) and India Pharmacopoeia (1985) for assay of cloxacillin, fluocloxacilin and ampicillin.

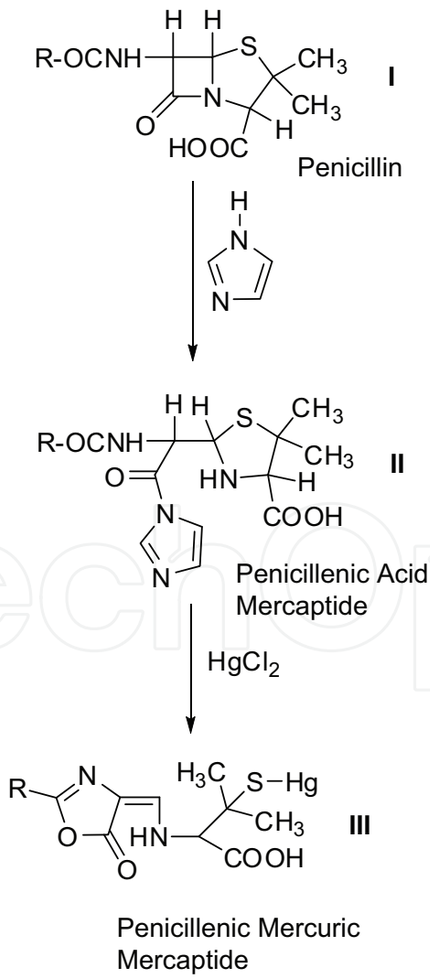


Fig. 7. Spectrophotometric analysis of Penicillin

The second instrumental method for the assay of penicillin was reported by Bungaard and Larsen,(1983) . They made use of sorbitol reagent in the analysis of Ampicillin, Amoxycillin and Cyclacillin. Sorbitol reagent is an hydroxyl compound, it was used to form a penicilloyl ester intermediate II, which rearranges to a corresponding piperizinedione derivative III. Treatment of the derivative with 1M NaOH gives a highly absorbing product with absorption maximum at 322nm. The equation of reaction is shown in figure 8.
The reaction is catalysed by the reaction in catalyzed by metal ions. Zinc ions were found to be most effective catalyst. Aminopenicillin such as Ampicillin, Amoxycillin and Cyclacillin can be determined quantitatively by this method.
Most official books such as, British Pharmacopoeia (1993), United states pharmacopoeia (1990) and International Pharmacopoeia (1979) described the analysis of tetracycline HCl using microbiological, non-aqueous and spectrophotometric methods.

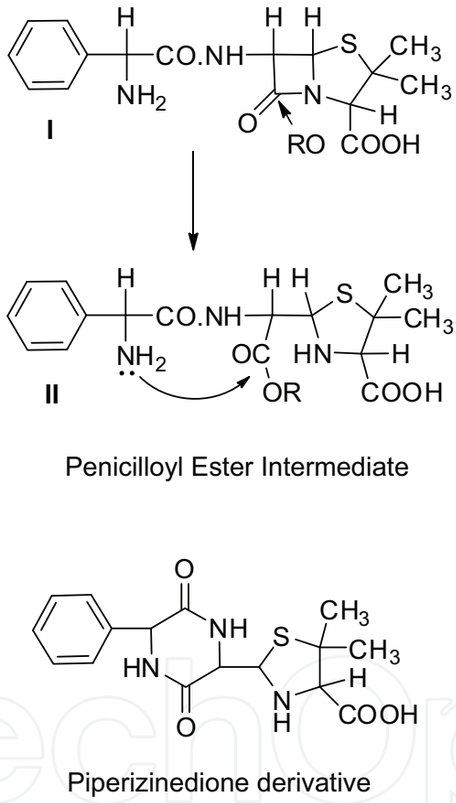


Fig. 8. Spectrophotometric analysis of Ampicillin

As far back as 1956, Woolford and Chiccarelli proposed first spectrophotometric method of analysis of tetracylines, which is based on the formation of yellow colour with an absorption maximum at 320nm when tetracycline HCl is dissolved in 0.2M sodium hydroxide. The disadvantage of the method is that it is not applicable to oxytetracycline and chlortetracycline.
Effort was made to develop analytical method that will be applicable to all three common tetracyclines. Monastero *et al.* (1951) were able to come up with a method which applied to all three tetracyclines. The method involves mixing of dilute hydrochloric acid solution with ferric chloride solution to form orange-brown colour which gives maximum absorption at 490nm. This method has been adopted as official method for the analysis of oxytetracylines

in Indian Pharmacopoeia., 1985). Phosphates, fluorides, thiocyanates and other substances that combine with iron (III) interfere and therefore if present must be removed before carrying out determination.

