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QUALITY ASSESSMENT STUDIES OF FIVE DIFFERENT BRANDS OF SILDENAFIL CITRATE MARKETED IN NIGERIA

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ABSTRACT

Quality is phenomenon that characterizes a thing and every pharmaceutical company strives for itbut often a time it is very difficult to achieve. The quality of a pharmaceutical product is very important to achieve by following certain parameters that are specified in respective monograph. This research work aim to investigate the quality of five different brands of Sildenafil Citrate (Viagra®, Upgra, Manup, Man-G, Vega) marketed in Nigeria which in turn would help determinewhether they meet the British or United States Pharmacopeia (BP /USP) requirement. The brands of these drugs were all purchased in Nigeria. The various brands were subjected to physical parameter tests such as weight uniformity, hardness, friability, disintegration, dissolution, and percentage content of active ingredient tests. All the brands except Upgra met the BP specificationfor weight uniformity. From the experiment on friability and disintegration it was seen that all thebrands met the official requirement. In the test for hardness all the tablets from the innovator brandpassed the test, only 8 tablets passed for Man-G, all the tablets from the remaining brand did not meet the specification. From the dissolution result it was seen that all brand failed as they did not meet the requirement of releasing at least 80% of its active substance at 30minutes. From the experiment on percentage content of active ingredient only three brands (Man-G, Vega, Upgra) fell within USP specifications, the innovator and Manup were outside USP specification (114.9 % and 113.9 % respectively).

KEYWORDS: Sildenafil, Disintegration, Friability, Weight uniformity, Dissolution.

INTRODUCTION

Quality control is a process that is carried out to ensure a desired level of quality of a product.[1-5] ISO84-1986 standard defines quality in the totality of features and characteristic of a product or service that bears its ability to satisfy stated or implied needs.[6-8] Quality control checks the quality of a product during manufacturing, it also directs the extent and degree of experience of the process and product.[9-10] Quality control sums up all the procedures and processes carried out to verify the efficacy, safety, and quality of drug products from the point of acquisition of raw materials used in production to the point of distribution which will in turn provide security todoctors, pharmacist, and patient.[11,12]

Importance of quality control

Quality control serves as a means of ensuring that pharmaceutical products meets the approved standards and hence fit for use. It is also necessary for the production and distribution of quality and effective pharmaceuticals since quality products are necessary to for the overall health and well-being of consumers. One of the aims of quality control is to ensure public safety and build trust and security for distributors and consumers alike. It provides a routine monitoring operatingsystem for drug manufacturing companies to ensure that both raw materials used and the final products are safe and effective.

Limitations of quality assessment of drugs

Manufacturing companies prioritize testing of the finished product with less scrutiny on the quality of the raw materials used[12] It is important to ensure that materials used in production are non-contaminated, safe and of pharmaceutical grade in order to establish the purity and safety of finished products. Another setback in quality assessment is the lack of periodical validation and calibration of instruments/equipments to ensure efficiency and accuracy.[12]

Instruments /equipments performance may decline over a duration of time, hence periodical checks are necessary to ensure that they meet approved standards. It is equally important to consider in-process sample testing (for blend uniformity or dissolution) which are usually not adequate in mass production processes. This is because sampled units are selected from a large population of materials and does not adequately represent the variability that may occur in a vastmajority of the whole batch.[12]

Description of compound

Sildenafil citrate is chemically designated as 2-Hydroxy-1,2,3-propanetricarboxylate-1-[3-(6,7- dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d-pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- 4-methyl-piperazine. It has a molecular formula of $C_{22}H_{30}N_6O_4S.C_6H_8O_7$, a molar mass of 474.5764 g/mol. Sildenafil citrate is a white to off-white crystalline powder soluble in Dimethyl formamide (DMF), acetic acid and slightly soluble in methanol. Solubility of sildenafil citrate is pH dependent and it decreases with increase of pH. pH ranges between 3.7 and 3.8 and the pKa from 8.2 to 9.6. Sildenafil citrate is an achiral substance. No polymorphic forms of sildenafilhave been observed.[13]

