

**Review Article**

A Review on the Microbial Contamination in the Non-sterile Pharmaceutical Products

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Abstract: This article aims to review available scientific data dealing with the Microbial contamination that may occur by some environmental factors (temperature, pH, and water activity), these factors are a major problem for the spoilage of pharmaceutical dosage form, and raw material, personnel, and other factor contributing to the transfer of the microbe into the pharmaceutical product. Non-sterile oral pharmaceuticals, including syrups, do not need to be sterile. At the same time, certain quality-control tests and some measures were followed, according to current good manufacture practice (cGMP), which are essential to keep the microbial content of these preparations safe and acceptable. Similarly, may manufacturer failures to comply with the Good Manufacturing Practice (GMP) at any stage of pharmaceutical production may consequently affect the microbiological quality of the product, and ultimately they caused economical loss for industrialists on the spoilage of pharmaceuticals. Microbial contamination in the pharmaceutical products increases from prescribed limits may change their Physico-chemical properties of the dosage form may be chances to hazardous for the immune-compromised patient due to overload microbial contamination. All the components of the non-sterile pharmaceuticals such as API and all kinds of excipients are at risk due to microbe overloaded and spoilage. Strictly the following (cGMP), continuous pharmaceutical surveillance is required to control microbial contamination within the pharmaceutical preparations.

Keywords: Microbial Contamination, Non-sterile Pharmaceuticals, pH, Germination, Pharmaco-chemical, Good Manufacturing Practice

1. Introduction

Presently, the standard of the non-sterile dosage forms has been enhanced by various pharmaceutical industries, which ultimately reduce microbial hazards [1]. To determine the source of contamination, the microbial load should be critically monitored at every step from the starting to the final stage of manufacturing [2]. The presence of microbial contamination in the pharmaceutical product may cause secondary infection in patients subject to therapy [3].

The use of these contaminated non-sterile preparations can cause hazards in the majority of ways as they may cause financial loss to the industrialists, alter the therapeutic effect

of the drug and affect the health [4]. There are specific guidelines particularly for immune-compromised personals like old, neonates, child and cancerous patients, the class of patients having precisely a lower limit of bio-burden than other patients because these types of patients are more likely to adapt infection from contaminated non-sterile pharmaceutical products [5]. The presence of microbial contamination even in traces may lead to severe infection in immune-compromised patients [6].

The pharmaceutical formulations ingredients such as API, preservatives, sweetening agents, and other components may be microbial attacked [7]. The overloaded microbial contamination may change in the physical appearance of a

dosage form, such as the texture of powder and tablets, consistency of gel and creams, phase inversion in emulsions, turbidity in solution, and syrups. [8].

2. Microbial Contamination of Non-sterile Solid Dosage Form

For the manufacturing of pharmaceuticals dosage form, many active and inactive substances were used and many processes involved for material manufacturing such as fermentation, isolation/separation/recovery from natural substances, chemical synthesis, and other biotechnology methods [9, 10]. The pharmaceutical products may be contaminated, driven from the raw material, and transferred into the final pharmaceutical products. [11].

Furthermore, many elements contribute to the bio-burden carried at every step manufacturing of pharmaceutical dosage form. These may include; raw material, personnel, processer of manufacturing, storage environment, and material of packing [12].

During the manufacturing of pharmaceutical products, most of the raw materials support some kind of microbial growth, which is dependent upon the moisture contents and nutritional aid. So capsules, tablets, and dry powder suspensions are capable of undergoing some kind of microbial degradation or spoilage. In the tablets, microbial contamination was a very critical problem, there is no apparent indication of spoilage. Therefore it is recommended that, know about the amount of bio-burden in pharmaceutical products, they are required to be sterile or non-sterile dosage forms, on the other hand, the preservative may be another source of contamination and use a shield in the formulation against microbes. They are also known as a ready source of nutrition for microbes.

3. Microbial Contamination Solid Dosage Form Tablets and Capsule

The fundamental benefit of tablets and capsules is to provide a correct and complete dose of active substance, which is required for therapeutic effect. Each solid dosage form should comprise a known amount of excipients and API. In the tablets, Lactose is the frequently used excipient. basically, It is whitish in color, and microbial contamination many tablets change their colors into brown. According to the literature reports, microbial contamination may change in cracks at the side and rough surfaces, physical changes like change in color, chemical changes of chemical modification in the tablet aspect, such as starch, through the microorganisms, at the ends, cracks on tablets due to loss of their binding properties. The capsules are softer after incubation of 3 weeks, as confirmed by the usage of low tensile force values. This collapse was due to the usage of starch as a binder, maybe because microbes transfer into vitamins for growth from it. On the storage of the capsule, the dissolution time elevated significantly after inoculation

with the microorganisms [14].