Yokohoma and Chatten, (1958) reported non-aqueous method for tetracycline. It was shown that tetracycline hydrochloride may be titrated non-aqueously with perchloric acid in dioxan by addition of mercuric acetate. Tetracycline which is halide salt is treated with mercuric acetate to precipitate the halide ion as undissociated mercuric (II) halide and form the acetate salts which reacts quantitatively with perchloric acid thus preventing interferences of halogen.The methods are not selective for separation and determination of tetracycline degradation products in tetracycline HC1 powder and capsules. In order to find solution to this problem, Omer *et al*, (1958) used thin layer chromatography for the separation and semiquantitative determination of tetracycline degradation products in tetracycline Hydrochloride powders and capsules.

It failed in an attempt to fully quantify the degradation products and content of residual drug. This led to the development of more sensitive technique that quantified and differentiate between the degradation products and intact molecule of drug by Kabela in 1982 using HPLC. He was able to determine the amount of degradation products (4-epianhydrotetracycline, Anhydrotetracyline and 4 - epitetracycline) present in tetracycline Hydrochloride.

British Pharmacopoeia (1980) described a spectrophotornetric method to measure the total absorbance of degradation products in tetracycline hydrochloride. The absorbance limit set by the British Pharmacopoeia (1980) is twice that which has been set for tetracycline hydrochloride capsules and powder. The samples of tetracycline hydrochloride capsules and standard were examined at 430nm.

Some official books British Pharmacopoeia (1993), International Pharmacopoeia (1979) described spectrophotometric method for the analysis of chloramphenicol, by taking the absorbance of chloramphenicol solution at 278nm.

Chloramphenicol eye drops, ear - drops and capsules can also be determined by colorimetric method based upon reduction of the nitro group with zinc, stannous chloride or better sodium dithionate followed by diazotization and coupling with N-(-1-naphthyl) ethylene diamine.

Most assay methods for the drug are based upon its functional groups and will not differentiate between chloramphenicol and its degradation products. It is known that chloramphenicol loses its antibiotic activity by the hydrolysis of the amide bond to give 2-amino-1-(4-nitrophenyl) propane-1,3-diol.

This latter compound commonly occur in pharmaceutical preparation and because of the structural similarity of the chloramphenicol and 2-amino-1-(4-nitrophenyl) propane-1,3-diol, the specific determination of chloramphenicol by spectrophotometer is unsuitable. The absorption is due principally to the nitrophenyl functional group and hence degraded chloramphenicol will also absorb at 278nm.

To ensure freedom from interference due to degradation of the chloramphenicol molecule, the chromatographic separation procedure is suggested preliminary to all analyses. Higuchi *et al*. (1954) developed a simple partition chromatographic procedure which separated degradation products of chloramphenicol from chloramphenicol molecule. Many other interferences are also removed, since partition method is extremely sensitive to differences in molecular structure. The eluate obtained containing chloramphenicol is then determined by spectrophotometer at 272nm.

