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Quality Control Tests for Different Types of Paracetamol Tablets Available in Iraqi Market

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Summery

According to World Health Organization, the term quality control refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical. Quality control is an essential operation of the pharmaceutical industry. In addition to the apparent features of tablets, tablets must meet other physical specifications and quality standards. These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. Thus in this project, five types of paracetamol tablets from different companies which are widely used in the private pharmacies in Hilla city were subjected to quality control tests to indicate whether these products will fit to the standard criteria of the United States Pharmacopeia or not. The data indicated that all brands succeeded to pass most quality control tests with some exceptions.

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بِسْمِ اللَّهِ تَعَالَى

وَمَا يَلْعَ أَشَدُّهُ وَاسْتَوَى اتِّينَاهُ حُكْمًا
وَعِلْمًا وَكَذَلِكَ نَجْزِي الْحَسَنِينَ ﴿١﴾

_الى الانوار التي احاط الله بها عرشه..
اصحاب الكساء الخمسة

_الى من يملأ الأرض عدلاً وقسطاً بعد أن تملأ
ظلماً وجوراً .. بقيه الله في أرضه

• يُوجِدُ أَنَاسٌ يَسْتَحِقُّونَ مِنَّا الشُّكْرَ
وأولى الناس بالشكر هما الأيوان لما لهما من الفضل ما
يبلغ عنان السماء

_الى صاحب السيرة العطرة والفكر المستنير
فلقد كان له الفضل الأول في بلوغي التعليم العالي
(والدي الحبيب) أطال الله في عمره.

_الى من وضعتني على طريق الحياة، وراعتني
حتى صرت كبيراً (أمي الغالية) طيب الله ثراها

_الى استاذي الجليل الذي علمني كيف اخوض معترك
البحث العلمي الجاد.. الدكتور/ظافر قحطان

_الى أبطال الحشد الشعبي المرابطين في ساحات القتال
الذين خطو بدمائهم الزكية أجمل ملاحم البطولة والانتصار
لولاهم لما اكتمل هذا العمل.

"نهديهم ثمره جهدنا حبا ووفاء"

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1. INTRODUCTION

1.1. Quality control

The concept of total energy quality control refers to the produce a perfect product by a series of measures requiring an organized effort by the entire company to prevent or eliminate errors at every stage in production. Although the responsibility for assuring product quality belongs principally to quality assurance personnel, it involves many departments and disciplined lines within a company. To be effective, it must be supported by a team effort [1].

Quality must be built into a drug product during product and process design, and it is influenced by the physical plant design, space, ventilation, cleanliness, and sanitation during routine production. The product and process design begins in research and development, and includes preformulation and physical, chemical, therapeutic, and toxicologic considerations. It considers materials, in process and product control, including specifications and tests for the active ingredients, the excipients, and the product itself, specific stability procedures for the product, freedom from microbial contamination and proper storage of the product, and containers, packaging and labeling to ensure that container closure systems provide functional protection of the product against such factors as moisture, oxygen, light, volatility, and drug/package interaction. Provision for a cross referencing system to allow any batch of a product to be traced from its raw materials to its final destination in the event of unexpected difficulties is required [2].

1.1.1 Quality assurance

The assurance of product quality depends on more than just proper sampling and adequate testing of various components and the finished dosage form. Prime responsibility of maintaining product quality during production rests with the manufacturing department. Quality assurance personnel must establish control or checkpoints to monitor the quality of the product as it is processed and upon completion of manufacture. These begin with raw materials and components

testing and include in process, packaging, labeling, and finished product testing as well as batch auditing and stability monitoring [1].

1.1.2 Sources of quality variation

Because of the increasing complexity of modern pharmaceutical manufacture arising from a variety of unique drugs and dosage forms, complex ethical, legal and economic responsibilities have been placed on those factors is the responsibility of all those involved in the development, manufacture, control and marketing of quality products. A systematic effective quality assurance program takes into consideration potential raw materials, manufacturing process, packaging material, labeling and finished product variables [1].

For example, for parenteral products which should be sterile and isotonic, a number of quality control tests have been used such as:

- Checking the bulk solution for filling, drug content, pH, color, clarity and completeness of solution.
- Checking the filled volume of liquids or filled weight of sterile powder for injection in final container at determined intervals during filling
- Testing for leakage from flame-sealed ampoules.
- Subject the product to physical examination (visually or mechanically) for appearance, clarity and particulate contamination.
- Examining the sterility indicator placed in various areas of sterilizer for each sterilization operation.
- Submitting the product for sterility testing other predetermined biological tests to establish the safety and other parameters of the product.

On the other hand, the standard quality controls tests that can be used for solid dosage direct compression tablets are:

- Checking the weight variation of tablets at predetermined intervals during manufacturing.