4. Environmental Factors Effect on Microbial Growth

4.1. Nutritional Factors

The microorganisms are required nutrition for metabolic activities and growth they many formulation additives for biosynthesis and growth. An extra nutritional environment is provided by crude vegetable or animal products contained in the formulation. On the other hand, deionized water is treated through an ion exchange technique that is normally incorporated of adequate amount of nutrients to the growth of a few species of pseudomonas.

The required particular growth factors for acute pathogens are frequently unavailable in pharmaceutical dosage form, but they do not replicate, remain viable in dosage form and cause infection at the proper time.

4.2. Moisture Contents (Water Activity - *a_w*)

Microorganisms required easy access to water in the count for growth, and aqueous formulations are given easy access to water for microorganisms. In aqueous formulation, water activity can be decreased by incorporating of high concentration of sugar or PEG via a drying process. On the surface of the dry product which, includes tablet and bulk oil condensed water films, can be accumulated due to storage high humidity environment may result in fungal growths.

4.3. Redox Potential

An environment is impacting on the usage of oxidation-reduction balance as they are required for their functions and biosynthesis of microbial growth. In emulsions the redox potential reactions can be easily carried out because of the high amount of oxygen molecules available in fat and oils.

4.4. Storage Temperature

Liquid dosage form and multi-dose eye drop packs were instructed in the range at 8-12°C, at this temperature maximum chances to reduce the growth of microorganisms during storage and use. For the prevention of possible growth, gram-negative bacteria in water for injection should be distillation, done before packing and sterilization held at 80°C [15]. Studied microbial examination of some non-sterile by computing the amount of living contaminant, using simple counting methodologies. The microbial count of liquid oral dosage forms after a storage period of 0, 6, and 12 months, was examined by storage on the specific microbial contamination levels. The dosage form microbial load varied from one dosage form to another dosage forms the lowest in tablets and the highest microbial load in suspensions. Amount of contamination at 6 and 12 months were found a considerable difference from that at 0 months [16].

5. Temperature Effect on Microbial Growth and Toxins Production

Pharmaceuticals would be spoiled on the rise of temperature varying from 20°C to 60°C. Nevertheless, it has happened even at a very low temperature. During storage and transportation of pharmaceuticals can be affected by the surrounding temperature in the region, tropical or subtropical in this respect.

It is noticed that the aflatoxins production and isolation from the *Aspergillusflavus* were worked for five days on media at different temperatures ranging from 2°C to 52°C. It is found that on two temperature units were maximum growth of isolate 29°C and 35°C C these isolate, the ideal temperature for the increase of every *Aspergillusflavus*, in the growth of aflatoxin optimum temperature was required. The growth rate varied with the effect of temperature from aflatoxin B1 to aflatoxin G1. It was observed that the growth of aflatoxin was not dependent upon the development of *Aspergillusflavus*, at the same time, at 35°C, aflatoxin B1 was produced. Furthermore, the determination of aflatoxin G1 production on the temperature 18°C and production starts between 7°C and 13°C and 24°C the maximum production. These differences affect can be via the variety of isolates [17].

The effect of temperature was observed on the aflatoxin production on a cereal substrate via *Aspergillusflavus* grown. On the determination of the ideal temperature for the development of aflatoxin B1 and G1, under the employed conditions changed to 28°C. At the same time, yields were obtained of aflatoxin B1 at the temperature of 32°C at the same temperature, the production of G1 was significantly lesser. It is found that Both B1 and G1 at a temperature above 32°C less amount, and incubation of aflatoxin content rice at 37°C turned low (300-700 ppb) even though growth becomes accurate. When reducing the temperature from 28 to 15°C, this may lead to steadily much less aflatoxin, but cultures were incubated for 3 weeks at 11°C B1 changed into detected, at 8°C no aflatoxin was produced, the average of the 4 aflatoxins became affected by temperature.

A fundamentally equal amount of aflatoxin B1 and G1 have been produced at the lower temperature, while on the contrary, at 28°C, around 4 times as much B1 was found as G1. Similarly, it was found that at higher temperatures, G1 production of extraordinarily lesser and much less than (10 ppb) was detected at 37°C.

