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In-Process Quality Checks and Post-Market Surveillance of Artemether-Lumefantrine Fixed-dose Combination Tablets and Suspensions: Current Procedures, Successes, Advances, and Challenges

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

In Southeast Asia and Sub-Saharan Africa, approximately 35% of antimalarial drugs are of substandard quality. Counterfeit and substandard medications constitute 10% of the global pharmaceutical trade. The World Health Organization (WHO) recommends artemether-lumefantrine (AL) as the first-line treatment for acute falciparum malaria in endemic regions. However, there is a lack of validated analytical methods to simultaneously determine the content of artemether and lumefantrine in these formulations, particularly in resource-limited settings. This paper focuses on quality concepts related to AL tablets and suspensions. It provides an overview of quality assessment techniques, including visual inspection, weight uniformity, content assay, and dissolution tests. Regulatory requirements and case studies are also discussed. By rigorously assessing AL quality, regulatory agencies, pharmaceutical companies, and healthcare professionals can ensure compliance with established standards and regulations.

Keywords: Post-market surveillance; quality assessment; antimalarials; artemether; lumefantrine; fixed-dose; pharmacovigilance.

1. INTRODUCTION

Malaria is a parasitic disease that has significant global public health implications. In 2010, there were an estimated 219 million cases and 660,000 deaths from malaria worldwide [1]. However, it is estimated that only a few of malaria cases are detected by global surveillance systems [2]. The development and spread of parasite resistance to antimalarials is a major barrier to malaria control [3]. The availability of effective antimalarials against *Plasmodium falciparum*, the deadliest form of malaria, is limited. This has made it more difficult to develop and implement effective treatment programs and manage the disease.

The problem is further compounded by the fact that 35% of all antimalarials in Southeast Asia and Sub-Saharan Africa are of substandard quality [4]. Counterfeit and substandard drugs account for 10% of the world's pharmaceutical trade. This means that people who are already vulnerable to malaria are at risk of being treated with ineffective or even harmful medications [5]. The global community must take urgent action to address the challenges posed by malaria. This includes investing in research and development for new antimalarials, strengthening surveillance and monitoring systems, developing improved and accurate analytical tools and techniques, and ensuring that people have access to affordable, high-quality medications [6].

Pharmaceutical tablets are a popular form of medication that consist of active pharmaceutical ingredients (APIs) and excipients that have been compressed into a specific size and shape [7]. They are widely used due to their ability to provide accurate dosing, be easily administered, and remain stable. Tablets have emerged as the foremost and broadly accepted drug delivery system, predominantly because of their ease of administration, portability, and stability [8]. This can be attributed to the fact that tablets are convenient to swallow and can be formulated to provide sustained release of over an extended period of time. Additionally, they possess the ability to protect the drug from environmental factors such as light, moisture, and air, which are known to cause drug degradation [9].

Pharmaceutical suspensions refer to liquid dosage forms that comprise insoluble solid

particles uniformly dispersed in a liquid medium with the assistance of a suspending agent [10]. These particles are unable to dissolve completely in the liquid medium, and the suspending agent keeps them dispersed uniformly throughout the formulation to ensure a homogenous distribution. Suspensions are a widely accepted dosage forms for delivering poorly soluble drugs orally and topically [11]. They enable insoluble drugs to be administered in a form that enhance absorption and bioavailability. Tablets and suspensions are fundamental dosage forms extensively utilized in pharmacy practice. Tablets are solid formulations designed for oral ingestion, whereas suspensions are liquid formulations meant for patients who encounter difficulty in swallowing solid dosage forms [12].

The history of tablet manufacturing dates back to ancient times, where medicinal compounds were prepared by mixing them with binding agents and shaping them into pellets. The introduction of modern manufacturing techniques in the 19th century brought about significant changes in tablet production, resulting in the development of the tablet press by William Brockedon in 1843 [13]. This invention enabled the large-scale manufacture of tablets with consistent quality. By the 1950s, tablets had become the most widely used dosage form for oral administration. Suspensions, on the other hand, have a more recent history, having been developed in the late 19th century to serve as an alternative method of administering medicines to patients who have difficulty swallowing pills. Early suspensions were made by mixing medicinal substances with water and a stabilizing agent to keep the particles suspended. Today, suspension manufacturing has been revolutionized through the use of advanced technology, ensuring consistent particle size distribution and stability.

Ensuring the quality of tablets and suspensions is a critical aspect of pharmaceutical manufacturing, as it guarantees that the final product is effective, safe, and meets the required specifications [14]. Quality assessment procedures involve a range of tests, evaluations, and analyses carried out at different stages of production to detect and prevent defects and ensure consistent quality [15]. For tablets, quality assessment begins with selecting high-quality raw materials, including active pharmaceutical ingredients and excipients, and testing them to ensure they meet necessary specifications, purity, and potency standards [16]. During tablet formulation, physical properties such as particle size, compression force, and blending time can impact the quality of the final product. Therefore, evaluating tablet properties such as hardness, friability, and disintegration time is necessary to ensure they meet required standards. In the case of suspensions, quality assessment involves monitoring the particle size distribution, stability, and homogeneity of the product.

Particle size distribution determines the rate of sedimentation and potential for agglomeration, while stability ensures that the particles remain suspended and do not settle over time [17]. Homogeneity, on the other hand, ensures the active ingredient's consistent concentration throughout the product.

Quality assessment for tablets and suspensions is also essential for regulatory compliance. Regulatory agencies, such as the FDA, impose strict quality standards that pharmaceutical manufacturers must adhere to guarantee their products' safety and effectiveness. Quality assessment procedures, including Good Manufacturing Practice (GMP) guidelines, ensure that pharmaceutical manufacturers comply with these regulatory requirements and produce high-quality products that are safe for patient use [18].

The findings from research conducted in Nigeria showed that all brands of artemether-lumefantrine tablets that were put to the test passed all of the tests for weight variation disintegration, and diameter. It was found that 80% of the tested brands conformed to the specified limit (4–10kp) for hardness, while 87% passed the friability test (1% deviation) and thickness test (5% variation). Only 67% of the assessed products met the 90–11% quantitative assay standard limit. In conclusion, the findings showed that just 47% of all the brands, including the innovator brand, successfully passed all of the tests that were administered to them [19].

