# Screening Microbial Contamination and Physical properties of Some Drugs in Erbil-Kurdistan Region - Iraq

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## Abstract

Present study attempted to determine the microbiological quality and the physical properties of same drug commonly used for disease medication in Erbil.A total of 3924 drugs samples from different retailer drug stores before using for the treatment of patients were subjected to microbiological examinations using: Sterility test and Limulus amebocyte lysate test for injection and medical products . Microbial Limited Test for capsules and syrup(oral suspension ) and biochemical method to detected the viable bacteria and fungi .out of 3924 different drugs samples, 128 samples 73 (57.1%) injection, 9(7.1%) oral suspension , 3(2.3%) capsule ,3(2.3%) eye drop, 2(1.6%) ointment, 9(7.1%) gel and oil and 29(22.7%) tablets samples were found to be contaminated by different types of bacteria. The results show the presence of gram negative pathogens including *Escherichia coli* and *Pseudomonas aeruginosa*, and gram positive pathogens including *Staphylococcus aureus*, there was no growth of fungi. The physical properties of total 403 oral suspensions samples only 9 (2%) samples were not comply with standard rule in assay and related substances test . From 850 injection samples only 73(8.6%) of them were not comply for only assay and related substances test. Out of 200,186,232 ointment, Gel and Oil samples respectively only 3(1.5%) ointment, 9 (3.9%) Gel and 2(1.1%) Oil samples did not comply for density, assay and related substances tests. from 721, 1332 capsules and tablets samples were in comply for most of the test except 3 (4%) capsules and ,29 (2.1%) tablets samples were not comply for assay and related substances test.

Existence of microorganisms in drug samples show that counterfeit and unapproved pharmaceuticals are not manufactured under the same hygienic conditions as medication products .A routine microbiological tests of such drugs are necessary.

**Keywords:** Drug, Microbiological contamination, Physical properties.

## الخلاصة

حاولت الدراسة الحالية تحديد النوعية المايكروبية والصفات الفيزيائية لبعض الادوية التي تستعمل بشكل عام لمعالجة المرضِى في مدينة أربيل. اخضعت مجموع 3924 عينة دواء من مخازن الادوية قبل استخدامها لمعالجة المرضى إلى فحوصِات مايكروبية مثل Sterility test and Limulus amebocyte lysate test lysate للحقنِة والمُنتَجاتِ الطبيةِ، و Microbial Limited test للكبسولاتِ والشراب (معلق فموي ) واستخدم الطرقِ الكيمياوية الحيويةِ للكشف عن البكتيريا والفطرِ تبين بان من مجموع 3924 عينةِ دواءِ مختلفةِ بأن، 128 عينة ,73 (57.1 %) حقنة، 9 (7%) معلق فموي، 3 (2.3 %) كبسولة، 3 (2.3 %) قطرات عينِ، 2 (1.6 %) مرهم، 9 (7 %) هلام وزيوت و29 (22.7 %) عينات أقراصِ كَانت ملوثة بالأنواعِ المختلفةِ مِنْ البكتيريا. بينت النَتائِجُ وجود بكتريا سالبة لصبغة كرام مثل *Escherichia coli*و *Pseudomonas aeruginosa*، ووجود بكتريا موجبة لصبغة كرام مثل *Staphylococcus aureus*، مع عدم وجود أي نمو فطري. وكَانت الصفات الفيزيائية لمجموعِ 403 عينةَ معلق فموي فقط 9 (2 %) ومِنْ 850 عينةِ حقنِة فقط 73 (8.6 %) عينة غير مطابقة للقاعدةِ القياسيةِ لاختبار assay and related substances.و من 200,186,232 عينات مرهمِ ,هلامِ وزيوت على التوالي فقط 3 (1.5 %) مرهم، 9 (3.9 %) هلام ، و2 (1.1 %) عينات زيوت كَانتْ غيرمطابقة لاختبار density, assay and related substances tests. و721, 1332 عينات الأقراصَ والكبسولاتَ كانت مطابقة لأغلب الإختباراِت الصفات الفيزيائية ماعدا 3 (0.4 %) كبسولات، و29 (2.1 %) عينات أقراصِ كَانتْ غير مطابقة لاختبار assay and related substances.

