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Pharmacopoeial Standards and Specifications for Pharmaceutical Oral Liquid Preparations

Md. Sahab Uddin[1*], Abdullah Al Mamun[1], Nahia Akter[2], Md. Shahid Sarwar[1], Mamunur Rashid[1] and Md. Shah Amran[3]

[1]Department of Pharmacy, Southeast University, Dhaka-1213, Bangladesh.
[2]Department of Pharmacy, University of Asia Pacific, Dhaka-1215, Bangladesh.
[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh.

Authors' contributions

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Author AAM managed the literature searches and helped with author MSU. Authors NA and MSS revised the final manuscript. Authors MR and MSA reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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ABSTRACT

Quality control is an essential operation of the pharmaceutical industry. It is the monitoring process which encompassing specifications, inspections, analysis and recommendations. The appropriate design and formulation of a dosage form requires discretion of the physical, chemical and biological characteristics of active pharmaceutical ingredients (APIs) and inactive pharmaceutical excipients (IPIs) to be used in formulating the pharmaceutical. The drug and others pharmaceutical materials utilized must be compatible with one another to produce a drug product that is stable, efficacious, potent, palatable, easy to administer and well tolerated. The quality of any drug in dosage form depends on its safety, potency, efficacy, stability, patient acceptability and regulatory compliance. In order to claim the pharmaceutical oral liquid preparations as quality drugs it must satisfy the aforementioned criteria. To conform the requirements of pharmaceutical oral liquids during

**Corresponding author: Email: msu-neuropharma@hotmail.com;*

manufacturing, in-process quality control (IPQC) tests are done as per specifications with a view to remove error or if necessary to adjust the process. The quality of final products depends on finished product quality controls (FPQC) test. So the quality of pharmaceutical oral liquids is strongly related to IPQC and FPQC tests. The purpose of this study is to focus on the different in-process and finished products quality control tests for pharmaceutical oral liquid preparations according to pharmacopoeias.

Keywords: Pharmacopoeia; standard; specification; pharmaceutical oral liquid preparation, quality control.

1. INTRODUCTION

The pharmaceutical industry is an important element of health care systems all over the world in order to discover, develop, manufacture and market medicines for human health [1]. The main goal of the quality control testing process in the pharmaceutical industry is to produce satisfactory results by investigating and monitoring the quality of manufacturing products to detect problems and prevent their repetition as per comply with pharmacopoeial standards and specifications. Oral liquids are homogeneous liquid preparations, usually consisting of a solution, an emulsion or a suspension of one or more medicaments in a suitable vehicle. Oral liquids are intended for oral administration either undiluted or after dilution [2].

The manufacturing process for oral liquid preparations must meet the requirements of Good Manufacturing Practice (GMP). In the manufacture of liquid preparations for oral use some measures are taken to assure that all ingredients are of appropriate quality, minimize the risk of microbial contamination and diminish the risk of cross-contamination [3]. In addition to this during packaging, storage and distribution of oral liquids, suitable means should be taken to ensure their best quality. Quality control (QC) refers to the sum of all procedures undertaken to produce a faultless product by a series of processes requiring a systematized effort by the QC personnel to prevent or reject errors at every stage in production that ensures the identity and purity of a particular pharmaceutical [4,5]. It indicates the degree or grade of excellence of a product [6,7]. It strengthens testing of products to prevent errors and asks to assure that the finished products consent to the specified standards of performance, utility and reliability [8-10].

The total qualities of the pharmaceuticals are ensured by both In Process Quality Control (IPQC) and Finished Product Quality Control (FPQC) tests. The whole dealing process (IPQC and FPQC tests) refers rigorous QC tests to make products fully faultless before they are delivered into the market. IPQCs are tests that are carried out at regular intervals before the manufacturing process is completed. The function of IPQC includes monitoring and if necessary, adaptation of the manufacturing process with a view to consent with the pharmacopoeias [11]. In process materials should be tested for identity, strength, quality and purity as appropriate and approved or discarded by the QC unit during the manufacturing process [12-14]. Discarded in process materials should be specified and controlled under a quarantine system designed to counteract their use in manufacturing [15]. In the pharmaceutical industry standard operating procedures (SOPs) should be established and followed that mention the IPQCs and tests. Specific tests carried out during the manufacturing process, where the acceptance criterion is identical to or narrower than the release requirement, (e.g., pH of a solution) which must satisfy requirements when the test is included in the specification. Finished product quality controls (FPQC) tests are performed when the manufacturing process is completed with a view to check qualitative and quantitative characteristics along with test procedures and their acceptance limits, by which the finished product must comply throughout its valid shelf-life [16]. With a view to determine the specifications of the finished product, the quality characteristics that are concerned to the manufacturing process should be taken into account. During the phase of development and the validation of the manufacturing process, an appropriate specification for each aspect of quality should be determined.