The World Health Organization (WHO) recommends artemether-lumefantrine as first-line therapy for acute *falciparum* malaria in endemic areas. This has led to the widespread use of this fixed-dose combination in tablets, dispersible tablets (DTs), and powders intended for reconstitution into paediatric suspensions (PSs) [20]. However, there are inadequate analytical validated methods by the various compendia for simultaneously

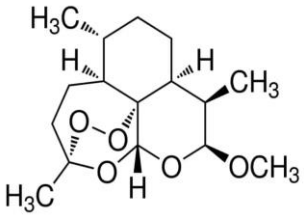
determining the content of artemether and lumefantrine in these formulations. Data available suggest that most industries rely on determining the individual Active Pharmaceutical Ingredient (API) or using other methods rather than High Performance Liquid Chromatography (HPLC) [21].

The primary objective of this review is to comprehensively explore existing research and pertinent issues related to the assessment of quality of artemether-lumefantrine fixed-dose combination tablets and suspensions, while also identifying any gaps. The review is structured around the major quality concepts of tablets and suspensions, including an overview of quality assessment of tablets and suspensions, quality attributes of tablets, quality attributes of suspensions, analytical techniques for quality assessment, regulatory requirements for quality assessment, and case studies in quality assessment.

2. PROFILE OF THE ARTEMETHER AND LUMEFANTRINE

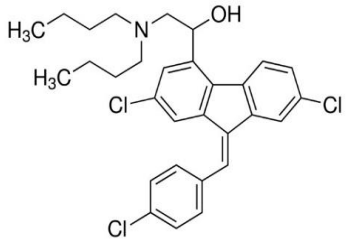
2.1 Artemether

Artemether is an artemisinin derivative in which the lactone has been converted to the corresponding lactol methyl ether [22]. It is used in combination with lumefantrine as an antimalarial for the treatment of multi-drug resistant strains of falciparum malaria. It is a sesquiterpenoid, a cyclic acetal, an organic peroxide, an artemisinin derivative and a semisynthetic derivative.

Description:	White crystalline powder
Solubility:	Insoluble in water but soluble in oil
Melting point:	86 °C -90 °C
Chemical formula:	Dihydroartemisinin methyl ether
Molecular formula:	$C_{16}H_{26}O_5$
Chemical structure	
Molecular mass:	298.3746 g/mol
Monoisotopic mass:	298.178023942 g/mol
Synonyms:	71963-77-4 beta-Artemether Dihydroartemisinin methyl ether Artemetherum
Chemical safety:	Irritant
Indication:	Artemether and Lumefantrine combination therapy is used for the management of acute uncomplicated malaria caused by *Plasmodium falciparum*, including the type acquired in areas where chloroquine resistance is prevalent. It may also be utilized to manage uncomplicated malaria in cases where the Plasmodium species has not been established. This therapy is indicated for both adult and children patients weighing more than 5 kg
Pharmacodynamics:	Artemether is a prodrug that is biotransformed in vivo to the active dihydroartemisinin metabolite. The drug's mechanism of action involves the inhibition of nucleic acid and protein synthesis, which ultimately impedes the erythrocytic stages of Plasmodium falciparum.
Mode of Action:	Artemether's mechanism of action involves interacting with ferriprotoporphyrin IX (heme) or ferrous ions in the acidic parasite food vacuole, generating cytotoxic radical species. Peroxide antimalarials, including artemether, are thought to interact with heme, a hemoglobin degradation byproduct, and produce various toxic oxygen and carbon-centered radicals, leading to their mechanism of action.
Absorption:	Food increases absorption

2.2 Lumefantrine

Lumefantrine is a member of the class of fluorenes that is 9-(p-chlorobenzylidene)-9H-fluorene which is substituted by chlorine at positions 2 and 7, and by a 2-(dibutylamino)-1-hydroxyethyl group at position 4 [23]. An antimalarial drug used in combination with artemether for the treatment of multi-drug resistant strains of falciparum malaria. It has a role as an antimalarial. It is a tertiary amine, a member of monochlorobenzenes, a secondary alcohol and a member of fluorenes. It was first developed and introduced by Novartis, a multinational pharmaceutical company, in collaboration with the WHO.

Description:	Yellow crystalline powder
Solubility:	Insoluble in water but soluble in oil
Chemical structure	
Chemical formula	$C_{30}H_{32}Cl_3NO$
Synonym	Benflumetol
Molecular weight	528.94 g/mol
Monoisotopic mass	527.154947772 g/mol
Indication	Artemether and Lumefantrine combination therapy is used for the management of acute uncomplicated malaria caused by Plasmodium falciparum, including the type acquired in areas where chloroquine resistance is prevalent. It may also be utilized to manage uncomplicated malaria in cases where the Plasmodium species has not been established. This therapy is indicated for both adult patients and children weighing more than 5 kg
Pharmacodynamics	Lumefantrine is a blood schizonticide effective against erythrocytic phases of Plasmodium falciparum. When combined with artemether, lumefantrine is thought to have enhanced antimalarial effects. Due to its extended half-life, lumefantrine is believed to clear remaining parasites. Mechanism of action not specified.
Mechanism of action	The precise mechanism of action of lumefantrine as an antimalarial agent remains unclear. Nonetheless, available evidence indicates that lumefantrine's mode of action involves inhibiting the formation of β-hematin by binding with hemin to form a complex, while also obstructing nucleic acid and protein synthesis.
Absorption	Food increases absorption

2.3 Artemether-Lumefantrine (AL) as a Treatment for Malaria

Malaria is a prevalent fever disease that often requires hospitalization after travel to areas where it is endemic, and artemisinin-based therapy is currently considered the most rapid and effective anti-malarial treatment available [24]. In 2005, Ghana switched from chloroquine to artemisinin-based combination therapy (ACT) as the first-line treatment for uncomplicated malaria, in line with WHO recommendations. Three ACTs, including Dihydroartemisinin-Piperaquine (DHAP), artemether-lumefantrine (AL), and artesunate-amodiaquine (AA), have been widely used in Ghana since 2014 to treat uncomplicated malaria. For severe malaria, preferred treatments are intravenous/intramuscular (IV/IM) artesunate, IV/IM quinine, and IM artemether (Prah et al., 2016).