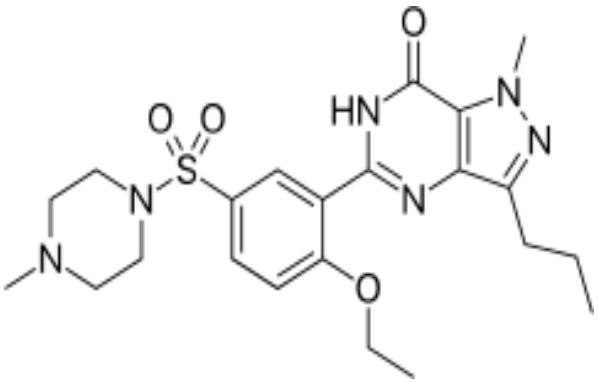
Indications: Sildenafil is used to treat erectile dysfunction and pulmonary arterial hypertension in adults.[14-16] It acts by inhibiting phosphodiesterase (PDE-5), increasing cyclic guanosine monophosphate cGMP to allow smooth muscle relaxation. The similarities between the structure of cGMP and sildenafil allows sildenafil the ability to mimic cyclic guanosine monophosphate (cGMP). This will prevent the cGMP-specific PDE-5 enzyme from breaking down cGMP thereby increasing its vasodilatory effect.[17-18] Preventing the breakdown of cGMP will increase blood flow to the penis, restore and maintain erectile function following sexual arousal.[14-18] In treating pulmonary hypertension, sildenafil works by dilating the blood vessels and relaxing the smooth muscles of the lungs resulting in a decrease in blood pressure.[16,19-21]

Dosage: For erectile dysfunction, the recommended dose of Sildenafil is 50 mg to a maximum of100mg and not more than one tablet per day.[13,22] It is available as 25mg, 50mg and 100mg tablets for oral administration. Patients are advised to take it about an hour before engaging in sexual activity with or without food, although the presence of food may delay its activity. Dose should be adjusted in patients with liver or severe kidney disease.

For pulmonary hypertension, the recommended dose of sildenafil is 5mg or 20mg for tablet andsuspension to be taken 3 times daily, as intravenous bolus of 2.5mg or 10mg administered 3 times a day. It is available as 20mg tablet, 10mg/ml oral suspension and 10mg/12,5ml injection.[19-21]

Side effects: Intake of sildenafil has been associated with prolonged erections, decrease in bloodpressure, headache, dizziness and vision loss.[22-23]

Interactions: Co-administration with drugs e.g. anti-virals such as ritonavir and indinavir, antibacterials such as clarithromycin and erythromycin, anti-fungals such as ketoconazole and itraconazole, antihypertensives such as amlodipine, tamsulosin, doxazosin etc. will increase the degree of these side effects[16, 22-24] Sildenafil was the first phosphodiesterase-5 (PDE-5) inhibitor approved for use, receiving US Food and Drug Administration approval for use in erectile dysfunction on March 27, 1998.[25]



Sildenafil citrate

Table 1: Different brands of sildenafil Tablets and Their drug information.

S/N	Brands And Manufacturing Companies	BatchNo	NAFDAC Reg No	MfgDate	Exp Date	Country OfOrigin
1	Sildenafil Pfizer	B324703	04_7734	08-2018	07-2023	United Kingdom
2	Sildenafil citrate Mancare pharmaceuticals PVT. LTD.	TSK30	A4-8147	11-2017	10-2020	India
3	Sildenafil citrate 100mg (Man-g) lesanto laboratories	L727001	B4-1257	08-2018	07-2021	India
4	Sildenafil citrate 100mg(Vega 100)	VJ-809		02-2018	01-2021	India
5	Sildenafil citrate 100mg (Upgraforte 100) Fredun Pharmaceuticals Ltd	B4-0945	FK789	11-2017	10-2019	India

Table 2: Organoleptic properties of brands of sildenafil tablets studied.

No	Brand Name	Color
1	Sildenafil citrate 100mg(Viagra)	Indigo Carmine
2	Sildenafil citrate 100mg(Manup)	Indigo Carmine
3	Sildenafil citrate 100mg (MAN-G)	Brilliant Blue FCF
4	Sildenafil citrate 100mg(Vega 100)	Indigo Carmine
5	Sildenafil citrate 100mg (UPGRA FORTE 100)	Brilliant Blue FCF

METHODS

Weight uniformity

This test was performed as described in the British Pharmacopoeia 2009. Twenty tablets were selected randomly and weighed individually using an analytical balance. The mean tablet weight and standard deviation were then calculated for.