Pharmacopoeias are referred as drugs standard [17]. They are authentic treatises on drugs and preparations, their description, formulation, analytic composition, physical constants, main chemical properties used in identification, standards for strength, purity, and dosage,

chemical tests for determining identity and purity of dosage forms etc [18]. Pharmacopeias play an important role in the regulatory process and the quality control of active pharmaceutical ingredients (APIs), inactive pharmaceutical excipients (IPIs) and finished pharmaceutical products (FPPs) that are used by pharmaceutical manufacturers and regulatory authorities. Pharmacopeias deliver standards, specifications, and test methods that are expected to be used in the pharmaceutical industry to ensure the perfect quality control tests of pharmaceuticals [19]. There are variant types of pharmacopoeias such as British Pharmacopoeia (BP), United States Pharmacopoeia-National Formulary (USP-NF), European Pharmacopoeia (PhEur), International Pharmacopoeia (PhInt), Japanese Pharmacopoeia (JP) and Indian Pharmacopoeia (IP) in different countries of the world and they have contained the specified limits within which the pharmaceuticals should fall in order to be compliant as per the standards.

To further improve the effectiveness and safety of the drug product in the global marketplace, many regulatory agencies such European Medicines Agency (EMA), Food and Drug Administration (FDA), Medicines and Healthcare products Regulatory Agency (MHRA) and Therapeutic Good Administration (TGA) are continuously developing rules regulation in the Europe, US, UK and Australia respectively [20-22]. FDA assures the quality of pharmaceutical products by carefully monitoring drug manufacturers with the compliance of current Good Manufacturing Practice (cGMP) regulations [23]. A drug product that does not consent the GMP requirements is considerate unacceptable according to FDA guidelines [1].

The objective of this study is to offer the quality control tests for pharmaceutical oral liquid preparations based on pharmacopoeial standards and specifications.

2. CLASSIFICATION OF ORAL LIQUID PREPARATIONS

2.1 Syrups

Syrups are viscous oral liquids that may contain one or more active ingredients in solution. The vehicle usually contains large amounts of sucrose or other sugars to which certain polyhydric alcohols may be added to inhibit crystallization or to modify solubilisation, taste and other vehicle properties. Sugarless syrups may contain sweetening agents and thickening agents. Syrups may contain ethanol (95%) as a preservative or as a solvent to incorporate flavoring agents. Antimicrobial agents may also be added to syrups [24].

2.2 Elixirs

Elixirs are clear, flavored oral liquids containing one or more active ingredients dissolved in a vehicle that usually contains a high proportion of sucrose or a suitable polyhydric alcohol or alcohols and may also contain ethanol (95 percent) or a dilute ethanol [25].

2.3 Linctuses

Linctuses are viscous oral liquids containing one or more active ingredients dissolved in a vehicle that usually contains a high proportion of sucrose, other sugars or a suitable polyhydric alcohol or alcohols. They are intended for use in the treatment or relief of cough, and are sipped and swallowed slowly without the addition of water [26].

2.4 Mixtures

Mixtures are oral liquids containing one or more active ingredients dissolved, suspended or dispersed in a suitable vehicle. Suspended solids may separate slowly on keeping but are easily redispersed on shaking [26].

2.5 Oral Solutions

Oral solutions are oral liquids containing one or more active ingredients and excipients dissolved in a suitable vehicle [27]. Water is the most common solvent, although organic solvents are used in combination with water or on their own. All the components of a solution are dispersed as molecules or ions, and the solution is optically clear [28].

2.6 Oral Suspensions

Oral suspensions are oral liquids containing one or more active ingredients suspended in a suitable vehicle. Suspended solids may slowly separate on keeping but are easily redispersed. In the manufacture of oral suspensions containing dispersed particles, measures shall be taken to ensure a suitable and controlled particle size with regard to the intended use of the product [29].