AL is a fixed-dose combination of 20 mg artemether and 120 mg lumefantrine and their multiples depending on the dose units. Most patients do not wish to take several tablets at a go and so to ensure compliance and patients adherence, the number of tablets are reduced by increasing the strength of a single tablet [23]. Both artemether and lumefantrine are blood schizonticides with distinct mechanisms of action and complementary pharmacokinetic profiles, resulting in synergistic anti-malarial effectiveness [22]. Artemether has a short half-life during elimination, approximately one hour, and eliminates most of the parasite biomass, providing rapid symptom relief during the acute treatment phase. Lumefantrine has a half-life of 3-6 days and variable absorption rates, which improve when taken with fat. Lumefantrine is more effective in eliminating residual parasites during the healing period [25]. However, there is a lack of information on the efficacy and safety of AL in treating malaria in non-endemic countries [26].

AL is available in both tablet and suspension forms for the treatment of uncomplicated malaria. The dosage of AL tablets and suspension varies according to the patient's body weight and the severity of the infection. For adults and children weighing 35 kg or more, the recommended dose is four tablets of AL (each tablet contains 20mg artemether and 120mg lumefantrine) twice daily for three days [27]. The tablets should be taken with food or a drink containing fat to enhance optimal absorption. Alternatively, patients can take the AL suspension, which is dosed according to body weight. The recommended dose for adults and children weighing 35 kg or more is four 5 mL spoonful of the suspension twice daily for three days. Children weighing less than 35 kg, the recommended dose of AL suspension is based on body weight. The suspension often comes with a dosing syringe to ensure accurate dosing. The suspension should also be taken with food or a drink containing fat. To deliver the tablets to young children, who are unable to swallow full tablets or endure the bitter taste of crushed tablets, oral paediatric formulations are urgently needed [28].

AL has gained widespread acceptance as a first- or second-line treatment for Plasmodium falciparum malaria in all malaria-endemic countries, especially in sub-Saharan Africa. Coartem® was the first ACT approved by the US Food and Drug Administration (FDA) for the treatment of uncomplicated falciparum malaria in the United States. It is now a recommended treatment option by the US Centers for Disease Control and Prevention (CDC). Additionally, other treatments for uncomplicated falciparum malaria include atovaquone-proguanil, quinine sulphate plus doxycycline, tetracycline or clindamycin, mefloquine, and chloroquine (for malaria contracted in areas with chloroquine-sensitive parasites) [29].

2.4 High Performance Liquid Chromatography Method Development for the Simultaneous Determination of the Content of Artemether and Lumefantrine in Tablets and Suspensions

Currently developing countries are confronted with enormous challenges of substandard (poor-quality) drugs [5]. Owing to the issues of lack of simple, less economic, robust and stable High-Performance Liquid Chromatography method that could simultaneously determine the content of the APIs in artemether-lumefantrine fixed-dose combination tablets and suspensions, there is therefore the need for methods that are accurate, cost-effective, easy to use, rapid and require the use of non-sophisticated equipment in order to facilitate easy identification and quantification of the active components in fixed-dose AL formulations [30].

HPLC is a widely used analytical technique for the separation, identification, and quantification of drugs in pharmaceutical formulations. It is a highly sensitive and selective method that can detect and quantify trace amounts of drugs [5,21]. However, developing an HPLC method for the simultaneous determination of artemether and lumefantrine in FDC has proven to be difficult due to the physicochemical properties of the drugs [21].

Artemether and lumefantrine have different physicochemical properties, such as different polarities, solubilities, and ultraviolet absorption characteristics. These differences make it challenging to develop an HPLC method that can separate and quantify both drugs simultaneously in the same sample. Additionally, artemether and lumefantrine have different retention times in HPLC columns, which further complicates the simultaneous determination of both drugs. Several attempts have been made to develop HPLC methods for the simultaneous determination of artemether and lumefantrine in

FDC drugs. However, most of these methods have limited sensitivity, poor selectivity, and low precision and accuracy. These limitations make it difficult to use these methods for routine quality control and pharmacokinetic studies.

Several studies have reported methods for the quantification of only artemether or lumefantrine in pharmaceutical and biological matrices. However, there are only a few methods that have been published for the simultaneous determination of artemether and lumefantrine in biological and drug formulation matrices. In 2011, Cesar et al [31] improved a method developed by Hodel et al [32]. using Liquid Chromatography Mass Spectrometry (LCMS) for the simultaneous quantification of artemether and lumefantrine, as well as 14 other antimalarials, in human plasma. This method eliminated the need for a sample drying step and reduced the total chromatogram run time. Also, in 2008, Cesar et al. developed a method for the simultaneous quantification of artemether and lumefantrine in fixed-dose combination tablets using HPLC with UV detection. However, the low sensitivity and selectivity of artemether in biological matrices made UV detection inadequate, necessitating the use of a more sensitive and selective detection method such as LCMS. Currently a novel RP-HPLC method was developed by Nyarko et al [33]. This method is capable of determining simultaneously the presence of artemether and lumefantrine in pharmaceutical dosage forms within a single short run.

The development of new and improved methods for the simultaneous determination of artemether and lumefantrine in biological and drug formulation matrices is important for the quality control of these products and for the monitoring of patient treatment outcomes.

2.5 Quality Attributes of Tablets

The properties of a tablet refer to physical qualities including size, shape, and color, which may affect how patients perceive and follow the recommended regimen. Also, the quality attributes, which include potency, purity, rate of dissolution, and stability, refer to the chemical and physical characteristics that influence the medicine’s effectiveness and safety. The design and production process have a big impact on the characteristics and qualities of the finished tablet [34]. The choice of excipient, the process of manufacture, and storage conditions all have an impact on these characteristics. Tablet properties and quality attributes must be carefully assessed and regulated to guarantee the best safety, efficacy, and patient compliance due to their impact on therapeutic results. Treatment outcomes may be strongly impacted by non-compliance caused by tablet properties such size or ease of swallowing [35]. Therefore, these variables should be taken into consideration when developing and manufacturing tablets.