- Checking the disintegration and/or dissolution time, hardness and friability of the tablets at least during the beginning, middle and end of production or at prescribed intervals during manufacturing.
- Testing soluble tablets for compliance with solution time requirements.
- Examining products by line inspection or other equally suitable means and removing the defective units prior to packaging.

1.2 Paracetamol

Paracetamol (acetaminophen) belongs to the NSAIDs family. It is widely used and well known by Iraqi population for headache relief and its antipyretic effects. Paracetamol is available as over the counter drug (OTC) and it is available in different dosage forms and different strengths [3].

1.2.1 Medical uses of paracetamol

Paracetamol is commonly used as analgesic and antipyretic in the treatment fever and as well used to reduce from mild to moderate pain. It has weak anti-inflammatory effects. Generally, paracetamol can be used to treat several conditions such as headache, muscle ache, fever and cold, arthritis, backache, toothache. Paracetamol combined with opioid pain is also used for severe pain such as cancer pain and pain after surgery [3].

1.2.2 Pharmacokinetics of paracetamol

The bioavailability of paracetamol is about 63-89% and its protein binding of it 10-25%. Its metabolism is predominantly in the liver and its urinary excretion is about 85-90% after administration [3].

1.2.3 Side effects of paracetamol

Usual side effects are nausea, vomiting, dark urine, yellowish skin, loss of appetite and stomach pain. Paracetamol toxicity may cause liver damage and skin reactions [3].

1.2.4 Dose and dosage forms of paracetamol

The commercially available dosage form of paracetamol includes tablets, caplets, capsules, effervescent tablets, suppositories, suspensions, parenteral injections, chewable tablets, oral drops, syrups, elixirs and extended release tablets. The recommended doses of paracetamol in different age groups are listed in table 1.1.

Table 1.1 The recommended doses of paracetamol based on age of patients.

Age	Daily dose
Adults	2-4 g
2-16 years	0.75-3 g
6-24 months	Up to 20 mg
2-6 months	40-75 mg
Below 2 months	Not recommended

Aim of the study

In this project we subjected five types of paracetamol tablets from different companies which are widely used in the private pharmacies in Hilla city to quality control tests to indicate whether these products will fit to the standard criteria of the United States Pharmacopeia or not. The types chosen were based on price criteria (cheap, moderate and relatively expensive) and based on the manufacturer (local private and government factories and international factories including Indian and European manufacturer).

2. MATERIALS AND METHODS

2.1 Materials

Paracetamol sheets from five different companies were bought from a native pharmacy in Hilla city. The selected types included Safacetol (SAFA Co.), Omol (NP Pharma Co.), Paracetol (SDI Co.), Apmol (AJINTA Co.) and Supofen (BASI Co.) which are shown in Fig. 2.1.



Fig. 2.1 Different types of paracetamol used in project

2.2 Methods

2.2.1 Physical examination

Ten tablets were removed from the sheet and carefully examined by naked eye to detect its physical properties (appearance, color, break line, any cracked edges or any deformations), (Fig. 2.2). The process was repeatedly performed for each type of paracetamol from different companies.



Fig. 2.2 Physical examination of different types of paracetamol tablets

2.2.2 Weight variation test

Ten tablets were removed from the sheet and the weight of each tablet was measured individually by H-digital sensitive balance (DENVER Instrument /China), (Fig. 2.3). The mean and standard deviation were calculated and the accepted values of variation of $\pm 5\%$ were measured and compared with the standard deviation [4].



Fig. 2.3 Four digits sensitive balance used for weight variation of different types of paracetamol tablets

2.2.3 Size variation test

Ten tablets were removed from the sheet and each tablet was placed in digital caliper (WEILIANG Co./ China), (Fig. 2.4) to measure its height. The steps were

repeated the rest of the tablets and then mean and standard deviation were calculated and compared with the accepted $\pm 5\%$ value [4].



Fig. 2.4 digital scale used for size variation of different types of paracetamol tablets

2.2.4 Friability test

Friability is the tendency of tablet to powder, chip or fragment and this can affect the elegance, appearance and the consumer acceptance of the tablet, and also added to tablet's weight variation or content uniformity problem. We used tablet friability tester (GUOMING CS-2 / China), (Fig. 2.5) to measure friability of the different brand of paracetamol tablet.



Fig. 2.5 Friability tester used for used for different types of paracetamol tablets

The weight of 10 tablets of each brand of paracetamol where measured and the tablets were loaded in the friability tester. The apparatus exposed tablets to rolling and repeated shocks as they fall 6 inches in each turn within apparatus. After 4

minutes of 100 cycles, the tablets were removed from the device, brushed to remove any powders and weighed again. The percentage of weight loss (Friability %) was calculated according to the following equation:

$$\text{Friability \%} = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100\%$$

Where W_{initial} is the initial weight and W_f is final weight

Friability values more than 5% were considered as unacceptable based on the USP [4].