2.7 Oral Emulsions

Oral emulsions are dispersions of at least two immiscible or partially miscible liquids. They are oral liquids containing one or more active ingredients and are stabilized oil-in-water dispersions, either or both phases of which may contain dissolved solids. Solids may also be suspended in oral emulsions. Emulsions may exhibit phase separation but are easily reformed on shaking. The preparation remains sufficiently stable to permit a homogeneous dose to be withdrawn [30].

2.8 Oral Drops

Oral drops are oral liquids that are intended to be administered in small volumes with the aid of a suitable measuring device such as a dropper [31].

3. UNIVERSAL TESTS FOR PHARMACEUTICAL ORAL LIQUID PREPARATIONS

The pharmaceutical oral liquid preparations accounts for approximately 20% of all dosage forms on the market. There are four tests that are generally applicable to pharmaceutical oral liquid preparations and other drug products:

3.1 Description

This test is often called appearance on a specification and is a qualitative description of the pharmaceutical oral liquid preparations. For example, the description of a syrup on a specification may read: red color, slight characteristic odor, mild taste etc [17,32].

3.2 Identification

The purpose of an identification or identity test is to verify the identity of the API in the pharmaceutical oral liquid preparations. This test should be able to discriminate between compounds of closely related structure that are likely to be present [17,32].

3.3 Assay

This test determines the strength or content of the API in the pharmaceutical oral liquid preparations and is sometimes called a content test [17,32].

3.4 Impurities

This test determines the presence of any component that is not the API or an excipient of pharmaceutical oral liquid preparations. The most common type of impurities that are measured is related substances, which are process impurities from the new drug substance synthesis, degradation products of the API, or both [17,32].

4. QUALITY CONTROL TESTS FOR ORAL LIQUID PREPARATIONS

4.1 Visual Inspection

Oral solution and oral drops should be clear and free from any precipitate. Discoloration or cloudiness of solutions may indicate chemical degradation or microbial contamination. Evidence of physical instability of oral suspension and oral drops that are suspensions is demonstrated by the formation of flocculants or sediments that do not readily disperse on gentle shaking. In case of oral emulsion and oral drops that are emulsions evidence of physical instability is demonstrated by phase separation that is not readily reversed on gentle shaking. Evidence of physical instability of powders and granules for oral solutions or oral suspensions and powders for oral drops is demonstrated by noticeable changes in physical appearance, including texture for example, clumping. Discoloration may indicate chemical degradation or microbial contamination of the oral suspension, oral emulsion, powders and granules for oral solutions or oral suspensions and powders for oral drops [33].

4.2 pH

pH of the oral liquid preparations must be optimum as they are administered. The pH value conventionally represents the acidity or alkalinity of an aqueous solution. In the pharmacopoeia, standards and limits of pH have been provided for those pharmacopoeial substances in which pH as a measure of the hydrogen ion activity is important from the standpoint of stability or physiological suitability. The determination is carried out at a temperature of 25±2℃, unless otherwise specified in the individual monograph. The pH value of a solution is determined potentiometrically by means of a glass electrode, a reference electrode and a pH meter either of the digital or analogue type [31].

4.3 Assay

The assay of oral liquids has to be done to detect API by using suitable analytical method to produce good finished pharmaceutical [34]. API is responsible for therapeutic activity of the pharmaceutical formulations. This test is one of the most important tests that determine the strength or content of the API.

4.4 Uniformity of Content

Unless otherwise prescribed or justified and authorized, according to BP this test is applicable for single-dose preparations that are suspensions. This test is also applicable for single-dose powders and granules for syrups, oral solutions, oral suspensions and single-dose powders for oral drops, with a content of active substance less than 2 mg or less than 2 percent of the total mass. Except single-dose preparations that are suspensions if the preparation has more than one active substance, the requirement applies only to those substances that correspond to the above conditions. According to IP unless otherwise specified, single dose liquids in suspension form or powders or granules presented in single dose containers and that contain less than 10 mg or less than 10 percent of active ingredient also comply with this test. For this test as per BP assay 10 units individually using an appropriate analytical method. Carry out the assay on the amount of well-mixed material that is removed from an individual container in conditions of normal use. Express the results as delivered dose. Calculate the acceptance value using the following formula:

$$\left| M - X \right| + KS$$

Where,

M = Reference value, X = Mean of individual content (x_1, x_2,..., x_n) expressed as percentage of the label claim, K = Acceptability constant, S = Sample standard deviation [31,34].