2.5.1 Size and shape

The acceptable size of a tablet in terms of thickness and diameter is dependent on the medication's intended use, but in general, tablets should not exceed 22mm in diameter or 25mm in length to minimize the risk of swallowing difficulties [36]. Tablets can have a variety of shapes, such as round, oval, oblong, square, or triangular, as well as straight or beveled edges. Tablets can also be pentagonal, hexagonal, or octagonal in shape, however, this is less usual. The size and shape of tablets are critical factors in their ability to pass through the pharynx and esophagus, and may directly impact a patient's ability to swallow. Larger tablets and capsules take longer to pass through the esophagus and can disintegrate there, producing pain and localized esophagitis [37]. This can result in serious consequences such as ulceration, stricture, and perforation. Furthermore, larger tablets and capsules might cause various unpleasant events during the oropharyngeal phase of swallowing, such as discomfort, gagging, choking, and aspiration.

2.5.2 Colour and odour

Odour and colour are two crucial properties of tablets that might influence how effective and well-accepted they are by patients. The odour of a drug is often influenced by the type of active compounds, excipients, coatings, and flavorings used. While an unpleasant odor can deter patients from taking their medication, some pharmaceuticals have distinct odors that are difficult to eradicate, necessitating special procedures such as coatings to avoid odors until they reach the stomach [38].

Patients may identify various colors with specific medications and may be hesitant to take a drug that appears different from what they have in mind [39]. Colors such as white are frequently used for generic drugs, whereas blue is commonly used for anxiety or depression medications. Orange is occasionally used in

drugs to increase immunity or energy [40]. Furthermore, some pharmaceuticals necessitate the use of special colors in order to identify them from other treatments or to meet regulatory standards. Certain prohibited substances are even required by law to be labeled with specified colors or marks in order to prevent misuse or abuse [41].

2.6 Common Quality Defects in Tablets

Any deviation from the quality of a tablet from the intended quality standards or specifications that occurs throughout the production, storage, or handling process is considered a defect of the tablet. Such flaws can harm the tablet's efficacy, safety, and overall quality, and may result in noncompliance with regulatory requirements. Physical defects and quality defects are the two main types of defects that can arise in tablets. Physical defects impair the tablet's appearance or structural integrity, and include concerns such as chipping, cracking, capping, and mottling. Quality defects, on the other hand, are related to the quantity or quality of the active component and include issues such as uniformity solubility, and potency. Capping occurs when there is partial or complete separation of the top or bottom of a tablet due to air entrapment in the granular material, while lamination occurs when a tablet separates into two or more layers for the same reason [42].

Cracking can happen when deep concave punches are used, causing rapid expansion of the tablets [22,43]. Chipping, on the other hand, is due to excessively dry granules. Sticking is the adhesion of granulation material to the die wall while picking refers to the removal of material from the surface of the tablet, which then adheres to the punch face. These defects can be observed visually or through quality control tests such as hardness, content uniformity, and mass variation.

2.7 Factors Affecting Tablet Quality

2.7.1 The Characteristics of the active pharmaceutical ingredients

The API is the most important component of any tablet formulation, as it provides the therapeutic effect. The quality of the API can affect the tablet's quality in terms of how well it works, its purity, and its ability to remain stable over time. It's important that the potency of the API falls within an acceptable range, and that it's pure enough to prevent contamination that could cause side effects [30]. It's also important to conduct stability studies to ensure the API does not degrade during storage. The physical and chemical properties of the API, such as particle size, crystal form, solubility, and stability, can significantly impact the tablet quality. In cases where APIs are poorly soluble or unstable, special formulation techniques such as micronization, complexation, or encapsulation may be necessary to ensure the tablet remains uniform and stable.

2.7.2 Excipient quality and quantity

Excipients are the inactive ingredients added to the tablet formulation to help in its processing, stability, and performance [44]. The quality of the excipients can affect the tablet quality in terms of its appearance, how fast it dissolves, and how much of it is available for the body to use. The excipients used should be of high quality and should be compatible with the API [25]. The quantity of each excipient should be within the acceptable range to avoid toxicity risks. The choice and quantity of excipients can influence the tablet properties, such as how hard it is, how easily it breaks, and how quickly it dissolves. For example, using too much lubricant can reduce tablet hardness [42], while using excessive amounts of fillers can affect tablet disintegration and dissolution [21].

2.7.3 Packaging and storage

The packaging of tablets can affect their quality. The packaging should protect the tablets from environmental factors such as light, moisture, and air. The packaging should also be designed to be tamper-evident and child-resistant to ensure that the tablets are not contaminated or misused [45]. The packaging and storage conditions can affect the stability and quality of the tablet. Improper storage conditions, such as exposure to moisture, heat, or light, can cause degradation of the API and affect the tablet properties [46].

2.7.4 Factors associated with manufacturing processes

The manufacturing process of tablets is critical in ensuring their quality. The process involves blending the API and excipients, compressing the mixture into a tablet, and coating the tablet if necessary. The tablet manufacturing process, including blending, compression, and coating,

can affect the tablet quality. Factors such as mixing time, compression force, and coating thickness can impact the tablet properties, such as how evenly the API is distributed, how much it weighs, and how it looks [47].

2.7.5 Quality and suitability of the manufacturing equipment and facilities

The quality and suitability of the manufacturing equipment and facilities, such as the compression machine, mixer, and coating pan, can affect tablet quality. Equipment that is poorly maintained or not calibrated can result in variations in tablet properties [48]. Therefore, it's important to use equipment that is regularly serviced and calibrated to ensure consistency in the manufacturing process.

2.8 Tests for Assessing Tablet Quality

In pharmaceuticals, various tests are used to evaluate the quality of tablets, including visual inspections and more advanced analytical techniques [49]. These tests assess different aspects of tablet quality, such as its physical and chemical properties and performance characteristics. Some of the commonly used tests to assess tablet quality are visual inspection, hardness, weight/mass uniformity, friability, disintegration time test, dissolution, drug content test/assay, and microbial limit test.