Friability test

The tablets were accurately weighed prior to testing. The weighed de-dusted tablets were then subjected to a well-defined level of agitation in a fixed geometry closed chamber (friability apparatus). The friability apparatus was placed at 25 rpm for 4 mins (100 revolution). After the revolution the tablets were weighed again.

Hardness test

The hardness of 10 tablets selected randomly from each batch was determined using a hardness tester. The mean hardness and the standard deviation were calculated.

Disintegration

The ERWKA disintegration test apparatus was used based on the British Pharmacopoeia 2009 method. The disintegration medium was water filled to 700 ml in the vessel maintained at 37^0C. Six tablets from each of the batches were selected randomly the disintegration time was taken as the mean time needed for the tablets to break into particles small enough to pass through the screeninto the disintegration medium.

Extraction of active ingredient

Four tablets of the innovator brand (Viagra), each containing 100 mg of sildenafil citrate was

weighed transferred into a ceramic mortar and crushed until a smooth powder was formed. A 400ml quantity of methanol was measured and transferred into the mortar. The mixture was stirred and transferred into a suction filtration unit, the mixture was carefully filtered. The filtrate containing dissolved pure drug sample were then poured into a crucible and placed over a water bath at 60^{o}C until all the solvent was evaporated. The crystals formed after evaporation were further purified by recrystallization and used for the calibration plot.

Preparation of stock solution and different concentrations of sample

50 mg of pure sample was weighed and transferred into a beaker, 100 ml of distilled water was then added to give a stock solution of 1 mg in 2 ml from which: 0.10 ml, 0.150 ml, 0.20 ml, 0.250 ml, 0.30 and 0.35 ml were pipetted respectively and transferred into a calibrated volumetric flask,distilled water was then added to make up 10 ml affording a concentration of 5 ng/ml, 7.5 ng/ml, 10 ng/ml, 12.5 ng/ml, 15 ng/ml, 17 ng/ml respectively.

Determination of beer-lambert curve

The UV spectrophotometer was then calibrated and a wavelength of 253 nm was ascertained for drug sample. The different concentrations of pure sample were placed in a cuvette and the absorbance was taken at various concentrations. The absorbance gotten was the used to plot the Beer-Lambert curve.

Dissolution test

A 900 ml quantity of distilled water was poured into the 1000 ml vessel and immersed into the dissolution apparatus. The water contained in the dissolution apparatus was placed and maintainedat a temperature of 37^{0}C. The tablets were then added to the center bottom of the vessel and the paddle was rotated at 100 rpm. 10 ml of the dissolution medium was withdrawn from each of the vessels with the aid of a pipette after 2,5,10,15,20,25,30,40,50 and 60 minutes respectively and an equivalent amount of the dissolution medium was immediately introduced as a replacement each time.

The samples were filtered and a 10-fold serial dilution (1 ml of the dissolution medium made up to with 10 ml of distilled water) was carried out. The actual concentration of the different batches was then determined by measuring the absorbance at 253 nm using a UV spectrophotometer. Usingthe standard curve already prepared with the reference standard the percentage of drug released was determined for the tablets.

Content of active ingredient

Twenty tablets were randomly selected from each of the batches and weighed together, the tablets were then crushed in a mortar with the aid of a pestle, an amount equivalent to the theoretical content of each tablet (average) of the crushed tablets was weighed out. The weighed powder was then dispersed in distilled water and filtered. Analysis was carried out for the content of active ingredient with the aid of a UV spectrophotometer.

Weight uniformity

Mean weight= total weight of tablets ÷ total number of tablet

$$\% \text{ deviation} = \frac{\text{weight of individual tablet} - \text{mean weight}}{\text{Mean weight}}$$

Friability

The abrasion resistance (**B**) is calculated as $B = (W0-W/W0) \times 100$

W0= Initial weight of tablets W= finial weight of tablets

Table 9: Results of friability tests for the different brands of sildenafil citrate tablets marketed in nigeria.

Drug	Initial weight(W0)	Final weight	Friability
Upgra	5.9330 g	5.9340 g	-0.02 %
Manup	6.8800 g	6.8810 g	-0.04 %
Man-G	6.0780 g	6.0770 g	0.02 %
Vega	6.1770 g	6.1770 g	-
Viagra	6,2610 g	6.2610 g	-

Hardness test

Table 10: Results of hardness test for different brands of sildenafil citrate tablets marketed in Nigeria.