2.2.5 Disintegration test

Disintegration is a process by which tablets are fragmented into granules or small particles. It is defined as the time required for a group of tablets to fragment into particles under a given set of conditions which is measured by disintegration tester. This test is basic for tablets intended that administration by mouth except those intended to be chewed before being swallowed or those that should dissolve slowly in the mouth, e.g. lozenges, glyceryl trinitrate, or effervescent tablets. Also, disintegration does not apply to similar types of sustained-release tablets.

Before each step the apparatus (Disintegration tester \GUOMING CS-2 / China), (Fig.2.6) was cleaned from any residue of another test. The tank of the device was filled with distilled water and left to reach the desired temperature (37°C). Six tablets of paracetamol were used by putting one tablet in each basket of the 6 tubes and fixed by the specified disk. The device was operated to start continuous immersing and lifting of the tubes in the tank. The tablets in each tube were carefully monitored until disintegrated completely and the time was recorded. The mean and standard deviation of the disintegration time were calculated and compared between different paracetamol brands. Values less than 10 minutes (600 seconds) were considered as accepted values [4].



Fig. 2.6 Disintegrator apparatus used for different types of paracetamol tablets

2.2.6 Hardness test

Hardness test (crushing strength) is the load required to crushing the tablet when placed on its edge. Hardness is the force required to break the tablet by diametric compression tester. Usually, tablet hardness tester is a portable semi-automatic electronic tablet hardness tester designed to accept tablet up to 30 mm in diameter. Unfortunately, in our project, such device was not available, and a manual hardness tester was used to perform this test.

The hardness of ten tablets was measured by placing 1 tablet each time in the hardness tester (Campbel electronics \ China), (Fig. 2.7) and recorded the force required to break or crack the tablet. The mean and standard deviation of the hardness were calculated and compared between different paracetamol brands. Based on the USP, conventional tablet hardness should range between 2.5 to 10 kg/cm² [4]. Values outside this range were considered unacceptable results.



Fig. 2.7 Manual tablet hardness tester used for different types of paracetamol tablets

3. RESULTS AND DISCUSSION

According to World Health Organization (WHO), the term quality control refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical [5]. Quality control is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. It not only protects the manufacturer against compensation claims, but also guarantees the patient a safe and effective product.

Thus, in addition to the apparent features of tablets, tablets must meet other physical specifications and quality standards. These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. These factors must be controlled during production (in-process controls) and verified after the production of each batch to ensure that established product quality standards are met.

3.1 Physical examination

The various types of paracetamol tablets were subjected to physical examination using naked eye. The shape, engravings, color, sharpness of edges and extent of powder loss were investigated and the results are listed in Table 3.1.

Table 3.1 Physical examination of different paracetamol brands

Product	Description
Paracetol	Round, white tablets with excessive loss of powders and irregular edges. The tablets contain break-line with engraved with "500" sign.
Safacetol	Round, white tablets with loss of powders and irregular edges. The tablets contain a break-line with no engravings.
Sapofen	Round, white tablets with moderate loss of powders and irregular edges also. The tablets do not contain break-line nor any engravings.
Apmol	Round, white tablets with excessive loss of powders and regular edges.

	The tablets contain break-line and engraved with "500" sign.
Omol	Round, white tablets with excessive powder loss and few tablets with irregular edges. The tablets contain a break-line with no engravings.

3.2 Weight variation

The average weights of ten paracetamol tablets of each brand were measured as well as the standard deviation and the accepted values based on the $\pm 5\%$. The results are listed in Table 3.2.

Table 3.2 Weight variation of different paracetamol brands

Product	Weight (mg)	SD	Acceptable value	Verdict
Paracetol SDI	616.07	9.19	30.80	Approved
Safacetol	605.73	6.31	30.28	Approved
Sapofen	681.64	10.72	34.08	Approved
Apmol	581.41	51.98	29.07	Rejected
Omol	555.93	7.11	27.79	Approved

The lowest weight variation was detected in Omol brand. The data indicated that all types of paracetamol tablets were within the accepted range except the Apmol type. The variation in weight in tablets dosage form may be caused by several factors such as flow properties of powders, size and shape of particles and the amount and type of excipients.

3.3 Size variation

The average size of ten paracetamol tablets of each brand were calculated as well as the standard deviation and the accepted values based on the $\pm 5\%$. The results are shown in Table 3.3.