According to IP, BP and PhInt the preparation complies with the test if not more than one individual content is outside the limits of 85 percent to 115 percent of the average content and none is outside the limits of 75 percent to 125 percent of the average content. The preparation fails to comply with the test if more than 3 individual contents are outside the limits of 85 percent to 115 percent of the average content or if one or more individual contents are outside the limits of 75 percent to 125 percent of the average content. If 2 or 3 individual contents are outside the limits of 85 percent to 115 percent but within the limits of 75 percent to 125 percent, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than 3 individual contents of the 30 dosage units are outside the limits of 85 percent to 115 percent of the average content and none is outside the limits of 75 percent to 125 percent of the average content. In accordance with BP and USP-NF limits for content uniformity (CU) and mass variation (MV) tests of oral pharmaceutical liquids are given in Table 1 [31,33-35].

Table 1. BP and USP-NF limits for content uniformity (CU) and mass variation (MV) tests [34,35]

Dosage form	Dose and ratio of active substance	
	≥ 25 mg and ≥ 25%	< 25 mg or < 25%
Solutions	MV	MV
Suspensions	CU	CU
Emulsions	CU	CU

According to PhInt this test is applicable for single-dose oral suspensions that contain less than 5 mg of active ingredient per dose or in which the active ingredient is less than 5 percent of the total weight per dose [33].

4.5 Uniformity of Mass

According to BP this test is applicable for single-dose preparations that are solutions or emulsions; single-dose powders and granules for syrups, oral solutions, oral suspensions; and single-dose powders for oral drops. For this test weigh individually the contents of 20 dosage units taken at random, emptied as completely as possible, and determine the average mass. As stated by BP, PhEur and PhInt for single-dose preparations that are solutions or emulsions not more than 2 of the individual masses deviate by more than 10 percent from the average mass and none deviate by more than 20 percent. For single-dose powders and granules for syrups, oral solutions, oral suspensions and single-dose powders for oral drops according to BP not more than 2 of the individual masses deviate from the average mass by more than the percentage

deviation shown in Table 2 and none deviates by more than twice that percentage [33,34,36].

Table 2. BP limits for uniformity of mass [34]

Average mass (mg)	Percentage deviation (%)
Less than 300	10
300 or more	7.5

4.6 Mass Variation

According to BP accurately weigh the amount of liquid that is removed from each of 10 individual containers in conditions of normal use. If necessary, compute the equivalent volume after determining the density. Calculate the active substance content in each container from the mass of product removed from the individual containers and the result of the assay. Calculate the acceptance value using the following formula:

$$X_i = W_i \times A/W$$

Where,

x_1, x_2,..., x_n = Individual estimated contents of the dosage units tested, w_1, w_2,..., w_n = Individual masses of the dosage units tested, A = Content of active substance (percentage of label claim) obtained using an appropriate analytical method (assay), W = Mean of individual weights (w_1, w_2,..., w_n) [34].

Unless otherwise specified, consistent with BP, the requirement is met if the acceptance value of 10 dosage units is less than or equal to 15 percent. If acceptance value is greater than 15 percent, test the next 20 dosage units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to 15 percent and no individual content of the dosage units is less than $(1 - 25 \times 0.01)M$ or more than $(1 + 25 \times 0.01)M$ in calculation of acceptance value under mass variation or content uniformity [34].

4.7 Uniformity of Volume

According to IP this test is suitable for oral liquids and oral suspensions of viscous preparations. For this test select a sample of 10 filled containers and determine the weight of the contents of each container. Determine the weight per ml and calculate the net volume of the contents of each container. For non-viscous and free-flowing liquids pour completely the contents of each container into calibrated volume measures of the appropriate size and determine the net volume of the contents of the 10 containers. Consistent with IP the average net volume of the contents of the 10 containers is not less than the labeled amount, and the net volume of the contents of any single containers is not less than the percentage deviation as shown in Table 3 [31].

If this requirement is not met, determine the net volume of the contents of 10 additional containers. The average net volume of the contents of the 20 containers is not less than the labeled amount and the net volume of the contents of not more than 1 of the 20 containers is less than 91 percent or more than 109 percent of the labeled amount where the labeled amount is 50 ml or less or less than 95.5 percent or more than 104.5 percent of the labeled amount where the labeled amount is more than 50 ml but not more than 200 ml or less than 97 percent or more than 103 percent of the labeled amount where the labeled amount is more than 200 ml but not more than 300 ml [31].