Laciaková study, that the time requirement for devitalization of *Aspergillusniger*, and *Penicilliumglabrum* fungus (*Aspergillus* and *Penicillium*spp) and other microbes at different temperatures [17- 20].

In addition, at the different temperatures ranging from 22, 37, and 60°C, all of the analyzed samples strain to incubate on sabouraud agar for 42 days at a temperature 22°C, the devitalization of *Penicillium glabrum* happened after 21 days, and *Aspergillusniger* devitalization occurred after 35 days, at the temperature of 37°C, the devitalization of all examined samples of microorganisms within five hours at the temperature of 60°C [19, 20].

Furthermore, it is observed that the optimum temperature for growth of *Aspergillus flavus* did not occur simultaneously, with those for aflatoxin formation and aflatoxin B1 maximum production happened at the temperature 24°C, nevertheless, they were found that maximum growth at 18°C, the optimum temperature for growth enhance at a lower temperature then ideal for aflatoxin production, at the same time, no products were found aflatoxin B1 at 36°C.

They also found that aflatoxinG1 production started between 18 to 24°C, and maximum production was observed at a temperature of 30°C [20, 21].

6. Effect of Temperature and Water Activity (aw)

Pitt and MISCAMBLE [22] were examined the water relations of three isolates which closely resemble the species *Aspergillusnomius*, *Aspergillusflavus*, *Aspergillusparasiticus*, and *Aspergillusoryzae* at three temperatures, 37°C, 30°C, and 25°C Respectively.

To observe a range of water activity from 0.996 to 0.75 and media were prepared accordingly, combine a mixture of glucose and fructose was used for controlling. The water relations of *Aspergillusflavus*, *Aspergillusoryzae*, and *Aspergillusparasiticus* have been very similar. The minimal (aw) for germination and increase of each of those three species turned into 0.82 at 25°C, 0.81 at 30°C, and 0.80 at 37°C. *Aspergillusnomius* become slightly much less xerophilic, with minimal (aw) values for production and development of 0.83 at 25 and 30°C, and 0.81 at 37°C. Stated differences in water relations among *Aspergillusflavus* and *Aspergillusparasiticus* had have been no longer considerable. The "domestication" of *Aspergillusoryzae* has no longer affected water relations.

Firstly Marin et al then secondly Samapundo and his colleague [23, 24] work on the impact and interaction of temperature (5–45°C), water availability (water activity values 0.95–0.75), at the temporal rates of germination and mycelial growth of mycotoxigenic strains of *Aspergillusflavus*, *Aspergillusochraceus*, *Aspergillusniger*, *Penicilliumhordei*, and *Penicilliumaurantiogriseum*, on a maize extract medium in vitro analysis. For all species germination process become very rapidly at >0.90 (water activity) with an almost steady growth time frame. Although, at <0.90 (water activity), *Aspergillusflavus* and *penicillium hordei* can be a slower rate of germination. The minimum water activity for germination is usually lower than for growth and depends upon temperature variances. During germination, the temperature and water activity interact with lag phase (h), before germination, and on the rate of germination (h-1), for the use of Gompertz version changed via Zwietering, predicted for the first time.

They confirmed that *Aspergillusflavus*, *Aspergillusniger*, and *Penicillium*s traces have short lag times in the middle of 0.995–0.95 (aw) over a wide range of temperatures. At the different ranges of temperatures, these have been remarkably

higher, especially at $< 10^{\circ}\text{C}$ for *Aspergillus* species and at $> 30^{\circ}\text{C}$ for *Penicillium* species. An isolate of *Aspergillus ochraceus*, a statistically more difference between lag phase and germination. The germination rate of *Aspergillus* species is speedy than the *Penicillium* species. The growth of mycelial is varying from species to species on the temperature and Water activity, both in the count of rate (mm/d) and tolerances.

Water activity (aw) and temperature (T) affect the growth of seven types of fungus such as (*Aspergillusflavus*, *Penicilliumchrysogenum*, *Alternariaalternata*, *Cladosporiumcladosporioides*, *Mucorramenosus*, *Rhizopusoryzae*, and *Trichodermaharzianum*) became judged by Sautour *et al.* and Kwon-Chung [25, 26]. In suboptimal conditions, they verify for the development of fungi, water activity (aw), on significant influence over temperature (T) activity. Water activity at 0.99, the optimum growth rate was observed for *Aspergillusflavus*, although, the growth rate remains low for *Penicilliumchrysogenum*, the average growth rate is three to six mm/day.