Table 3.3 Size variation of different paracetamol brands

Product	Size (mm)	SD	Acceptable value	Verdict
Paracetol SDI	4.303	0.095	0.215	Approved
Safacetol	4.369	0.286	0.218	Rejected
Sapofen	4.273	0.255	0.233	Rejected
Apmol	4.273	0.096	0.213	Approved
Omol	4.137	0.124	0.206	Approved

Two types of paracetamol (Safacetol and Sapofen) failed to pass the test of size variation while the rest of the types were within the accepted range. The Paracetol SDI and Apmol brands showed the best values with minimum size variation.

The thickness of a tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the force or pressure applied during compression. Many of these factors are affected by the flow properties of powders, size and shape of particles and the amount and type of excipients (glidants). To produce tablets of uniform thickness during and between batch productions for the same formulation, care must be exercised to employ the same factors of fill, die, and pressure.

3.4 Friability test

Friability is the phenomenon where the surface of the tablet is damaged or shows a site of damage due to mechanical shock. The purpose of the test is to evaluate the ability of the tablets to withstand the breakage during the packaging, transportation and handling. The average percentages of weight loss of paracetamol tablets of each brand were calculated and the accepted values based on the $\pm 5\%$. The results are shown in Table 3.4.

Table 3.4 percentage of weight loss of different paracetamol brands

Product	% Wt. loss	Verdict
Paracetol SDI	7.71	Rejected
Safacetol	6.53	Rejected
Sapofen	7.29	Rejected
Apmol	0.2	Approved
Omol	0.24	Approved

The results revealed that only 2 brands of paracetamol (Apmol and Omol) succeeded to pass the test. However, other brands (Paracetol SDI, Safacetol and Sapofen) were out of the accepted range. The friability is affected by the type and amount of binder, method of preparation and the force of compression.

3.5 Disintegration test

For the medicinal agent in a tablet to become fully available for absorption, the tablet must first disintegrate and discharge the drug to the body fluids for dissolution. Tablet disintegration also is important for tablets containing medicinal agents (such as antacids and antidiarrheals) that are not intended to be absorbed but rather to act locally within the gastrointestinal tract. In these instances, tablet disintegration provides drug particles with an increased surface area for activity within the gastrointestinal tract. All USP tablets must pass a test for disintegration, which is conducted *in vitro* using a disintegrator testing apparatus. The average disintegration time of different paracetamol brands were determined and the results are shown in Table 3.5.

Table 3.5 Disintegration time of different paracetamol brands.

Product	Disintegration time \pm SD (sec)	Verdict
Paracetol SDI	109 \pm 11	Approved
Safacetol	378 \pm 68	Approved
Sapofen	161 \pm 21	Approved
Apmol	34 \pm 5	Approved
Omol	141 \pm 21	Approved

The disintegration of all types of paracetamol tablets were accepted and below the ten minutes threshold. However, the fastest time was shown by Apmol brand (34 sec). The faster disintegration time will improve rate of dissolution rate of absorption, bioavailability, rapid onset of action and faster response [6]. The longest disintegration time was related to Safacetol brand which reached almost 7 minutes.

3.6 Hardness test

Generally, the greater the pressure applied, the harder the tablets, although the characteristics of the granulation also have a bearing on hardness. Certain tablets, such as lozenges and buccal tablets, are intended to dissolve slowly and are intentionally made hard; other tablets, such as those for immediate drug release, are made soft [6]. In general, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet. Multifunctional automated equipment can determine weight, hardness, thickness, and diameter of the tablet. The average hardness of different paracetamol brands were determined and the results are shown in Table 3.6. It should be kept in mind that this test was performed using a manual device which

gives rough results rather than the automatic apparatus, thus results close to 10 kg/cm² were considered as approved results.

Table 3.6 Hardness of different paracetamol brands.

Product	Hardness \pm SD (Kg/cm ²)	Verdict
Paracetol SDI	12.21 \pm 1.3	Approved
Safacetol	12.23 \pm 1.1	Approved
Sapofen	11.01 \pm 1.4	Approved
Apmol	10.32 \pm 0.9	Approved
Omol	9.31 \pm 1.1	Approved

Conclusion

The data indicated that all brands succeeded to pass most quality control tests with some exceptions. It should be highlighted these results were obtained for the specific batches used in the experiment, however, different results may be obtained if different batches were used for the same products and this is the core of quality control studies. One of the major tests of quality control for tablets is the quantitative determination of the tablets contents especially for the active ingredient(s). Unfortunately, this test was not performed in our project due to time and facility limitations. However, such test (quantitative determination of paracetamol contents in each brand using high performance liquid chromatography) could be included in any future work to shed more light on this issue and strengthen the scientific aspects of the project.

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