UPGRA force)	MANUP force)	MAN-G force)	VEGA force)	VIAGRA force)
9.5	4.0	8.0	4.5	7.5
4.0	3.5	7.5	2.0	6.5
4.0	3.5	8.5	3.5	6.0
3.0	3.0	11.5	2.5	7.5
4.5	3.5	8.5	2.0	6.5
4.5	2.0	8.5	3.5	7.0
4.5	3.0	7.5	3.5	6.0
4.5	3.0	8.5	3.5	6.0
3.5	3.0	8.5	3.5	7.5

4.5	3.5	9.0	3.5	6.5
Mean/SD 4.65±1.780293	Mean/SD 3.2±0.537484	Mean/SD 8.6±1.125463	Mean/SD 3.2±0.788811	Mean 6.7±0.632456

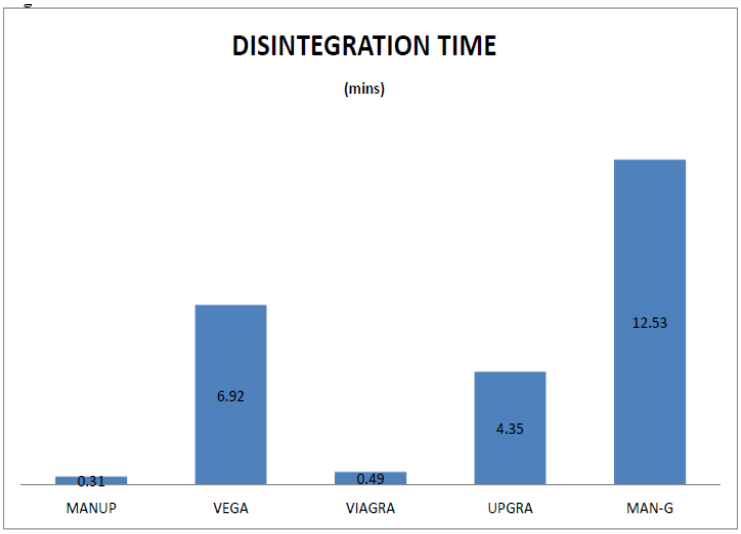
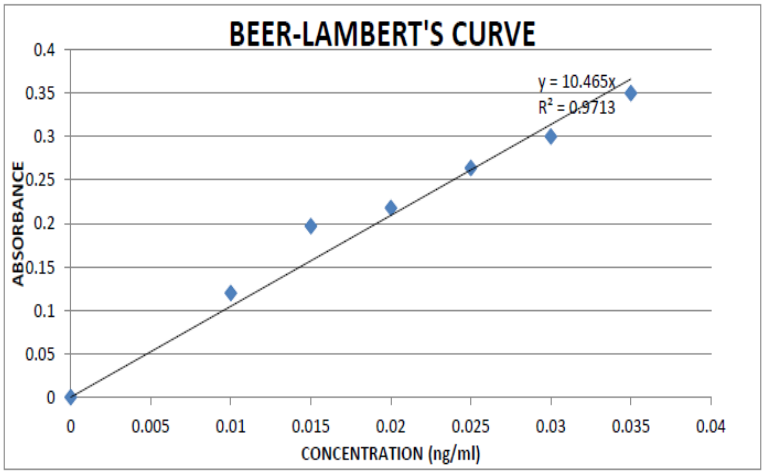


Fig 1: Results of disintegration time for the different brands of sildenafil marketed in nigeria.



Wave length of UV= 253 nm

Fig. 2: Standard calibration curve for sildenafil citrate.