Piergiorgio, 1979 proposed the application of simplified TLC method for the simultaneous determination of chloramphenicol and 2-amino-1-(4-nitrophenyl) propane-1,3-diol. The principle of this method consists of spotting the solution on a Thin layer chromatography plate together with standard solution and developing the plate with an ethyl acetate-formic Acid - water (10:2:8, upper plate) solvent. The intensities of the various spots are then measured by a densitometer and the peak height of the standards are used to calculate the concentration of chloramphenicol and 2-amino-1-(4-nitrophenyl) propane-1,3-diol. in unknown sample. This procedure is too laborious, not precise and tedious.
A more rapid, precise and accurate method was developed by Belle and Young,(1979). The method was based on the use of High performance Liquid chromatography for determination of chloramphenicol and 2-amino-1-(4-nitrophenyl) propane-1,3-diol. in Pharmaceutical formulations.
The method possesses a distinct advantage because the method does not require extraction nor derivatization for the determination of both chloramphenicol and 2-amino-1-(4-nitrophenyl) propane-1,3-diol. in capsule, ophthalmic solution and ophthalmic ointment formulation.
The solvent extraction method has been described in British Pharmacopoeia (1980) for the determination of 2-amino-1-(4-nitrophenyl) propane-1,3-diol. Albendazole is a broad anthelmintic (figure 9). It is used for the treatment of threadworm, hookworm and tapeworm.

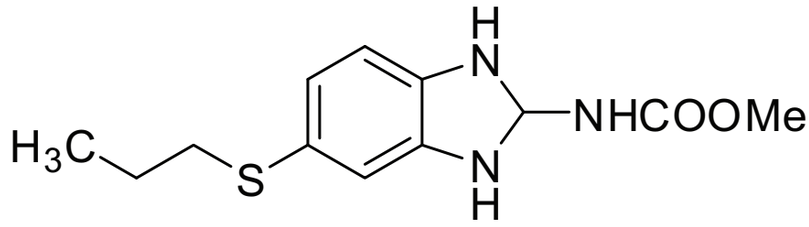


Fig. 9. Structure of Albendazole

Extensive literature survey reveals that the estimation of Albendazole in dosage and suspension forms are not available in pharmacopoeia and therefore require much investigation. The drug is readily available in Nigeria market in tablet, bolus (veterinary preparartion) and suspensions. The need to come up with a simple and sensitive method of analysis for the estimation of drug in pharmaceutical preparations therefore arises. Spectrophotometric method for the estimation of Albendazole in both solid and liquid preparation was developed (Tella *et al*,2010). Treatment of Albendazole with methanolic-glacial acetic acid gives a highly absorbing product with absorption maximum at 235nm. Beer law was obeyed in the concentration range 2.5-20µg/ml

Brands	Forms	Label claim(mg,mg/ml)	Found(mg,mg/ml)
A	Tablet	200	194.24±0.553
B	Bolus	250	243.07± 0.512
C	Bolus	500	497.6 ± 0.272
D	Suspension	25	25.11± 0.386
E	Suspension	25	24.60± 0.246

Table 7. Results of assay of Albendazole of different brands in solid dosage and suspension form

The results obtained from analysis of different brands of Albendazole tablets, bolus and suspension were in good agreement with the the label claims as shown in Table 7.
The little difference might be due to batch variation of medicaments in tablets, bolus and suspension, instrumental errors or degradation of active ingredients with time. The method could be considered for the determination of Albendazole in quality control laboratories.
Another alternative method developed for estimation of sulphadimidine in tablets is simple and rapid titrimetric method (Back titration). Sulphadimidine is bacteriostatic. It is an antibacterial (intestinal drug) (Figure 10).