The determination of the variations within the ideal growth rate between molds can be characteristics and nature of the microorganisms for the growth rate the ideal temperature was almost 25°C separately from *Aspergillusflavus* and *Rhizopusoryzae*, which shows values of 31 and 35°C , respectively. At temperatures between 15 to 40°C , at that temperature, the genus *Aspergillus* grows easily [27].

With decreasing water activity from 0.99 to 0.97 at the temperature of 31°C , outstanding increase in the growth rate of *Aspergillusflavus* and accelerated from 5.7 to 9.7 mm/day. *Penicilliumchrysogenum* at the 0.985 water activity, growth rate faster than at 0.99 (aw), hence the growth rate of these molds higher in a less humid environment and that environment grow at the ideal rate.

Abellana *et al.* and Dagnas *et al.* these groups of the researcher [28, 29] compared the growth rate of mycelial, and they observed the effect and interactions of temperature and water activity, these mycelial of *Penicilliumaurantiogriseum*, *Penicilliumchrysogenum*, *penicillium corylophilum*, and *Aspergilla flavus* on a sponge cake analog. As anticipated, the growth rates indicate completely dependent on water activity and temperature. Although all the isolates have been not huge variations were found within the growth rate. They observe that the minimum water activity values for growth of *Penicillium* species, small change into 0.85-0.90.

The ability of *Aspergillusflavus* grows at 0.90 (aw) when above the temperature from 15°C .

Plaza *et al.* and Garcia *et al.* Both researcher teams [30, 31], analyze the water activity (0.87-0.99) and temperature ($4-37^{\circ}\text{C}$) and their effect on the rate of germination, before germination lag time, and mycelial growth (in vitro) of *Penicilliumitalicum*, *Penicilliumdigitatum*, and *Geotrichumcandidum*. The temperature (t) and water activity (aw) remarkably facilitate growth and germination rate. Generally, when the temperature and water activity were not an ideal condition, at that time, lag times were longer while germination rate has been slower.

The germination over a wide range of 4 to 3°C temperature at 0.995 water activity for all the examined species, however in suboptimum circumstances for *Penicilliumdigitatum* excellent reached 40 to 60% for the germination conidia. At the low temperature, the growth and germination rate of *Penicilliumitalicum* is faster than the *Penicilliumdigitatum* and *Geotrichumcandidum*, particularly at 0.95 (aw). In dry conditions, *Penicilliumitalicum* is capable of developing and germinating on a 0.87 (aw) value.

Lahlali *et al.* [32] to find the effect of water activity (aw) 0.89-0.98, at the temperature (5 to 25°C) and treated with glycerol, sorbitol, glucose, and sodium chloride; Important spoilage of citrus products with fungi at the lag phase and radial growth (mm/day), some other fungi grown in potato dextrose agar (PDA) medium such as *Penicillium italicum* and *Penicillium digitatum*. Water activity, temperature, and solutes build the impact on the radial growth rate. The water activity of the medium decreased their were disturbing the radiate growth, inhibit or suppress, and the lag phase lengthened. At the same time, sodium chloride can cause significant pressure on growth as compared with non-ionic solutes. Similarly, at 0.93 and 0.96, water activity has stopped the growth of *Penicillium digitatum* and *Penicillium italicum*, respectively. On the observation growth rate in the dry situation, they found *Penicillium italicum* grows faster than *Penicillium digitatum* at low temperature and ambient temperature for *Penicillium digitatum* growth rate more lively.

Kulshrestha *et al.* and de FreitasAraújo [33, 34] analyzed the selected ten medicinal herbs; and observed the growth of *Aspergillusflavus* with a water activity (aw) above 0.81 when stored at different temperatures 25°C , 30°C , and 40°C with the margin of $\pm 2^{\circ}\text{C}$ excluding this two *Picrorhizakurrooa* and *Alpinia galangal* which was found that to have antifungal properties.

All the samples of medicinal herbs with a water activity below 0.81 at different temperatures 25, 30, 40°C with a margin $\pm 2^{\circ}\text{C}$ were found free from the development and growth of *Aspergillus flavus*. Furthermore, any samples of medicinal herbs are also free from *Aspergillusflavus* fungus when water activity is above 0.81 while stored below 10°C with the margin of $\pm 2^{\circ}\text{C}$. Consequently, this study concludes that medicinal herbs contamination with aflatoxins, overcome by under controlled temperature and moisture. Most usefully drying was determined, by using sorption isotherms (desorption) drying, which helps decrease the water activity inhibiting the growth of *Aspergillus flavus*, and establishing an excellent quality of herbal medicines on drying destroyed unwanted microbes. At the same time, it additionally was saving extra cost in extended drying over optimal drying. At the same time, it is additionally saving cost in extends on drying over optimal drying.