إن وجود الكائنات الحيّة المجهرية في عيناتِ الدواءِ يبين أنّ بعض المواد الصيدلانيةِ لَمْ تُصْنَعُ تحت نفس الشروطِ الصحّيةِ كمُنتَجات دوائية؛ لذا من الضروري إجراء الفحوصات المايكروبية الروتينية لهذه الأدوية .

**الكلمات المفتاحية:** الأدوية ، التلوّث المايكروبي ، الصفات الفيزيائية

## Introduction

The microbiological contamination extent in the pharmaceutical drugs, especially those with liquid and semi-solid formulations are not unlikely due to several discrepancies in the Good Manufacturing Practice (GMP), presence of microorganisms in the manufacturing water, raw materials, lack of microbiological monitoring of the equipments and manufacturing environment, packaging defect, personal unhygienic casualty, improper storage humidity and temperature, etc. (Hossain *et al*.,2014; Das *et al*.;2013).

The major advantage of tablets as a dosage form is that they provide an accurate dosage of medicament. Each tablet must contain a known amount of drug and must be uniform in diameter, appearance and weight. Tablets for oral use once swallowed whole, should readily disintegrate in the stomach. This property represents a great paradox in formulation, hence tablets should be produced with sufficient strength to withstand the rigors of processing coating and packaging, yet be capable of order to release the drug rapidly. This disintegration involves the bursting apart of the compact by aqueous fluids penetrating the time residual pore structured the tablet (Ifeyinwa and Florence, 2006).

The active ingredient must be pharmacologically available and since drugs cannot be absorbed into the blood stream from the solid state, the active ingredients must dissolve in the gastric or intestinal fluids before absorption can take place. One of the major setbacks commonly encountered is that carried by the storage due to microorganisms. Spoilage of pharmaceutical products could occur over a temperature range from about -20$^{O}$C to 60$^{O}$C, although it is generally poor at the extremes. The effect of transportation and storage of products at ambient temperatures in the tropics or subtropics should be considered in this respect.It is known that some microorganisms make use of some tablets such as starches used as binders and disintegration as substrates for their growth (Ifeyinwa and Florence ,2006).

The aim of the study is to detect important contaminants (bacteria and fungi) for all kinds of pharmaceutical products and the physical composition of same drug commonly used for disease.Drug product is critical quality attribute of pharmaceutical products. Safety and efficacy of drug product are important during development via clinical studies

## Materials and Methods

### Study protocol

This study was conducted between January 2014 and July 2015. The Ethics Committee of Hawler Medical University, Erbil, Iraq, approved the protocol. A total of 3924 different drugs samples labeled with manufacturing and expiry dates from different retailer drug stores in Erbil city before using for the treatment of patients were subjected to microbiological examinations; i.e. Sterility test and Limulus amebocyte lysate (LAL) test for injection and medical products, Microbial Limited Test for capsules and syrup, to detect the viable bacteria and fungi. Then the physical properties of same drug were studied.

### Microbiological tests:

**1- Sterility test for detection of bacteria and fungi in intravenously injection and medical products samples**.

Bacteria and fungi are important contaminants for all kinds of pharmaceutical products, including biopharmaceuticals; hence, the control of them is of critical importance. The control of both bacteria and fungi is considered to be worthy of mandatory tests for nearly all kinds of pharmaceuticals in pharmacopoeias. Since

almost all the biopharmaceuticals are administered intravenously, general sterility testing must be carried out for these products to evaluate whether a sterilized pharmaceutical product is free of contaminating microorganisms. This test is done as following:

**Procedure**

The main method used for sterility test was filtration of the test material through a sterile membrane filter with a pore size of 0.45 μm; which is designed to retain microbial contaminants while permitting the passage of liquid by using a Laminar Air Flow (LAF),then, the filter containing any microorganisms present in the fluids is divided aseptically,and portions are transferred to the media. The European Pharmacopoeia proposes two media for sterility testing:(1) fluid mercaptoacetate medium (also known as fluid thioglycollate medium), which is mainly appropriate for the culture of anaerobic organisms at 30–35°C; and (2) soya bean casein digest medium (Trypton Soya Broth), which is used for the culture of both aerobic bacteria at 30–35°C and fungi at 20–25°C. If the product cannot be filtered, then direct inoculation, immersion, in-situ incubation or combination methods as appropriate are acceptable (European Pharmacopoeia ,2002;Pharmacopocia, 2006).

**2. Limulus amebocyte lysate (LAL) for detection of Endotoxins**

This is a post sterilization test; bacterial endotoxin is the most significant pyrogen in the parenteral drug and medical device industries because of its extreme potency and ubiquity in nature. Pyrogen is found on every site or substance where bacterial growth takes place. The endotoxin limit for the intravenous administration of pharmaceutical and biological products is 5 endotoxin units (EU)/kg of body weight/hour by all pharmacopoeias, most of the biopharmaceuticals are administered intravenously, finished-product biopharmaceuticals must be sterile and free from pyrogenic substances (Magalhaes *et al*., 2007). Hence, the detection and removal of pyrogenic substances, especially endotoxins (lipopolysaccharides in the cell wall of gram-negative bacteria), are necessary to ensure safety of biopharmaceutical products. Nowadays, the most widely used endotoxin detection systems are based on the highly sensitive LAL test. It is based on the coagulation cascade of the blood of a horseshoe crab, Limulus polyphemus, which is induced by lipopolysaccharide. The LAL reagent is introduced to a sample, and the test material is considered endotoxin positive if a gel is formed via a clotting reaction. Color intensity produced is proportional to the amount of endotoxin present in the sample. (Petsch and Anspach, 2000; Salema *et al*.,2009).

**3-Microbial Limited Test (MLT)**

Generality: This test provides estimation of the number of viable aerobic microorganisms present and for freedom from designated microbial species in pharmaceutical articles of all kind products. The microbial limits test includes total aerobic bacteria , molds and yeasts in tablet, capsules, cream and syrup. This test is done as following:

**Procedure**

1-To minimize the risk of extraneous contamination in preparing and applying the microbial tests care were taken. In this test 45ml of Soya bean Casein Digest Broth media for bacteria and Sabouraud Dextrose agar for fungal with 10% of polysorbate for dissolved the sample.Ten gram or 10mL for each specimen to be tested provide separately). 1 mL of the specimen was transferred onto each of 2 sterile Petri dishes containing about 20mL of medium allowed the liquid to be absorbed into the agar by rotating the Petri dishes.

2-The Petri dishes were covered inverted and incubated at 35+ 2$^{o}$C for 48 to 72 hours for bacterial growth and at 22.5 + 2.5$^{o}$C for 5 to 7 days for fungal growth.

3- Following incubation, the results were observed by examine the plates for growth: In case no growth appeared in the media: The result was: Absence of pathogens.In case growth appeared in the media, screening is performed by other tests.

4-Colonies showing characteristics of the specific organism are then confirmed using appropriate tests and biochemical tests. If upon examination, Yellow colonies with yellow zones appeared, gram stain: positive cocci in clusters may indicate the presence of *Staphylococcus aureus*. Tests for Identification of *Staphylococcus aureus* were done as follows:

To identify Staphylococcus from other cocci perform, the pure colony streak onto a Mannitol salt agar plate and incubate at 32 $^{\circ}$C for growth for a maximum of 3 days. At the same time streak the suspected organism onto a nutrient agar plate and incubate at 32 $^{\circ}$C for 48 hours. Also mannitol salt agar was used for selective *Staphylococcus aureus*. Then Coagulase test was done in which by an inoculating loop, suspect colonies transferred representative from the agar surfaces (Mannitol Salt Agar Medium) to individual tubes, each containing 0.5ml of mammalian, preferably rabbit or horse ,plasma with or without suitable additives. Incubated at 37$^{\circ}$C, the tubes examined at 3 hours and subsequently at suitable intervals up to 24 hours. Test positive and negative controls simultaneously with the unknown specimens. If no coagulation in any degree is observed, the specimen meets the requirements of the test for absence of *Staphylococcus aureu*s (Panjarathinam 2009). Also Catalase test which is an enzyme that provides the destruction of peroxides obtained during the oxidation reaction. $2H_2O_2 \rightarrow 2H_2O + O_2$ were done if Catalase (+): the microorganism is *Staphylococcus* spp (Panjarathinam ,2009).

5-For gram negative bacteria, the pure colony streak onto a MacConkey agar and eosin methylen blue agar plate and incubate at 32 $^{o}$C for growth for a 24-48h for identification of *Escherichia coli*. If brick red gram negative rods and red/pink colonies appeared on the MacConkey agar plate, dark blue-black colonies with metallic green sheen on Eosin Methylen Blue agar plate indicates the presence of *Escherichia coli* ( Panjarathinam 2009).

At the same time the suspected organism was streaked onto a Pseudomonas Cetrimide agar plate and incubate at 32 $^{o}$C for 48 hours for, *Pseudomonas aeruginosa*, If upon examination, greenish colonies appeared, gram stain: negative rods may indicate the presence of *Pseudomonas aeruginosa*. Oxidase test: Discs was impregnated with dimethyl-p-phenylene diamine. The disc was take out with sterile forceps and soaked in sterile distilled water. A suspect colony on the agar was placed alongside. If the suspect colony contains oxidase, it was turned dark purple, then black indicating the presence of *Pseudomonas aeruginosa* if oxidase test is negative, colony undergoes no change in color indicating the "absence of *Pseudomonas aeruginosa*". Also at the same time the suspected organism was streaked onto a Bismuth Sulphite agar ,Brilliant green agar and XLD agar for *Salmonella* sp. (In the case of needing to perform the test).The motility test were also done ( Panjarathinam 2009).There was no growth of fungi.

**Common physical tests for Injection, oral suspension, eyes drops , capsules and tablets:**

Common tests include description, identification, average fill volume, particulate matter contamination(Visible particle-Necked eyes and sub-visible particle-instruments for Injection), density, assay and related substances (Average

weight, uniformity of weight, uniformity of content, hardness, disintegration test ,dissolution test for tablets).All these tests were done as in The European Pharmacopoeia (European Pharmacopoeia ,2002).

## Results and discussion

A total of 3924 different drug samples labeled with manufacturing and expiry dates from different retailer drug stores located within the city of Erbil were subjected to microbiological examinations, Sterility and Limulus amebocyte lysate (LAL) tests for injections and medical products. Microbial Limited Test (MLT) was also used for capsules and syrup, to detect the viable bacteria and fungi. As it can be noticed in (Figure 1) 48.20% of the samples subjected to LAL and sterility test and 51.80% samples subjected to MLT test.