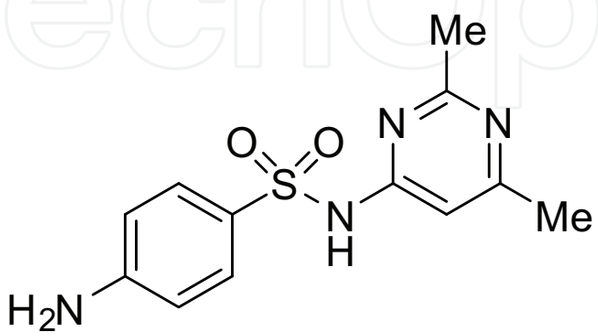


Fig. 10. Structure of Sulphadimidine

The drug is presented in tablets, injections, suspension and veterinary tablets.
Official methods for the analysis of the drug in pharmaceutical preparations are the potentiometric and Nitrite Titrations. The end point of Nitrite titration method is detected either electrometrically or by using an external indicator. By streaking a few drops of the titrated solution upon starch iodide paper or paste, a dark blue colour is obtained. Excess nitrous acid oxidizes the iodide in the indicator to give iodine which gives blue color with starch. The disadvantage of this method is that the visual end point with external starch iodide indicator may seem somewhat indefinite and difficult to determine. The great disadvantage of the electrometric end point and the potentiometric titration is lack of specificity. They also require expensive equipments, some level of expertise and are time – consuming. The average time to complete the reaction requires about 2 hours. However , the proposed method can be completed within 20minutes (Tella *et al,* 2010). The reagents are also available.
The procedure is described as follows: Standard drug solution was prepared by dissolving 250mg of Sulphadimidine B. P. in 30ml ethanol (96%) in a 250ml conical flask. 40ml of 0.1M sodium hydroxide solution was then added.
The content of the flask was mixed well and warmed on water bath for 5 minutes. It was allowed to cool. The excess alkali was then titrated with standardized 0.1M hydrochloric acid using 3 drops of Phenolphthalein solution as indicator. The operation was repeated without the substance being examined.
The difference between the titrations represents the amount of 0.1M sodium hydroxide required by the Sulphadimidine. Each milliliter of 0.1M sodium hydroxide is equivalent to 0.02783g of $C_{12}H_{14}N_4O_{25}S$ (Sulphadimidine)
Equation of the reaction is shown below (Figure 11)
The result obtained by the proposed and reported methods for the weighed Sulphadimidine B. P. and commercial samples of Sulphadimidine tablets are given in Table 8. The percentage recoveries show that the proposed method can be adopted for routine analysis of

Sulphadimidine tablets. The results obtained by the proposed method were in good agreement with the labeled amount.

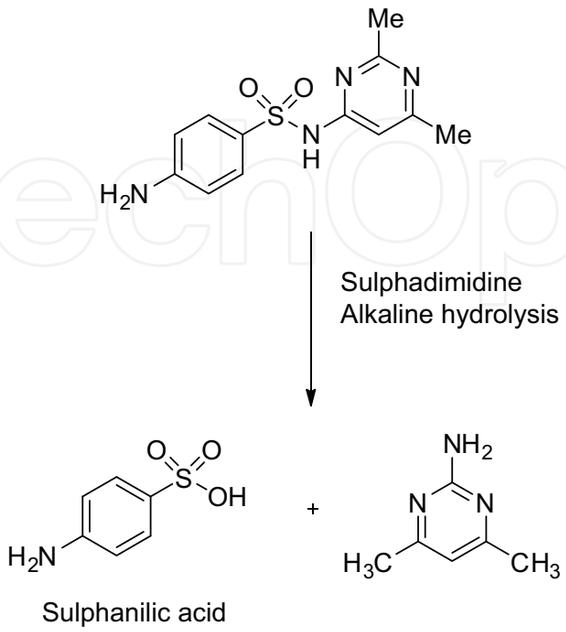


Fig. 11. Titrimetric analysis of Sulphadimidine

Titrimetric method (back titration)				Reported method (nitrite titration)		
Labeled Amount (mg)	Quantity Found (mg)	Recovery (%)	Standard Deviation	Recovery (mg)	Recovery (%)	Standard Deviation
500	498.98	99.80	± 0.06	496.24	99.25	± 0.07
500	495.43	99.09	± 0.09	490.83	98.17	± 0.05
500	493.43	98.69	± 0.10	500.00	100.00	± 0.06
500	500.18	100.04	± 0.08	494.56	98.91	± 0.03
500	499.24	99.85	± 0.03	492.48	98.50	± 0.02

(Average of 10 determinations)

Table 8. Average recoveries from the various commercial samples of Sulphadimidine tablets.

4. Adsorption of drugs on pharmaceutical exicipents

It has been established that the presence of adsorbent, such as activated charcoal interferes with the drug adsorption process resulting in a decrease bioavailability of some drugs. The interference in the systematic availability of drug is brought about by its adsorption on the activated surface of the solid adsorbent, thus preventing the adsorbed fraction of the drug from permeating through the gastro- intestinal mucosa into the blood stream.
Some of these drugs may be lost when adsorbent are administered concomitantly with the drugs.