Table 3. IP limits for uniformity of volume [31]

Net volume (ml)	Percentage deviation (%)
50 or less	9
More than 50 but not more than 200	4.5
More than 200 but not more than 300	3

4.8 Uniformity of Weight

Consistent with IP this test is suitable for powders for oral liquids. For this test select a sample of 10 filled containers and remove any labeling that might be altered in weight while removing the contents of the containers. Clean and dry the outer surfaces of the containers and weigh each container. Remove quantitatively the contents from each container. If necessary, cut open the container and wash each empty container with a suitable solvent, taking care to ensure that the closure and other parts of the container are retained. Dry and again weigh each empty container together with its parts which may have been removed. The difference between the two weights is the net weight of the contents of the container. As per IP the average net weight of the contents of the 10 containers is

not less than the labeled amount and the net weight of the contents of any single containers is not less than the percentage deviation as shown in Table 4 [31].

Table 4. IP limits for uniformity of weight [31]

Net weight (g)	Percentage deviation (%)
50 or less	9
More than 50 but not more than 100	4.5

If this requirement is not met, determine the net weight of the contents of 10 additional containers. The average net weight of the contents of the 20 containers is not less than the labeled amount and the net weight of the contents of not more than 1 of the 20 containers is less than 91 percent or more than 109 percent of the labeled amount where the labeled amount is 50 g or less than 95 percent or more than 104.5 percent of the labeled amount is more than 50 g but not more than 100 g [31].

4.9 Dose and Uniformity of Dose

According to BP and PhInt this test is applicable for oral drops. For this test, into a suitable graduated cylinder, introduce by means of the dropping device the number of drops usually prescribed for one dose, or introduce by means of the measuring device the usually prescribed quantity. The dropping speed does not exceed 2 drops per second. Weigh the liquid, repeat the addition, weigh again and carry on repeating the addition and weighing until a total of 10 masses are obtained. Following BP no single mass deviates by more than 10 percent from the average mass. The total of 10 masses does not differ by more than 15 percent from the nominal mass of 10 doses. If necessary, measure the total volume of 10 doses. The volume does not differ by more than 15 percent from the nominal volume of 10 doses [33,34].

4.10 Uniformity of Mass of Delivered Doses

According to BP and PhInt this test is applicable for liquid preparations for oral use supplied in multi-dose containers except oral drops. For this test, weigh individually 20 doses units taken at random from one or more containers with the measuring device provided and determine the individual and average masses. As stated by BP and PhInt not more than 2 of the individual masses deviate from the average mass by more than 10 percent and none deviates by more than 20 percent [33,34].

4.11 Phase Separation

This test is applicable for pharmaceutical emulsion. An approximate estimation of phase separation may be obtained visually. In general, creaming, flocculation, and coalescence have occurred before phase separation is visible, thus sometimes making quantitative evaluations more difficult. The rate and degree of phase separation in an emulsion can be easily determined by keeping a certain amount in a graduated cylinder and measuring the volume of separated phase after definite time intervals. The phase separation may result from creaming or coalescence of globules. The phase separation test can be accelerated by centrifugation at low or mild rate speeds [37].

4.12 Droplet Size

This test is applicable for pharmaceutical emulsion. Growth in the droplet size after the preparation of an emulsion is an indication of its physical instability. The droplet size is measured by microscopic methods or by electronic devices such as coulter counter. In emulsions containing droplets greater than 1 µm, optical microscopy is particularly useful because it provides a direct and reassuring measurement of individual droplet sizes. The tedium of counting droplets to obtain size distributions is reduced by the use of image analysis. Indirect methods generally involve laser light scattering techniques are used extensively with emulsions containing sub-micrometre droplets. In either of these techniques often the original products has to be suitable diluted before estimation. The dilution may introduce errors because of incomplete de-flocculation or new pattern of flocculation [37,38].

4.13 Thermal Stress

This test is applicable for pharmaceutical emulsion. It is usual to evaluate the stability of an emulsion by subjecting it too high and low temperatures in alternating cycles. The samples are first exposed to 60℃ for a few hours and then to 40℃. Such exposures are repeated a number of times and emulsion stability assessed after each cycle [39].