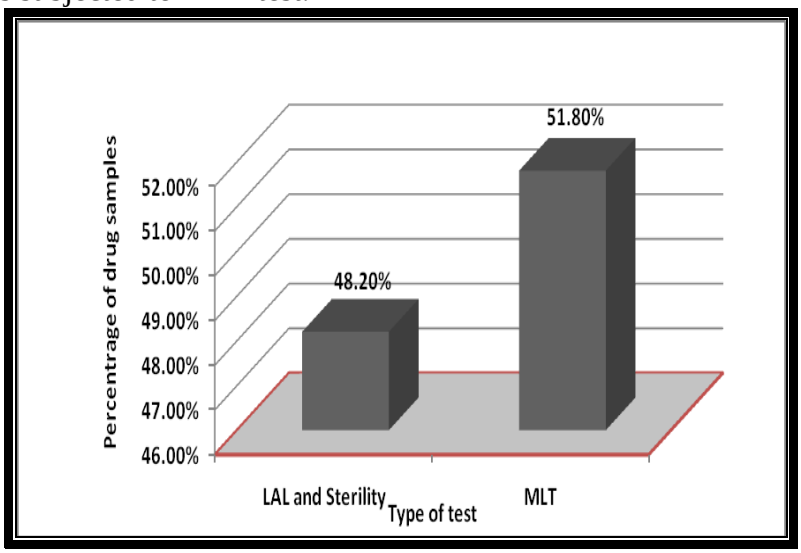


**Figure (1) Percentage of drug samples subjected to LAL, Sterility and MIT test.**

Smaller numbers of opportunistic pathogens become infectious when resistance mechanisms are impaired, either by severe underlying disease, or through receiving immunosuppressive drugs (Manu-Tawiah *et al*.,2001,Noor *et al*.,2012). Microbial contamination of drugs is more important for patients, who are taking the drugs. Therefore, it is very necessary to examine the efficacy and/or potency of some drugs, those are very commonly used for the diseases medication. However, microbiological studies of these drugs in Erbil are still in infancy. (Table 1) showed that, out of 3924 different drug samples labeled with manufacturing and expiry date that have been studied, 128 samples were contaminated by different types of bacteria [73 (57.1%) injections,9(7%) oral suspension, 3(2.3%) capsule, 3(2.3%) eye drop, 2(1.6%) ointment ,9(7%) gel and oil and 29(22.7%) tablets samples]. There was no growth of fungi .

In MLT, in case growth appeared in the media (Figure 2), screening was supported by other tests. Examination for the presence of gram negative pathogens including *Escherichia coli* and *Pseudomonas aeruginosa*, and gram positive pathogens including *Staphylococcus aureus* explained in (Table 2) which shows morphological and characteristic of specific pathogenic bacteria on selective media in all the samples tested. If upon examination, yellow colonies appeared, gram stain: positive cocci in clusters may indicate the presence of *Staphylococcus aureus*. To identify Staphylococcus from other cocci the colonies were subcultured onto a

Mannitol salt agar plate (Figure 3). Coagulase and Catalase tests were also done to support the cultivation results. For gram negative bacteria, the pure colony streak onto a MacConkey agar and Eosin Methylen Blue agar plate and for identification of *Escherichia coli*. If brick red gram negative rods colonies appeared on the plate, the test specimen indicate the presence of *Escherichia coli* (figures 4 and 5). At the same time the suspected organism was streaked onto a Pseudomonas Cetrimide agar plate for *Pseudomonas aeruginosa*, if upon examination colonies appeared, gram stain: negative rods may indicate the presence of *Pseudomonas aeruginos*a for which Oxidase test was performed. Characteristics of the specific organism are then confirmed using appropriate biochemical tests (Table 3).

**Table (1) Number of contaminated drug samples by different types of bacteria**

| Samples | Injection | Oral suspension | Capsules | Eye drops | Ointment | Gel and Oil | Tablet | Total |
|---|---|---|---|---|---|---|---|---|
| Number | 73 | 9 | 3 | 3 | 2 | 9 | 29 | 128 |
| Percentage | 57.1 | 7 | 2.3 | 2.3 | 1.6 | 7 | 22.7 | 100% |

**Table (2) Morphological and characteristic of bacterial colonies on selective edia**

| Isolates | Selective medium | Characteristic colonial morphology | Oxidase test | Coagulase test | Catalase test | Gram stain |
|---|---|---|---|---|---|---|
| ***S.aureus*** | Mannitol salts agar medium (Chapman) | Yellow colonies with yellow zones | - | + | + | Positive cocci clusters |
| ***P.aeruginosa*** | Cetrimide agar medium | Greenish | + | | + | Negative rods |
| | Pseudomonas Selective agar | Greenish | + | | + | Negative rods |
| | Hektoen agar medium | Green colonies with black centers | - | | - | Negative Rods |
| ***E. coli*** | MacConkey agar medium | Brick red | - | | + | Negative Rods |
| | Eosin Methylen Blue Medium | Brick red | - | | + | Negative Rods |