Furthermore, in sub-Saharan Africa, the abuse of various drugs has increased considerably in the last decades. Many drugs used in treatment of tropical diseases have been implicated in various intentional and accidental poisoning. Adsorption and interaction of chlorapheneramine and chloroquine phosphate on pharmaceutical materials like magnesium trisilicate, Activated charcoal, magnesium carbonate and magnesium stearate was investigated by our research team. Freudlich Adsorption isotherm was adopted to evaluate adsorption capacity of each adsorbent on chloroquine phosphate. The freudlich parameter kf which is adsorption capacity obtained for the adsorbents are 0.053, 0.145, 0.131 and 0.173mg/g for magnesium carbonate, magnesium stearate, magnesium trisilicate and activated charcoal respectively showed that these adsorbents have ability to adsorb or remove chloroquine phosphate molecules from solution at PH 5.0 (Adediran *et al*,2006)

The extent of adsorption of chloroquine phosphate by the adsorbents followed the sequence; Activated charcoal > magnesium trisilicate > magnesium stearate > magnesium carbonate. Differences in surface characteristics and chemical structure of adsorbent may be responsible for the trend observed above.

Activated charcoal has the highest adsorption capacity which may be due to its organic nature and presence of phenolics and carboxyl moieties.

Magnesium trisilicate (Antacid) adsorbed Chloroquine better than magnesium stearate, because there is chemisorptions interaction between the negative charge of the adsorbent and positive charge of the drug molecule. The presence of small amount of oleate molecules in magnesium stearate enhances adsorption over magnesium carbonate. The findings are in agreement with the work of Mcginity and Lach, 1976, Cooney 1977 and Guay et al, 1984. Our investigation revealed that concurrent administration of these pharmaceutical adsorbents and chloroquine drug might interfere with chloroquine adsorption. Furthermore, these adsorbents can serve as alternative antidote for chloroquine poisoning. We also investigated the in-vitro absorption of chlor pheniramine maleate on these adsorbents. Chlorapheniramine maleate is an antihistamine which reliefs red, itchy and watery running nose. The study was carried out at P^{H} = 5.0 and 37°C using Batch method. Freudlich parameters were determined for each adsorbents as shown in Table 9). The freudlich parameter (kf) are 4.68, 4.47, 4.80 and 1.91 for activated charcoal, magnesium trisilicate, magnesium stearate and talcum powder (Tella and Owalude, 2007). The adsorbents have ability to adsorb or remove chlorapheniramine maleate from solution at 3.0 – 5.0mg/l adsorbate. The drug was mostly adsorbed by the activated charcoal and least absorbed by talcum powder.

We concluded that concurrent administration of these pharmaceutical adsorbents and chlorapheniramine maleate might induce interference between them thereby affecting the bioavailability of the drug to the system. There is possibility of using these adsorbents as antidote in case of Chlorapheniramine maleate over dose or poisoning.

Absorption	**1/n**	**Kg x 10^{-3}mg/g**
Activated charcoal	0.65	4.68
Mg Si O_3.	0.66	4.47
Magnesium stearate	0.77	3.80
Talcum powder	0.99	1.91

Table 9. Freudlich adsorption parameters of CPM on Adsorbents

5. Intravenous fluids

An intravenous fluid is a sterile, pyrogen-free, particle-free solution used for therapeutic purposes by infusion through the veins.
Intravenous fluids (I.V. Fluids) are solutions sometimes containing electrolytes such as sodium chloride, potassium chloride and calcium chloride; energy-giving compounds like dextrose and other ion-balancing solutions such as compound of sodium lactate (Hartman's and Ringer Lactate Solutions).
Examples of I.V. Fluids are:

- Normal Saline (0.9%$^{w}/_{v}$ Sodium Chloride in water)
- Dextrose 5% $^{w}/_{v}$ Saline (containing g/Litre Sodium Chloride and 50g/Litre dextrose anhydrous).
- Dextrose 5% $^{w}/_{v}$ (containing 50g/litre dextrose anhydrous).
- Dextrose 4.3% $^{w}/_{v}$ + 0.18% Saline (containing 43g/Litre dextrose anhydrous + 18g/Litre Sodium Chloride).
- Dextrose 50% $^{w}/_{v}$ Solution (containing 50g/100ml Dextrose anhydrous)
- Dextrose 10% $^{w}/_{v}$ Solution (containing 100g/Litre dextrose anhydrous).
- Metronidazole Injection – 0.5% $^{w}/_{v}$ (containing 0.5g metronidazole / 100ml).
- Hartman's Solution
- Darrow's Solution – Full strength and ½ Strength.
- Plasma expanders such as 4% polyvinyl pyrollidone (povidone k30 – in water).