Gqaleni *et al.* [35] study outcome show the interactions between water activities, temperatures, time of incubation, and substrate for growth and development of aflatoxins & cyclopiazonic acid, by *Aspergillus flavus* isolation. The analysis of variance confirmed that the complex interaction among all of these factors encouraged the relative

concentrations of mycotoxins produced. The growth of aflatoxins and cyclopiazonic acid, the most effective temperature is 25°C and 30°C. Each mycotoxin incubates for almost 2 weeks, and optimum growth was observed at (0.306-0.330µg of aflatoxins/ml of medium (40.04-6.256µg of cyclopiazonic acid/ml of medium); at (aw) of 0.996. On the yeast extract agar and Czapek yeast autolysate agar medium in both of these media no growth was found at a water activity of 0.90; at 20°C and 37°C for the incubation period of 2 weeks; similarly, under the same condition (0.077 to 0.439µg of cyclopiazonic acid/ml) growth was found. The extract yeast agar media facilitate the optimum growth of aflatoxins; cyclopiazonic acid maximum growth was observed on the Czapek yeast autolysate agar media.

6.1. pH

In the prevention of microbial attacks, pH plays an important role at extreme pH levels; spoilage is rare at the pH level above 8 (soap-based emulsions). At the very low pH levels within the products, such as syrups, citrus fruit juice, and flavored or non-medicated syrups with a pH level among 3 to 4 yeasts or molds more likely to be attacked, Yeast can be able to raise the level of pH within the product by producing metabolite of organic acids and may cause secondary growth of bacterial.

6.2. pH Level Impact on the Growth of Microbe and Toxins Production

Klich and Wheeler et al. [36, 37] to analyze the effect of pH levels on the rate of growth, 61 different microorganisms associated with 13 essential toxigenic fungi obtain from *Penicillium* species, *Aspergillus* species, *Fusarium* species, above the pH scale 2 to 11 at the different temperatures 25, 30, 37°C. Almost all the examined species completely grow on a laboratories agar medium, with a complete range. Although, in general, *Penicillium* species is more tolerant in Acidic pH, while *Aspergillus* species was more tolerant in basic pH.

Joffe and Nevarez et al. [38, 39] observed the production of aflatoxins of *Aspergillus flavus* in the presence of pH and under the light-medium. Clearly show results that the production of toxin more than 26 to 83 times, when modifying the pH level between (4 to 7.4). In the production of toxins, the effect of light plays an important role, the data showed in the presence of light toxin production damaging, production of toxin increased fivefold in the complete absence of light. Observe microbial growth with the combined effects of water activity (aw), pH, and antimicrobial (Preservative).

López-Malo et al. and Manjulata [40, 41] researchers observe the combined effects of water activity (0.95 to 0.99), pH (3.5 to 4.5), and antimicrobial preservatives such as (sodium benzoate, sodium bisulfate, potassium sorbate, citral, carvacrol, thymol, vanillin, and eugenol) with different concentrations (0, 100, 200, as much as 1800ppm) in the growth of *Aspergillus flavus* on potato dextrose agar (PDA). At the (P-value <0.05) and radial growth rates of mold spores, with disturbed by the variables. The lowering the radial

growth rate and delaying germination time by adopting some measures such as the use of effective concentration of preservative, reduction in pH, and water activity. *Aspergillus flavus* show more sensitivity to antimicrobial preservatives such as eugenol, carvacrol, sodium benzoate, sodium bisulfate, potassium sorbate, thymol (at the value pH 3.5) than vanillin or citral.