Figure (2) Bacterial colonies on nutrient agar


Figure (3) *S.aureus* colonies


Figure (4) *E.Coli* colonies on MacConkey agar


Figure (5) *E.Coli* colonies on EMB agar

**Table (3) Confirmative biochemical identification of the isolates**

| TSI | | | | Motility | Indol production | MR | VP test | Citrate utilization | Confirmed bacterial isolate |
|---|---|---|---|---|---|---|---|---|---|
| Slant | Butt | H2S | Gas | | | | | | |
| A | A | − | − | − | − | − | + | + | *P.aeruginosa* |
| K | A | − | − | − | − | − | + | − | *S.aureus* |
| K | A | + | + | + | − | + | − | − | *E. coli* |

Ingredients, raw materials, unhygienic environmental condition and lack of aseptic handling would be the main factors for the observed microbial growths in the samples studies (Lund, 1994; Parker ,2000 ; Najmuddin *et al*., 2010). To minimize the load of microbes and the possibility of spoilage during the preparation of liquid drugs, different antimicrobial agent or chemical preservatives(parabens, quaternary ammonium compounds, sorbic acids, formic acids etc.) may be used (Denyer *et al*.,2004). *Staphylococcus* spp. might transmit from soil and hands of handler during the preparation of drugs, their incidence does not always mean that the consumption of drugs is potentially be hazardous to users as not all the strain of *Staphylococcus* spp. can necessarily produce enterotoxin (Gad *et al*.,2011). Present of

coliform and pathogenic bacteria indicated that fecal contamination of water might occur. Unhygienic environmental condition and improper handling of raw materials, ingredients and products might be the cause of contamination **(**Beys and Hoest , 1971).

Most patients are usually supposed to be immune-compromised when they taking drugs which accelerate the chances of diseases acquired by opportunistic pathogens. Therefore, presence of any microorganism should be considered undesirable for all drugs. Presence of specific gram negative enteric bacteria was found in the tested samples, presence of viable bacteria especially gram positive ones along claimed a sort of public health risk associated with the consumption of those drugs. The compliance sectors among the different retailer drug stores located within the city of Erbil should strictly deal with microbial stringency within the manufacturing, packaging, distribution and storage of pharmaceutical products. Present situation might be of global significance in terms of public health measure and hence, a regular microbiological examination of oral drugs is suggested, especially in the developing countries.

Physical properties were examined by some common tests for different types of drugs. Table (4) demonstrated the description, identification, average fill volume ,average fill volume ,particulate matter contamination ,density, assay and related substances tests for oral suspensions, total 403 oral suspensions samples were in comply with standard rule for description, identification ,average fill volume ,average fill volume ,particulate matter contamination and density test and only 9 (2%) samples was not comply with standard rule in assay and related substances test . Table (5) shows the common tests for 850 injection samples only 73(8.6%) of them was not comply for only assay and related substances test. Common tests for eyes drops and ointment, Gel and Oil were explained in table ( 6) out of 200,186,232 ointment ,Gel and Oil samples respectively only 3(1.5%) ointment ,2(1.1%) Oil and, 9 (3.9%) Gel samples not comply for density ,assay and related substances tests .The common tests for capsules and tablets was detail in table (7) in which all 721, 1332 capsules and tablets samples were in comply for most of the test except 3 (0.4%) capsules and,29 (2.1%) tablets samples was not comply for assay and related substances test.