Visual inspection is an essential quality control step in the manufacture of tablets. It is a non-destructive method of evaluating the appearance and integrity of tablets, ensuring that they meet the standards of quality, safety, and efficacy [50]. The United States FDA and the United States Pharmacopeia (USP) have established guidelines for visual inspection of tablet quality. The FDA's Current Good Manufacturing Practices (cGMP) guidelines require manufacturers to visually inspect all finished drug products, including tablets, for defects that may affect the safety, efficacy, or quality of the product. The guidelines state that visual inspection should be performed under adequate lighting conditions and using appropriate equipment such as magnifying glasses, mirrors, and cameras [16]. Information such as the closure, the manufacturer name and address, date of manufacturing and expiry, batch number, registration number, the strength and storage conditions must be visible on the drug package system [51]. Also, the shape, size, color, and texture, and any visible defects of the drug itself should be noted and evaluated before use.

It is required that the weight of each tablet in a batch should fall within a specific range. The weight variation test ensures that the tablets are consistent in weight, and any significant deviation from the specified weight range may indicate a problem in the manufacturing process.

The hardness of a tablet refers to its ability to resist breaking or crumbling under pressure. A tablet with insufficient hardness may break or crumble during handling and transportation, affecting its efficacy [52]. The hardness test evaluates the tablet's resistance to crushing using a tablet hardness tester.

Friability of a tablet can be explained as the tendency of a tablet to crumble or break into small pieces when subjected to mechanical stress [28]. The friability test measures the weight loss of a sample of tablets when subjected to repeated tumbling in a drum. If tablets are more friable then it implicates their inability to be subjected to stress during packaging and distribution, especially over long distances. It is obvious that the hardness and friability have a good correlation. If the tablet is too hard, it may not be able to withstand mechanical stress, leading to increased friability. On the other hand, if the tablet is too soft, it may crumble or break apart more easily, also leading to increased friability. Therefore, finding the right balance between hardness and friability is essential in tablet manufacturing to ensure the quality and performance of the final product.

The disintegration time test is a physical test that measures the physical properties of the dosage form, such as its ability to break apart and dissolve in a specified medium. The test is designed to simulate the conditions in the human body and ensure that the dosage form will release the active ingredient(s) in a timely and effective manner. The test helps to ensure that the tablet disintegrates in the body, releasing the active ingredient for absorption. How tablets or capsules dissolve in a liquid medium, releasing the active ingredient for absorption over time is performed by the dissolution test. With time, the active ingredient(s) in the sample are released into the medium and their concentration is measured using analytical techniques, such as UV-Vis spectrophotometry or HPLC. It helps ensure that the product will release the active ingredient(s) in a consistent and reproducible

manner, and that it will be bioavailable to the patient. The test is often used in combination with other tests, such as the dissolution test, to provide a comprehensive evaluation of the performance of the drug product. The results of the dissolution test are typically reported as a dissolution profile or dissolution curve, which shows the percentage of the active ingredient(s) released over time. The dissolution profile is compared to a standard or acceptance criteria specified in the relevant pharmacopeia to ensure that the product meets the required dissolution specifications.

One quality test that is essential to ensure drug safety, efficacy and quality is the drug content uniformity test. The content uniformity test evaluates the uniformity of the active ingredient in a batch of tablets. The test measures the amount of the active ingredient in individual tablets and ensures that the tablets contain the specified amount of the active ingredient. This test helps to evaluate whether a drug is of acceptable quality, poor quality or counterfeited. The pharmacopoeia typically recommends HPLC as one of the preferred analytical methods for drug content testing due to its precision and accuracy. Other analytical techniques, such as infrared spectroscopy, gas chromatography is also used drug assay. The standard values for content uniformity are specified in the USP and BP.

One quality control test that needs to be mention is the microbial limit test. The microbial limit test is a quality control test that is required by regulatory authorities to ensure that the drug product is free from harmful microorganisms and meets the required specifications. The test is performed on both raw materials and finished products to ensure that they are safe and free from contamination. The presence of microbial contaminants in a tablet can pose a serious health risk to the patient. The microbial limit test evaluates the presence of bacteria, yeast, and molds in a batch of tablets. The results of the microbial limit test are compared to the acceptance criteria specified in the relevant pharmacopoeia or regulatory guidelines. If the number of microorganisms present in the sample exceeds the specified limits, the drug product is considered to be contaminated and may pose a risk to patient safety.

2.9 Quality Attributes of Suspensions

The properties and quality attributes of a suspension play a critical role in determining its effectiveness and safety for patients, as well as their willingness to use it. In this article, the researcher explored these properties and attributes in greater detail.

One common property of suspensions includes, the particle size distribution. The size and distribution of particles in a suspension are crucial properties that impact its physical stability and effectiveness. It is recommended that the particle size must be small enough to prevent settling, but not so small that the particles clump together or form aggregates. Techniques such as microscopy or laser diffraction can be used to measure the particle size distribution. Another property is the rheology. The rheological properties of a suspension refer to how it flows, its viscosity, and the thixotropic nature. Depending on the suspending medium and particle concentration, the flow behavior can be either Newtonian or non-Newtonian. Ideally the viscosity should be low enough for easy administration but high enough to prevent settling. Thixotropy describes how the suspension becomes less viscous under stress. Also, the sedimentation rate of a suspension is a crucial property to discuss. The rate at which particles in a suspension settle is determined by factors such as particle size, density, and medium viscosity. A slow sedimentation rate is preferable to ensure consistent dosing and to reduce the need for shaking or re-suspension. Another property of interest is redispersibility. The ability of a suspension to redisperse after settling is an essential property that affects its shelf life and ease of administration. The use of stabilizers, surfactants, or smaller particle sizes can improve redispersibility. Also, the pH and osmolality of a suspension can impact its chemical stability and tolerability. The pH should be near neutral to prevent chemical breakdown or irritation, while the osmolality should be similar to that of body fluids to avoid discomfort or tissue damage.