Content of active ingredient

The content of active ingredient of a tablet is given as

% content = (Absorbance of drug sample ÷ Absorbance of pure sample) x 100 [26]

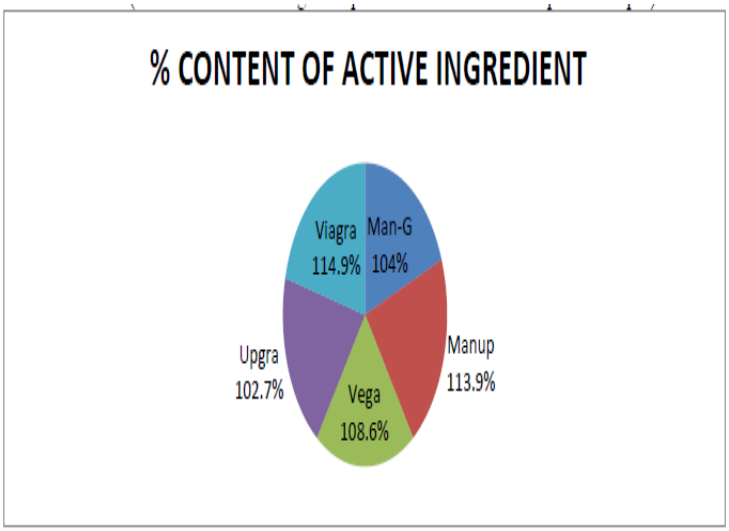


Fig 3: Chart Result for % Content Of active Ingredient of Different Brands of SildenafilCitrate Tablets Marketed in Nigeria.

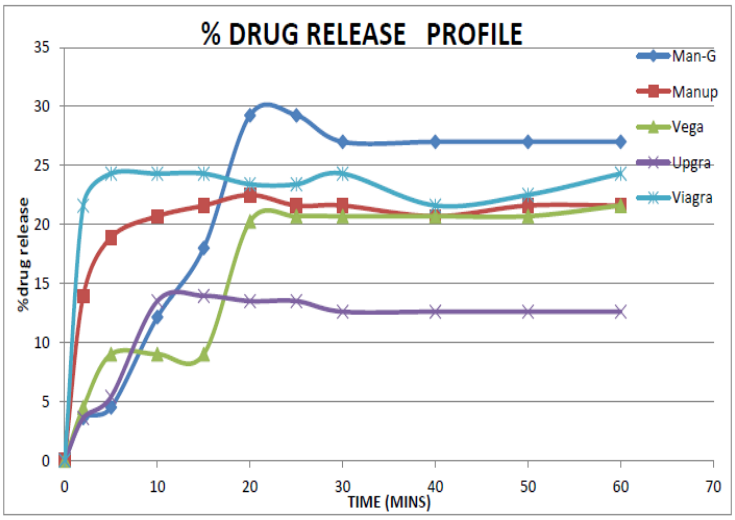


Fig. 4: % Drug release profile for different brands of sildenafil citrate tablets marketed in nigeria.

DISCUSSION

Weight uniformity

The weight uniformity is of concern because it ensures the even distribution of ingredient in a drug. Uneven distribution of ingredient may alter doses of individual tablets which may lead to loss of therapeutic effect or over dosing of the drug.

The British Pharmacopoeia 2012 specifies that for tablets weighing 324 mg and above, weights of not more than two tablets should deviate from the average weight by more than 5%. From the experiment carried out on Ugra, the average weight was 0.6004 g, 3 tablets

exceeded the 5% specification of the British Pharmacopeia 2012, they deviated from the average by 7.13%, 18.64%, and 9.09%. Therefore, this brand did not meet the BP specification for weight uniformity. The average weight of drugs from Manup brand was 0.6706 g, from the experiment, it was seen that the individual tablets met with the BP specification deviating with not more than 5% as required.From brand Man-G average weight of drug was 0.6163 g, it was seen that individual tablets met with the Bp requirement by not deviating from the average by more 5%. For Vega brand the average weight of the drugs was 0.6166 g, individual tablets in this batch met the not more than 5% deviation from the average requirement of the BP. The average weight from the innovator brand gave 0.6327 g, all tablets in the batch passed the BP requirement for weight uniformity.

Friability

Friability is the phenomenon where the surface of the tablet is damaged or shows a site of damage due to mechanical shock, the essence of friability is to evaluate the ability of the tablets to withstand breakage during the transportation and handling.

According to the BP, percentage of friability should not be greater than 1%. From the experiment carried out, it was seen that all the brands passed the test according to the BP specification of not exceeding 1%. Two of the batches (Upgra and Manup) gave a negative value as a result of moisture effect. Two other batches (Viagra and Vega) gave a zero value which inferred that there was damage to the tablet during the course of the experiment. Factors such as sufficient binder concentration which will result in a tightened interparticulate bonding and adequate compression pressure may have resulted to why these batches were not affected by the mechanical shock.