5.1 Uses / functions of I.V. Fluids

I.V. Fluids are normally infused into ambulatory patients - usually very weak, unable to eat or drink, or totally of unconscious, in shock or acetate coma. I.V. Fluids are therefore, a life saving device for critical care of patients. I.V. Fluids have constituents that are used selectively to correct certain imbalances in the body fluids of patients and to supply, the required energy by directly infusing the metabolisable carbohydrate monomer – D-glucose in the various concentrations, depending on the specific requirement of the patient.
I.V. Fluids essentially do the following:

a. Rehydrate patients
b. Replace lost ions such as sodium ion, chloride ion from normal saline (0.9% sodium chloride I.V. Solution). potassium, calcium and chloride ions from Darrow's solutions full strength and half strength. Calcium, sodium, potassium and chloride ions. Lactates from ringers (Hartman's solution).
c. Increase total blood volume in short time (in cases of server blood loss) for accident victims. Plasma expanders such as Isoplasma (4%$^{w}/_{v}$ polyvinyl pyrollidone in 0.78%$^{w}/_{v}$ saline) he as to replace blood volume without affecting ion – balance in the patients.
d. Supply energy in the form of dextrose anhydrous. All dextrose containing I.V. Solutions are energy sources for ambulatory patients. The specific need of each patient must be ascertained to determine what to give him/her.
e. Lactate – containing products help to correct low pH in the blood by metabolizing lactate to release bicarbonate ions (HCO_3^-) into the blood and hence neutralize the excess hydrogen ions in the blood.
f. Amino Acid, fatty acids, mineral and vitamin nutritional supplements are nowadays available as intravenous infusions

Intravenous fluids belong to a group of pharmaceuticals called parenterals. i.e. medications that are administered by other routes than through the intestinal absorption into the blood.

Other parenteral preparations include irrigation solutions, Peritoneal Dialysis Solution, Heamodialysis Concentrates e.t.c.

5.2 Quality of intravenous fluids

Intravenous fluids are administered directly into the blood stream through the veins. The veins empty it through the heart, which pumps it round the body. Hence it is very easy to deliver proper medication and hence therapy through I.V. Fluids or poison contaminations or germs through the same route if the I.V. Fluid is not of the right quality. I.V. Fluids must be sterile, pyrogen-free, particle – free and contain the right quantity of constituents as per the labelled amount of the product. The acceptable limit of the constituent throughout the shelf life of the product must remain between 95% and 105% of the label claim and in some case 90% to 110% at most.

5.3 Critical quality of I.V. Fluids

Sterility

I.V. Fluids must be free of viable organisms be it bacteria, fungi, algae or any microbe. If the I.V Fluid is not sterile after preparation it may remain clear for a while and later turn cloudy or show massive macroscopic growth. A seemingly clean pouch may actually not be sterile. But such contaminated pouch will later turn cloudy. A non-sterile material when infused poses dangers of sepsis (heavy blood contamination by germs) to the patient and resultant adverse reaction and death. Therefore, sterility is a critical quality of I.V. Fluids.

Pyrogen – Free status

Pyrogen simply means a substance which when injected elicits adverse reactions such as fever, rigours, palpitations and restlessness in the patients that receive it. Pyrogens are endotoxin produced by Gram negative bacteria. The bacteria may be killed (destroyed) by sterilization but the endotoxin present in them is released into the fluid medium. The pyrogenic solution when injected cause adverse reactions in the patient. Therefore, pyrogen–free status is a critical, acceptable quality of I.V. Fluids. I.V. Fluids must be free of solid or suspended particles I.V. Fluids packaged must remain intact. A broken package that lets in air becomes contaminated and loses its sterile status.