The quality of suspensions is a crucial factor in ensuring patient compliance and satisfaction with medication. Key qualities of suspensions, such as consistency of active ingredient content in each unit dose, ability to maintain properties and characteristics over time, integrity and potency of the active ingredient, resistance to microbial growth or contamination, and overall acceptability to patients in terms of taste, odor, and texture, must be carefully considered. Adhering to these quality standards is essential for ensuring optimal therapeutic outcomes and patient safety.

2.10 Common Quality Defects in Suspensions

Suspensions are a widely used dosage form in the pharmaceutical industry, but they are not immune to quality defects. Quality defects in suspensions can have significant implications for patient safety and efficacy of the drug product. Some common quality defects in suspensions are explained below.

2.10.1 Particle settling or caking

This is one of the most common quality defects in suspensions. When the particles in a suspension settle, they can form a cake at the bottom of the container, leading to non-uniform dosing and reduced effectiveness of the drug product. The problem of particle settling or caking can be exacerbated by the presence of larger particles or high particle concentrations. This issue can be addressed by using appropriate stabilizers, surfactants, or by reducing the particle size.

2.10.2 Poor redispersibility

Redispersibility refers to the ability of a suspension to redisperse after settling. Poor redispersibility can lead to non-uniform dosing and reduced effectiveness of the drug product. The use of appropriate stabilizers, surfactants, or reducing the particle size can help to improve the redispersibility of a suspension. The particle size and distribution of a suspension can affect its physical stability, flow behavior, and efficacy. Smaller particles can lead to better particle dispersion and higher surface area, which can improve the solubility and bioavailability of the active ingredient. However, if the particles are too small, they can aggregate or flocculate, leading to poor redispersibility and sedimentation.

2.10.3 Agglomeration or flocculation

Agglomeration or flocculation refers to the formation of clusters or clumps of particles in a suspension. This can lead to reduced efficacy and safety of the drug product, as well as poor patient acceptance due to changes in texture or appearance. This issue can be addressed by using appropriate stabilizers or surfactants, or by adjusting the pH or ionic strength of the suspending medium. The surface charge of the particles can affect their interaction with the suspending medium and other particles. Particles with a high surface charge can repel each other, leading to better particle dispersion and stability. However, particles with the same surface charge can also attract each other, leading to agglomeration or flocculation.

2.10.4 Crystallization

Crystallization is another common quality defect in suspensions. It occurs when the active ingredient or excipients in the suspension form crystals, leading to changes in the physical and chemical properties of the drug product. This can lead to reduced efficacy and safety of the drug product, as well as poor patient acceptance due to changes in texture or appearance. Crystallization can be prevented by controlling the pH, temperature, or concentration of the suspending medium.

2.10.5 Inadequate microbial stability

Microbial contamination can be a significant quality defect in suspensions. It can lead to infections or adverse reactions in patients, as well as reduced efficacy of the drug product. Microbial contamination can be prevented by maintaining appropriate environmental conditions during manufacturing, storage, and distribution of the drug product.

2.10.6 Inaccurate dosing

Inaccurate dosing can occur due to improper measuring or mixing of the suspension. This can lead to under or overdosing, which can have significant implications for patient safety and efficacy of the drug product. Accurate dosing can be ensured by using appropriate measuring devices or techniques, and by following the instructions provided with the drug product.

2.11 Tests for Assessing Suspension Quality

Tests for assessing suspension quality are important in ensuring that the drug product is safe and effective for patient use. These tests are designed to evaluate various aspects of suspension quality, such as particle size, uniformity, stability, and redispersibility. Here are some common tests used for assessing suspension quality:

2.11.1 Particle size analysis

Particle size is an important factor affecting the quality of a suspension. Small particle size is

desired to ensure uniformity and stability of the suspension. Particle size analysis can be done using various techniques such as laser diffraction, sedimentation analysis, or microscopy.

2.11.2 Uniformity of dosage units

The uniformity of dosage unit's test is used to ensure that the amount of drug in each unit of the suspension is consistent. This test is important to ensure accurate dosing and prevent under or overdosing of the drug. The test involves sampling a number of units from the batch and analyzing the amount of drug in each unit.

2.11.3 Redispersibility test

The redispersibility test evaluates the ability of the suspension to redisperse after settling. This test is important to ensure that the drug is uniformly distributed throughout the suspension and to prevent non-uniform dosing. The test involves measuring the sedimentation volume and the time taken for the sediment to redisperses back into the suspension.

2.11.4 pH measurement

pH measurement is important for ensuring the stability of the suspension. The pH of the suspension should be within a certain range to prevent chemical degradation of the drug or excipients. pH measurement can be done using a pH meter or pH indicator paper.

2.11.5 Microbial limits testing

Microbial limits testing is important for assessing the microbial contamination of the suspension. This test involves sampling the suspension and testing for the presence of microorganisms such as bacteria or fungi. The test is important for ensuring the safety of the drug product and preventing infections or adverse reactions in patients.

2.11.6 Appearance and texture evaluation

Appearance and texture evaluation are important for assessing the patient acceptance of the suspension. The suspension should have a uniform appearance and texture, and should not have any visible particles or sediment. The evaluation can be done by visual inspection or by measuring the rheological properties of the suspension using techniques such as rheometry.

2.12 Analytical Techniques for Quality Assessment

In the pharmaceutical industry, analytical techniques refer to the various methods used to measure the quality and quantity of the components present in a sample. These techniques are extremely important during the manufacturing process to ensure that drugs are safe and effective for use by patients. Commonly used analytical techniques include hardness test, friability test, pH test, disintegration time test, drug content test, and dissolution testing using the appropriate test equipment. Their role is crucial in quality control and assurance as they help measure the components in a drug formulation with high accuracy, which helps ensure that the drug product meets established standards for safety, efficacy, and purity. Moreover, these techniques are also useful in identifying potential issues in the formulation, such as impurities or inconsistencies in the manufacturing process, and taking corrective action. Ultimately, the use of analytical techniques is crucial in ensuring that drugs are safe and effective for patients.