Sautour, teammates [26] analyzed the pastries production procedure under control conditions, conidial germination of *Penicillium chrysogenum*. Many environmental factors observe during the experiment, these factors having experimental values such as temperature (15 to 25°C), pH (3.5 to 5.5), and water activity ranging from (0.75 to 0.85). For observation of spore germination, a closed device was prepared, which maintained all the specifications of culture medium among water activity and maintained humidity condition all-around 25 days. At the same time, spore germination was studied by adopting design methodology in this study to find out the temperature, water activity, and pH values with a combined effect. The rate of Spore germination directly depends upon the water activity, the higher degree of water activity increases the rate of germination. On the conidial germination, incubation temperature plays a crucial role, at the same time, pH did not significantly affect. Result data showed the rate of germination increased almost 10-fold at a low temperature (15°C) when the water activity increased (from 0.75 to 0.85), and at the temperature (25°C), this observation was confirmed. Similarly, on spore germination temperature effect was more reported on the higher water activity value (0.75 to 0.85) under the specific experimental condition, pH confirmed no effect on conidia germination after incubate for 25 days [26].

Dantigny, Nanguy, Judet-Correia, and Bensoussan [42] researcher studied the development of *Aspergillus parasiticus* and *Aspergillus flavus* on subouraud dextrose agar and corn media and observed the effect under different conditions such as temperature, pH, water activity, and nine antifungal agents. At the temperature of 33°C, 2 molds growth maximum on pH of 5.0, with a water activity of 0.99 at 15°C, growth was observed at a water activity of 0.95, but not 0.90, minute growth was found at water activity, of 0.85 at 27°C and 33°C respectively. At the same time, they were examined for inhibition growth of different antifungal agents (sodium propionate, sodium sulfite, DDVP- 2,2dichlorovinyl dimethyl phosphate, Poly-ram80, Topsin-M, Imazalil, Botran, and Orthocide). In the presence of a lower degree of humidity, the activity of antifungal agents expanded. All antifungal agents establish inhibitory activity, whatever, at the low concentration of two antifungal Imazalil and DDVP is more effective.

7. Packaging Design

Packaging plays an important role in controlling the entry of microorganisms in the pharmaceutical products during store or usage of dosage form packaging also influences the microbial stability of formulations during shelf life. The

multi-dose injection containers used self-sealing wads for the prevention of the entry of microbial contaminations in the dosage form. On the other hand, the packaging of wide-mouthed cream jars containers was replaced; with narrow nozzles and flexible screw-capped tubes for maximum prevention from the entry of microorganisms.

Shaqla *et al.*, 2014 [43] Judge the microbial Quality of Blister Pack Tablets, by the study, was conducted in Amman Jordan. *Aspergillus* and *Penicillium* were founded in little quantity in certain formulations. Results of the study revealed that blister packaging of tablets is safe for living contamination, while another type of packaging still needs to improve for safety and protection from microbial contaminations.

8. Effect of the Compaction Process

In the manufacturing of tablets, raw materials used have been analyzed the microbial Quality by Byl Lebeer. And Kiekens [44, 45]. Tablets were prepared to direct compression method through moist granulation and evaluated compliance according to the specification of British pharmacopeia. Investigate the preparation of the tablets dosage forms the effect of microbial activity in raw material and formulation methods. Outcomes show the microbes affect the microbial quality of tablets; they started from the raw materials, manufacturing conditions, at the end methods of manufacturing. Chances of tablets less the degree of contamination than another dosage form because of the pill manufacturing through granulation by direct compression method. The method of compaction applies lethal impact on the survival of microbes. Villena *et al.* [45] study the effect of lethal compression of compaction method on *Aspergillus niger* present indirect compression materials.

Results data show that low pressures don't produce such kind of effect on *Aspergillus niger*. Excessive pressure enhances the destroying of microorganisms to determine the range of killing microorganisms through their size of the inactive substance and organisms. In the end, results show that the fatal compression technique produces due to shearing forces resulting from inter-particulate movements.

9. Conclusions

Every pharmaceutical dosage form must be evaluated by predictive studies of microbiological and analyzed the behavior of microbes under the different parameters such as physical, physicochemical, or chemical conditions, furthermore other factors also included antimicrobial compounds, water activity, pH, and temperature. It can be helpful for the identification of key components of optimization of pharmaceutical production chain distribution technique, also analyzed the germination rate interact with the lag times, germination of mycelia, and development play a major role in the development of hurdle technology approaches to forecasting fungal spoilage in foodstuff products as well as in pharmaceutical products. The microbial

stability of formulation plays an important during shelf life packaging plays a vital role for entry of microbe in the dosage forms during storage and usage of pharmaceuticals. The contaminated drugs may accelerate the chances of diseases acquired by opportunistic pathogens; usually, most of the patients are immune-compromised. Therefore, any microorganisms' presence of a small amount or above the prescribed limits should be considered undesirable for all pharmaceuticals.

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