4.14 Sedimentation Volume

This test is applicable for pharmaceutical suspension. Sedimentation volume, F of a suspension is expressed by the ratio of the equilibrium volume of the sediment, V_u to the total volume, V_o of the suspension. The following formula is used:

$$F = V_u/V_o$$

The value of F normally lies between less than 1 to 1 or it may exceed 1 for any pharmaceutical suspension. The larger the value, the better is the suspendability. The value of F provides a qualitative knowledge about the physical stability of the suspension (Table 5).

Table 5. Physical stability of the suspension based on F values [37,40]

F values	Comments
F = 1	No sedimentation, no clear supernatant.
F = 0.5	50% of the total volume is occupied by sediment.
F = > 1	Sediment volume is greater than the original volume due to formation of floccules which are fluffy and loose.

Redispersibility of suspension is also importance. To help quantitates this parameter to some extent, a mechanical shaking device may be used. It simulates human arm motion during the shaking process and can give reproducible results when used under controlled conditions [37,40].

4.15 Degree of Flocculation

This test is applicable for pharmaceutical suspension. Degree of flocculation**,** ß is the ratio of the sedimentation volume of the flocculated suspension, F to the sedimentation volume of the deflocculated suspension, F_∞. The following formula is used:

$$ß = F/F_\infty$$
$$ß = (V_u/V_o)/(V_\infty/V_o)$$
$$ß = V_u/V_\infty$$

The minimum value of ß is 1, this is the case when the sedimentation volume of the flocculated suspension is equal to the sedimentation volume of deflocculated suspension. ß is more fundamental parameter than F since it relates the volume of flocculated sediment to that in a deflocculated system [37,40].

4.16 Redispersibility

This test is applicable for pharmaceutical suspension. If a pharmaceutical suspension produces sediment upon storage, it is essential that it should be readily dispersible so that uniformity of dose is assured. The amount of shaking required to achieve this end should be minimal. Various redispersibility tests have been described. For example, the test suspension is placed in a 100 ml graduated cylinder, which, after storage and sedimentation, is rotated through 360° at 20 rpm. The endpoint is taken when the inside of the base of the graduated cylinder is clear of sediment. The ultimate test of redispersibility is the uniformity of suspended drug dosage delivered from a product, from the first to the last volumetric dose out of the bottle, under one or more standard shaking conditions [37].

4.17 Zeta Potential

This test is applicable for pharmaceutical emulsion and suspension. The zeta potential of emulsion droplets stabilized by a charged interfacial film is particularly useful or assessing instability due to flocculation. It can be determined by observing the movement of droplets under the influence of an electric current (electrophoretic mobility measurements), often in conjunction with photon correlation spectroscopy [38].

4.18 Rheology

This test is applicable for pharmaceutical emulsion and suspension. The rheology of an emulsion is often an important factor in determining its stability. Rheological properties of an emulsion system depend upon globule size, emulsifier and its concentration, phase volume ratio etc. Any variation in droplet size distribution, degree of flocculation, or phase separation frequently results in viscosity changes. Since most emulsions are non-Newtonian, the cone-plate type device should be used to determine their viscosity rather than the capillary viscometer. A practical approach for the determination of creaming or sedimentation, before it becomes visibly apparent utilizes the

Helipath attachment of the Brookfield viscometer [37,39].

Most of the pharmaceutical suspension exihibit plastic or pseudoplastic characteristics along with thixotropic properties. Rheological properties of suspension depend on the degree of flocculation of the dispersed phase as well as on the type and quantity of the suspending and thickening agent added to the system. A practical rheological method involves the use of the Brookfield viscometer mounted on a Helipath stand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various levels in a sediment. In this technique, the T-bar is continually changing position and measures undisturbed samples as it advances down into the suspension. This technique also indicates in which level of the suspension the structure is greater, owing to particle agglomeration, because the T-bar descends as it rotates, and the bar is continually entering new and essentially undisturbed material. Infact the viscosity of the dispersion medium of suspension is measured before mixing with dispersed phase and also viscosity after mixing is determined to ensure optimum viscosity of the medium so a stable, re-dispersible suspension can be formed [37,39].