2.13 Regulatory Requirements for Quality Assessment

Regulatory requirements for quality assessment of tablets and suspensions are put in place to ensure that the drugs are safe, effective, and of high quality for patient use. These requirements are established by regulatory bodies such as the US FDA, EMA, and other national regulatory agencies.

One important regulatory requirement for quality assessment is the need for manufacturers to follow GMPs. GMPs provide a framework for the production and control of pharmaceutical products, including tablets and suspensions. GMP requirements cover various aspects of manufacturing, such as facility design, equipment calibration, personnel training, documentation, and quality control. By adhering to GMPs, manufacturers can ensure that their products are consistently produced to meet established quality standards.

Another regulatory requirement for quality assessment is the need for manufacturers to conduct stability studies on their products. Stability studies are designed to evaluate the stability of drugs under various storage conditions over time. These studies are important to ensure that the drugs maintain their quality

and effectiveness throughout their shelf life. Manufacturers must submit stability data as part of their regulatory submissions to demonstrate the safety and efficacy of their products.

Furthermore, regulatory bodies require manufacturers to conduct bioequivalence studies for generic drugs. Bioequivalence studies compare the pharmacokinetic properties of a generic drug to those of the innovator drug to demonstrate that the generic drug is equivalent in terms of safety, efficacy, and quality. These studies are important to ensure that patients can safely switch from the innovator drug to the generic drug without compromising their treatment outcomes.

2.14 Current Good Manufacturing Practices (cGMPs) for Pharmaceutical Manufacturing

Current Good Manufacturing Practices (cGMPs) are a set of guidelines and regulations that govern the manufacturing of pharmaceutical products. These guidelines are enforced by regulatory agencies such as the US FDA and the EMA. These guidelines ensure that pharmaceuticals are consistently produced and controlled to meet the established quality standards for their intended use.

The cGMPs for pharmaceutical manufacturing cover all aspects of the production process, from the sourcing of raw materials to the distribution of finished products. Compliance with cGMPs is critical for ensuring the safety and efficacy of pharmaceutical products. Failure to comply with cGMPs can result in regulatory enforcement actions, such as warning letters, fines, and even product recalls. On the other hand, compliance with cGMPs can help pharmaceutical manufacturers avoid these risks and ensure that their products are of consistent quality and meet the highest standards of safety and efficacy.

The cGMPs establish standards for the manufacturing process are summarized in the Table 1.

2.15 Case Studies in Quality Assessment

Quality assessment is an ongoing process throughout the drug development lifecycle, from early-stage research through clinical trials and post-market monitoring [53]. In a study conducted by Basha and colleagues [54], revealed that changing the formulation and manufacturing process of famotidine tablets improved their dissolution rate, resulting in improved bioavailability and therapeutic efficacy.

Table 1 cGMPs established standards for manufacturing processes

Parameter	Requirements
Facilities	The manufacturing facility must be designed and constructed to meet the requirements for pharmaceutical manufacturing. This includes having adequate space, lighting, ventilation, and equipment.
Equipment	All equipment used in the manufacturing process must be properly designed, installed, calibrated, and maintained to ensure that it functions correctly and consistently.
Raw materials	Raw materials used in the manufacturing process must be properly identified, tested, and stored to ensure their quality and purity.
Production	The production process must be properly controlled to ensure that the product meets its established quality standards. This includes establishing standard operating procedures, monitoring the manufacturing process, and conducting regular quality checks.
Testing	Finished products must be tested to ensure that they meet their established quality standards. This includes testing for identity, purity, potency, and stability.
Documentation	All aspects of the manufacturing process must be properly documented, including raw material sourcing, production, testing, and distribution. This documentation provides a record of the entire manufacturing process and allows for traceability in the event of any issues or recalls.

Also in a study published in the International Journal of Pharmaceutics, the researchers found that increasing the compression force used during tablet manufacturing reduced the friability of the tablets, resulting in improved physical strength and stability [55]. Several other instances where quality assessment has played a greater role in ensuring quality globally include the following:

The COVID-19 pandemic has brought increased attention to quality assessment in the development and manufacture of vaccines. In the case of the Pfizer-BioNTech COVID-19 vaccine, for example, rigorous quality assessment was conducted throughout the development and manufacturing process to ensure that the product was safe and effective. This included testing for identity, purity, potency, and sterility, as well as testing for potential contaminants [56]. Also in 2020, a case study of the quality control failures in the production of hand sanitizers was reported during the COVID-19 pandemic. The US Food and Drug Administration (FDA) found that some hand sanitizers contained high levels of methanol, a toxic substance that can cause serious health problems when absorbed through the skin or ingested. The incident led to a recall of several hand sanitizer products and highlighted the importance of quality control testing in the production of essential healthcare products [57]. Then again in 2019, a study published in the Journal of the American Medical Association (JAMA) [58], found that some popular sunscreens did not meet the FDA's standards for quality assessment. Specifically, the study found that some sunscreens had lower levels of active ingredients than claimed on the label, and some had higher levels of contaminants. The findings raised concerns about the quality assessment processes for sunscreen products, and prompted the FDA to investigate further. Another incidence also happened in 2019 where the US FDA announced the discovery of a contaminant called N-Nitrosodimethylamine (NDMA) in ranitidine products, which are used to treat heartburn and other gastrointestinal issues [59]. NDMA is a known carcinogen and is not supposed to be present in pharmaceutical products. The discovery led to recalls of ranitidine products and increased scrutiny of quality assessment processes for other pharmaceutical products.

In 2018, a global recall of blood pressure medication (Valsartan) due to contamination with a potential carcinogen, N-nitrosodimethylamine occurred. The incident was linked to poor quality control practices at several manufacturing facilities in China and India. The recall affected millions of patients and led to increased scrutiny of the pharmaceutical industry's supply chain and manufacturing practices. It also highlighted the need for greater regulatory oversight of drug manufacturing facilities and supply chains. Finally, one such situation is the 2012 fungal meningitis outbreak in the United States, which was linked to contaminated steroid injections. The injections, which were produced by a compounding pharmacy, were contaminated with fungus due to poor quality control practices. The outbreak resulted in over 750 cases of fungal meningitis and more than 60 deaths [60]. The incident highlighted the importance of proper quality control and testing procedures in compounding pharmacies and led to increased regulatory oversight of the industry.