Bacterial endotoxin as impurity in sterile pharmaceuticals

Gram negative bacteria produce bacterial endotoxin. They are made up of the lipopolysaccharide (LPS) that constitute the cell walls of Gram negative bacteria. They are called endotoxin because they are not released to the outside environment of the bacteria until the cells die. They are released after cells disruption. Bacterial endotoxin abounds everywhere. The Gram negative bacteria exist in particulate matter, in air, water and soil (Schaumann, *et al.*, 2008).

Endotoxin is detectable in ambient aerosols and it is an important component of tobacco smoke. (Larson *et al.*, 2004) It has been reported that early life exposure to endotoxin protects against the development of allergies. (Braun-Farhlander, *et al.*, 2002). Exposure to household endotoxin is a significant risk factor for increased asthma prevalence in adults. Higher levels of exposure to endotoxin were significantly associated with asthma diagnosis (Schaumann, *et al.*, 2008). It is a known fact that in asthma patients' inhalation of endotoxin causes a significant decrease in lung functions with enhanced airway hyperactivity (AHR). (Schaumann *et al,.* 2008). Endotoxin is also an impurity in sterile pharmaceuticals especially

Large Volume Parenterals (LVPs) and it has to be tested for in the products meant for intravenous administration (Radhakrishnan, 2010).

6. Current methods and manufacturers (users) experience

The test for pyrogens in LVPs was recognized during the 1940's in the US when the Food and Drug Administration, the National Institutes of Health and fourteen pharmaceutical manufacturers, undertook a collaborated study. This study led to the adoption of the procedure, which first appeared in the XII Edition of The United States Pharmacopoeia and was the only official test for the detection of bacterial endotoxin until the discovery of LAL.

6.1 Limitations to the rabbit test of pyrogen (bacterial endotoxin)

Rabbit test is limited by the elaborate nature of the test. It is expensive, time-consuming and subject to the variability of animal test. Rabbit test can detect endotoxin but cannot determine the actual concentration or endotoxin present in a solution. The Limulus Amebocyte Lysate (LAL) test had been described in literature as the most sensitive convenient method currently available for detecting bacterial endotoxin. (Bergheim, 1978) LAL being an *in vitro* test is useful in In-process detection, an important practice in In-process quality control. This is a quantitative determination of the negative side or the limit. In-process material cannot be injected into rabbits since final sterilization had not been done on the product. An un-sterilized product portends greater risks to the animals. Hence, LAL has an edge over the Rabbit test of pyrogen in this regard.

In 1973, Travenol laboratory developed its own in-house LAL test which measured the activated amounts of protein precipitated. In the LAL gelation reaction, samples were tested for the presence of protein using the Lowry protein assay and resulting differentials were read on spectrophotometer. This eliminates the problem of subjective reading the gel-clot endpoint (Bergheim, 1978).

6.2 The Nigerian experience

LAL in this part of the world (Nigeria) is not readily in use because the kits have to be imported. In the US, a laboratory will charge up to $140 per sample to run LAL test.

There are about six LVP - manufacturing plants in Nigeria as at 2010. None of the plants used LAL to test for pyrogen, perhaps due to non-availability of the material locally. There is need to develop other in-vitro tests similar to LAL, but using extracts from animals readily available in the tropics.

In an on-going research, Salawu *et al*., (2010) have demonstrated that delay in sterilization of parenteral solutions of up to 48 hrs could lead to production of highly pyrogenic solutions, provided the solution had been contaminated with Gram negative organism like *Escherichia coli* before the delayed sterilization. In their report the resultant increase in the population of the contaminating bacteria before sterilization caused an intolerable rise in pyrogen level even after sterilization. Such a product in real production must be discarded after the production cycle had been completed. This was because only sterilzed product can be admisnistered to rabbit for pyrogen tests.