4.19 Microbiological Test

Microbial contamination is determined by the total viable aerobic count, which is the sum of the bacterial count and the fungal count. The tests allow quantitative enumeration of mesophilic bacteria and fungi that may grow under aerobic conditions. Membrane filtration, plate count methods and most-probable-number method are used for determination of total viable aerobic count. According to IP the acceptance limit for this is not more than 10^3 bacteria and not more than 10^2 fungi per g or ml of the preparation. Test for specified microorganisms such as *Escherichia coli* contamination is also determined. Growth of colonies indicates the possible presence of *E. coli*. This is confirmed by identification tests [30]. According to USP-NF the product complies with the test if no colonies are present or if the identification tests are negative [34]. As per IP *E. coli* contamination must be absent in 1 g or 1 ml of the preparation [31].

4.20 Antimicrobial Effectiveness Testing

According to USP-NF the test can be conducted either in 5 original containers if sufficient volume of product is available in each container. Inoculate each container with one of the prepared and standardized inoculum, and mix. The volume of the suspension inoculum used is between 0.5 percent and 1.0 percent of the volume of the product. For oral products other than antacids, made with aqueous bases or vehicles, the concentration of test microorganisms that is added to the product are such that the final concentration of the test preparation after inoculation is between 1×10^5 and 1×10^6 CFU per ml of the product. For antacids made with an aqueous base the final concentration of the test preparation after inoculation is between 1×10^3 and 1×10^4 CFU per ml of the product [35].

The initial concentration of viable microorganisms in each test preparation is estimated based on the concentration of microorganisms in each of the standardized inoculum as determined by the plate-count method. Incubate the inoculated containers at 22.5±2.5℃. Sample each container at the appropriate intervals specified in Table 7. Record any changes observed in appearance at these intervals. Determine by the plate-count procedure the number of CFU present in each test preparation for the applicable intervals. Incorporate an inactivator (neutralizer) of the specific antimicrobial in the plate count or in the appropriate dilution prepared for plating. These conditions are determined in the validation study for that sample based upon the conditions of media and microbial recovery incubation times listed in Table 6. Using the calculated concentrations of CFU per ml present at the start of the test, calculate the change in log10 values of the concentration of CFU per ml for each microorganism at the applicable test intervals, and express the changes in terms of log reductions [35].

According to USP-NF the requirements for antimicrobial effectiveness are met if the criteria specified under Table 7 are met. No increase is defined as not more than 0.5 log10 unit higher than the previous value measured [35].

Table 6. Culture conditions for inoculum preparation [35]

Organism	Suitable medium	Incubation temperature (℃)	Inoculum incubation time (hours)	Microbial recovery incubation time (days)
Escherichia coli	Soybean–Casein Digest Broth; Soybean–Casein Digest Agar	32.5±2.5	18 to 24	3 to 5
Pseudomonas aeruginosa	Soybean–Casein Digest Broth; Soybean–Casein Digest Agar	32.5±2.5	18 to 24	3 to 5
Staphylococcus aureus	Soybean–Casein Digest Broth; Soybean–Casein Digest Agar	32.5±2.5	18 to 24	3 to 5
Candida albicans	Sabouraud Dextrose Agar; Sabouraud Dextrose Broth	22.5±2.5	44 to 52	3 to 5
Aspergillus niger	Sabouraud Dextrose Agar; Sabouraud Dextrose Broth	22.5±2.5	144 to 240	3 to 7

Table 7. Criteria for tested microorganisms [35]

Organism	Category of products	Acceptance limit
Bacteria	Oral products other than antacids, made with aqueous bases or vehicles.	Not less than 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days.
Yeast and Molds		No increase from the initial calculated count at 14 and 28 days.
Bacteria, Yeast, and Molds	Antacids made with an aqueous base	No increase from the initial calculated count at 14 and 28 days.

5. CONCLUSION

Quality control of pharmaceutical is very much important in pharmaceutical industry. Physicians always need a good quality pharmaceutical for treatment. Pharmacist and pharmaceutical industry are responsible for generating superior quality pharmaceutical. All the factors which contribute either directly or indirectly to the purity, safety, effectiveness potency, stability and reliability of the pharmaceutical will be includes under the term quality. To achieve all these mentioned characters there is need to undertake quality control from procurement of the raw materials to the finished product until it gets consumed by the patient as per pharmacopoeial standards and specifications. Although various pharmacopoeias suggest various types of tests for pharmaceutical oral liquid preparation, but the main purpose of the all pharmacopoeias is to produce superior quality pharmaceuticals for the betterment of health sector.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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