2.16 Challenges and Successes in Ensuring Quality of Tablets and Suspensions

Ensuring the quality of tablets and suspensions is critical for the pharmaceutical industry to deliver safe and effective medications to patients. However, there are several challenges that manufacturers face in ensuring quality, as well as successes that have been achieved through innovation and improved quality assessment processes.

2.16.1 Challenges

- Variability in raw materials: The quality of the final product is highly dependent on the quality of the raw materials used. However, raw materials can vary in quality and consistency, which can impact the final product.
- Manufacturing processes: Tablets and suspensions require complex manufacturing processes that involve several stages, such as mixing, granulation, and compression. Any deviation in these processes can affect the quality of the final product.
- Stability issues: Tablets and suspensions can be affected by factors such as moisture, light, and temperature, which can impact their stability and shelf life.
- Analytical challenges: Quality assessment of tablets and suspensions involves complex analytical methods,

such as HPLC and spectrophotometry, which require specialized expertise and equipment.

2.16.2 Successes

- Continuous manufacturing: Continuous manufacturing is a process that eliminates many of the variability issues associated with traditional batch manufacturing. It involves continuously feeding raw materials into a system, which produces a steady stream of high-quality tablets or suspensions. This process has been shown to improve quality and consistency while reducing costs and waste.
- Quality by design (QbD): QbD is a systematic approach to quality assessment that involves designing products and processes with quality in mind from the outset. This approach focuses on identifying critical quality attributes and developing methods to measure and control them throughout the manufacturing process.
- Improved analytical methods: Advances in analytical methods, such as mass spectrometry and nuclear magnetic resonance spectroscopy, have improved the accuracy and sensitivity of quality assessment for tablets and suspensions. These methods have also reduced the need for complex sample preparation and increased the speed and efficiency of quality assessment.
- Risk-based approaches: Risk-based approaches to quality assessment involve identifying potential risks and developing strategies to mitigate them. This approach has been shown to improve the efficiency and effectiveness of quality assessment while reducing costs and minimizing the risk of product recalls.

2.17 Implications for Future Research and Development of Quality Assessment Methods

As the pharmaceutical industry continues to evolve and new products are developed, there is a need to continually improve the methods and techniques used for quality assessment. Here are some implications for future research and development of quality assessment methods in pharmaceutical industry

2.17.1 Advancements in analytical techniques

The development of new analytical techniques, such as HPLC, gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy, have greatly improved the accuracy and precision of quality assessment methods. However, there is a need for continued research in this area to develop more sensitive and specific analytical techniques that can detect impurities and contaminants at even lower levels.

2.17.2 Predictive models

The development of predictive models for quality assessment could greatly improve the efficiency of pharmaceutical development and manufacturing. These models could use data from previous quality assessments to predict the likely outcomes of future assessments, reducing the need for extensive testing and accelerating the time to market for new products.

2.17.3 Advances in technology

The development of new technologies, such as nanotechnology and 3D printing, could have significant implications for quality assessment in pharmaceutics. These technologies could lead to the development of new dosage forms that are more effective and have fewer side effects. However, there is a need for extensive research to determine the safety and efficacy of these new technologies, and to develop appropriate quality assessment methods.

2.17.4 Regulatory compliance

The pharmaceutical industry is highly regulated, and regulatory compliance is a critical aspect of quality assessment. The development of new quality assessment methods must take into account the regulatory requirements of various countries and regions, including the US FDA and the European Medicines Agency (EMA).

2.17.5 Advanced in vitro and in vivo testing

In vitro and in vivo testing are essential for assessing the safety, efficacy, and bioavailability of pharmaceutical products. Further research is needed to improve these testing methods and to develop new models that more accurately mimic human physiology and disease states. For

example, the development of 3D cell culture models and organ-on-a-chip systems may provide more accurate and reliable data for drug development and quality assessment.

2.17.6 Quality-by-design (QbD) approach

The QbD approach is a systematic method for developing pharmaceutical products that considers the impact of formulation and process parameters on the quality of the finished product. This approach can help to reduce the need for extensive quality testing and to improve the efficiency of drug development and manufacturing. Further research is needed to refine the QbD approach and to develop new tools and methods for implementing it in practice.

2.17.7 Artificial intelligence and machine learning

Artificial intelligence and machine learning are increasingly being used in pharmaceutical research and development to analyze complex data sets and to identify patterns and trends that may not be visible to the human eye. These technologies have the potential to transform quality assessment by providing more accurate and reliable data, as well as by reducing the time and cost of drug development. Further research is needed to develop new algorithms and models that are tailored to the specific needs of pharmaceutical research and development.

2.17.8 Regulatory frameworks

The regulatory frameworks that govern the development and manufacture of pharmaceutical products are constantly evolving, and quality assessment methods must keep pace with these changes. Further research is needed to ensure that quality assessment methods are aligned with regulatory requirements and that they can be adapted to new regulatory frameworks as they emerge.

3. CONCLUSION

In-process quality checks and post market surveillance of drugs play a crucial role in ensuring the safety, efficacy, and reliability of these medications. Through a careful quality assessment processes, regulatory authorities, pharmaceutical companies, and healthcare professionals can evaluate various aspects of FDC drugs to guarantee their compliance with established standards and regulations. By conducting rigorous routine post-market surveillance of drugs, regulatory authorities can grant marketing authorizations or approvals, indicating that the FDC drugs have met established quality standards. Healthcare professionals can confidently prescribe and administer these medications, knowing that they have undergone robust evaluations to ensure patient safety and therapeutic effectiveness. Continuous monitoring and post-market surveillance further contribute to the ongoing assessment of FDC drug quality, ensuring their consistent performance and addressing any emerging concerns

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL STATEMENT

This study did not require an ethical board approval because it utilized only secondary data from peer reviewed research articles in reputable journals.

CONFLICT OF INTERESTS

Authors declare that, no conflict of interests exist. All authors read and approved the manuscript

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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