Hardness test

Generally, it is expected that tablet should be hard enough to withstand pressure from handing, shipping and distribution yet soft enough to be disintegrated after it has been swallowed. The hardness of a tablet is influenced by the amount of pressure applied at the compression stage. It is very important to monitor hardness for drugs that possess real or potential bioavailability problem or drugs that are sensitive to altered dissolution release profile as a function of compressed force employed. The minimum hardness a tablet is expected to have is 5 kg force and the maximum is 8 kg force.[5]

From the experiment, the innovator brand gave the best result for hardness as all its values

fell within expected limit (5-8 kg force). All tablet of brand Vega, Upgra and Manup failed the test, 8tablets in the batch Man-G fell within the expected limit of 5-8 kg force

Disintegration

The rate of drug absorption as well as the therapeutic efficacy of the drug depends on the disintegration time. If the disintegration time is not perfect, we cannot say that effectiveness of thedrug is good.

According to BP 2012, film coated tablets are meant to disintegrate within a period of 30 mins. From the experiment, all the batches passed the test and fell within the normal time limit. Factorssuch as the type and concentration of binder used, method of incorporation, the presence of excessive and overly mixed lubricant, and compression force may affect the way tablets disintegrate.[2]

Dissolution

Both the United States Pharmacopeia 2005 and British Pharmacopeia 2012 specifies that the amount of a drug released (dissolution) should not be less than 80% of the labeled amount at 30 minutes.[10-11]

In the case of the drug studied, the label claimed 100 mg which puts 80% at 80 mg, that is to say at 30 mins, 80 mg of the drug should be released.

Man-G gave the highest release of the drug, at 30 mins it released 27% (27 mg) of its content. Theinnovator brand Viagra at 30mins released only 24.3% (24.3 mg) of its content. Manup and Vega 21.6 %(21.6 mg) and 20.70 %(20.7 mg) respectively. The lowest release was Upgra, at 30 mins,it released only 12.6 %(12.6 mg) of its content.

From the USP and BP specification, it can be inferred that these tablet completely failed the requirement for dissolution profile. Factors that may have resulted to failure of dissolution test include; compressional force used in preparing tablet. The effect of compressional force on dissolution of normal release tablet is difficult to predict. If during the compression fragmentation of granules occur, the dissolution will occur faster as compressional force is increased. This is because the fragmentation increases the specific surface area. However, if bonding of the particles is the predominant phenomenon in compression, the increase in compressional force causes a decrease in the dissolution.[2] Properties of the medicinal compound, excipients present, the type and concentration of disintegrant and lubricant used,

film coating may affect the release of s drug. This because, the presence of film coating increases the adhesive strength of a tablet there by reducing or decreasing its rate of release.[27]

Content of active ingredient

The aim was to assure the presence of the required amount of active ingredient because any significant variation in the amount present in the dosage unit could lead to sub-therapeutic drug levels or overdosing. According to the United States Pharmacopeia convention 2012, the content of active ingredient of a film coated tablet should be within 90-110%. From the experiment three of the brand passed the test and were within pharmacopeia range. The two other brands that did not meet up to specification had a value of 114.9 % and 113.9 % respectively.

CONCLUSION

From the present study, it was clearly demonstrated that not all the brands of Sildenafil Citrate (100 mg) marketed in Nigeria met the official requirement in the quality control tests except for disintegration and friability of which all the brands complied with pharmacopeia specifications. Itwas seen that all the brands in the dissolution test did not release up to 80% of the active ingredientas expected by the official standard. In the weight uniformity only one of the brand (Upgra) deviated from official requirement. Results gotten from hardness test inferred that only two brands (the innovator and Man-G) were within specifications. All the brands except the innovator brand and Manup passed the test for percentage content of active ingredient. There was a significant difference in the quality across the brands of the drug, hence they are not pharmaceutical equivalence. For good quality pharmaceutical product, it is therefore important for regulatory bodies to be more stringent in product evaluation before giving approval for sale and use. Further, there is need for periodic assessment of pharmaceutical products, proper consideration of all the physiochemical properties of the drug and excipient to ensure good quality which in turn infers safe and therapeutically active product.

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