6.3 Investigation of endotoxin-induced protein coagulation in *Archachatina marginata*

Archachatina marginata is a gasropod, found in the forest and savannah zones of West Africa. In Nigeria, it is a source of dietary protein, eaten in stews and soups. In traditional practice,

the haemolymph of the snail is applied as disinfectants to baldes and fresh cuts of circumscicion. This was believed to prevent sepsis of the wound and speed of healing of the fresh cuts of circumscision. Endotoxin–binding properties of the snail's haemolymph fraction was first reported by Salawu *et al.* (2011).

Fig. 12. *Archachatina marginata* (Source: Salawu, 2011)

In the research, the haemolymphs of the snails were collected by the apical cracking method (Ogunsanmi *et al*., 2003). The haemolymph was mixed with anticoagulant and plasma was obtained by centrifugation. The pellets was washed with anticoagulant, followed by 0.1 M $CaCl_2$ and the pellet containing the hemocytes (amebocytes) were homogenised and suspended in buffer. Exposure of the fractions from the hemocytes: hemocyte lysate (HL), hemocyte lysate supernatant (HLS) and hemocyte lysate debris (HLD) and the plasma were respectively incubated at 37°C for 1 h with endotoxin (1EU/ml) and calcium ions. Controls were set up with the fractions exposed to endotoxin-free water (<0.025 EU/ml) and calcium ions. The fraction exposed to endotoxin produced coagulates which had higher protein content than those exposed to endotoxin-free water. Further investigation reveaealed that combination of plasma and HL of the snail in various ratios produced optimal protein coagulation at a plasma: HL ratio of 1:1. Exposure of the mixture producing the optimal coagulation to varied concentrations of endotoxin ranging from 1 to 5.0 EU/ml, followed by incubation at 37 °C for 1h produced protein coagulation in the mixture which was linear up to a concentration of 1EU/ml. Further increase in endotoxin did not elicit icrease in protein coagulation. There was a drop in coagulation at endotoxin concentrations above 1EU/ml. From this study, it was concluded that the haemolymph of A. marginata contained endotoxin-binding proteins. It was suggested that the haemolymph may serve as a souce of endotoxin detection and quantification kit for testing parenteral solutions in the future (Salawu *et al*., 2011).

The choice of *Archachatina marginata* was inspired by the traditional medicine practice which had no scientific backing. *A. marginata* moves by creeping on soil, wood and rock surfaces and produces slime from its foot which binds dirt and possibly entraps microbes found along its path. Such an immunological adaptation suggests a very strong defence againt

pathogens which was thought to be worthy of study in respect of endotoxin. This effort has opened more investigation and a possibility for development of '*Archachatina Amebocyte* Lysate' (AAL) kit for testing endotoxin.
This on-going research in the University of Ilorin, Nigeria, is promising in terms of having a tropical source of test kit for pyrogen status of parenterals and hence more affordable and safer, locally produced intravenuous fluids in Nigeria. A success of this research will be a great contributon to delivery of critical care in the developing countries, especially Nigeria.

7. Conclusion

Emphasis should be placed on degradation/stability studies of drugs because improper storage and distribution of pharmaceuticals can lead to their physical deterioration and chemical decomposition resulting in reduced activity and occasionally, in the formation of toxic degradation products.
The increasing rate of introduction of fake and adulterated drugs into sub-saharan Africa countries markets makes development of alternative analytical methods a necessity due to lack of reagent and unavailability of equipments required in official books
Studies of Adsorption of pharmaceuticals to excipients and additives are needed in order to investigate their interaction which may affect bioavailaibility of the drug. The clinical usefulness of these additives and excipients in the management of acute toxicity in drug overdose patients can be discovered from in-vitro adsorption study.

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Wide Spectra of Quality Control

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Quality control is a standard which certainly has become a style of living. With the improvement of technology every day, we meet new and complicated devices and methods in different fields. Quality control explains the directed use of testing to measure the achievement of a specific standard. It is the process, procedures and authority used to accept or reject all components, drug product containers, closures, in-process materials, packaging material, labeling and drug products, and the authority to review production records to assure that no errors have occurred.The quality which is supposed to be achieved is not a concept which can be controlled by easy, numerical or other means, but it is the control over the intrinsic quality of a test facility and its studies. The aim of this book is to share useful and practical knowledge about quality control in several fields with the people who want to improve their knowledge.

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