The major advantage of tablets as a dosage form is that they provide an accurate dosage of medicament. Each tablet must contain a known amount of drug and must be uniform in diameter, appearance and weight. Tablets for oral use once swallowed whole, should readily disintegrate in the stomach. This property represents a great paradox in formulation, hence tablets should be produced with sufficient strength to withstand the rigors of processing coating and packaging, yet be capable of order to release the drug rapidly (Obuekwe *et al*.,2001). This disintegration involves the bursting apart of the compact by aqueous fluids penetrating the time residual pore structured the tablet. The active ingredient must be pharmacologically available and since drugs cannot be absorbed into the blood stream from the solid state, the active ingredients must dissolve in the gastric or intestinal fluids before absorption can take place. The incidence of counterfeiting pharmaceutical products and the proliferation of substandard quality medicines has been well identified internationally and constitutes serious health hazards. It is primarily flourishing in developing countries where institutional capacity in regulation, inspection and law enforcement is weak and adequate funds for regular drug quality monitoring are missing (Najmuddin *et al*.,2010).

Counterfeiting of pharmaceutical products can take all kinds of form, but the end result is, when administered to a patient that the consequences range from

treatment failure increased toxicity, increased drug resistance to malaria, TB and AIDS, and even outright death as a result of any of the above (Richard,2008).

**Table (4) Common tests for oral suspensions**

| Common tests | Total sample | No. of not comply sample | percentage of not comply sample |
|---|---|---|---|
| Description | 403 | 0 | 0% |
| Identification | 403 | 0 | 0% |
| Average fill volume | 403 | 0 | 0% |
| Particulate matter contamination | 403 | 0 | 0% |
| Density | 403 | 0 | 0% |
| Assay | 403 | 9 | %2.2 |
| Related substances | 403 | 9 | %2.2 |

**Table (5) Common tests for injection samples**

| Common tests | Total sample | No. of not comply sample | percentage of not comply sample |
|---|---|---|---|
| Description | 850 | 0 | 0% |
| Identification | 850 | 0 | 0% |
| Average fill volume | 850 | 0 | 0% |
| Particulate matter contamination | 850 | 0 | 0% |
| Visible particle-Necked eyes | 850 | 0 | 0% |
| Density | 850 | 0 | 0% |
| Assay | 850 | 73 | 8.6% |
| Related substances | 850 | 73 | 8.6% |

**Table (6): Common tests for eyes drops and ointment, Gel and Oil**

| Common tests | Total sample eyes drops , ointment ,Gel and Oil | No. of not comply sample | percentage of not comply sample |
|---|---|---|---|
| Description | 200,186,232 | 0 | 0% |
| Identification | 200,186,232 | 0 | 0% |
| Average fill volume | 200,186,232 | 0 | 0% |
| Particulate matter contamination | 200,186,232 | 0 | 0% |
| Density | 200,186,232 | 3,2,9 | 1.5%,1.1%,3.9% |
| Assay | 200,186,232 | 3,2,9 | 1.5%,1.1%,3.9% |
| Related substances | 200,186,232 | 3,2,9 | 1.5%,1.1%,3.9% |

**Table (7): Common tests for capsules and tablets**

| Common tests | Total sample Capsules ,Tablets | No. of not comply sample | percentage of not comply sample |
|---|---|---|---|
| Description | 721, 1332 | 0 | 0% |
| Average weight | 721, 1332 | 0 | 0% |
| Uniformity of weight | 721, 1332 | 0 | 0% |
| Uniformity of content | 721, 1332 | 0 | 0% |
| Hardness | 721, 1332 | 0 | 0% |
| Disintegration test | 721, 1332 | 0 | 0% |
| Dissolution test | 721, 1332 | 3,29 | 0.4%,2.1% |
| Assay | 721, 1332 | 3,29 | 0.4%,2.1% |
| Related substances | 721, 1332 | 3,29 | 0.4%,2.1% |

**Acknowledgements**

We would like to acknowledge the staff of Kurdistan Medical Control Agency (KMCA) in Erbil City, Iraq for their outstanding support during the conduct of the study for providing us all the facilities which needed for conducting the study.

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