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Shelf stability study of granules from *Pleurotus ostreatus* mushroom

Estudio de estabilidad en estante de un granulado del hongo *Pleurotus ostreatus*

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ABSTRACT

The most straightforward solid dosage form comprises granules prepared from the drug and other stable components in a size that allows its precise handling and bulk dispensing. The increasing prevalence of a multitude of ailments has prompted the utilization of novel therapeutic agents, such as *Pleurotus ostreatus* mushroom. The objective of the present study was to evaluate the physical, chemical, and microbiological stability of a *Pleurotus ostreatus* granulate over a 12-month period. An experimental study was conducted to assess the quality through physical, chemical and microbiological parameters over one-year period for three batches of the granulate. The results demonstrated the presence of a heterogeneous granulate with a distinctive aroma and flavor profile, typical of dried mushrooms, and a brown coloration. The residual moisture exhibited a slight increase (2, 85–4,70 %), while a decrease of 5 % in phenolic concentration was observed. Additionally, the microbiological analysis did not indicate the presence of pathogenic microorganisms. The pharmaceutical stability of all three evaluated batches was maintained throughout the study period.

Keywords: pharmaceutical stability; granules; quality control*; Pleurotus ostreatus*; mushroom.

RESUMEN

La forma farmacéutica sólida más sencilla comprende gránulos preparados a partir del fármaco y otros componentes estables de un tamaño que permita una manipulación precisa y la dispensación a granel. La creciente prevalencia de un gran número de enfermedades, ha propiciado el uso de nuevos agentes terapéuticos, como el hongo *Pleurotus ostreatus*. El objetivo del presente trabajo fue evaluar la estabilidad física, química y microbiológica de un granulado de *Pleurotus ostreatus* en vida de estante por un período de 12 meses. Para ello, se realizó un estudio experimental que permitió determinar la calidad, a través del comportamiento de los parámetros físicos, químicos y microbiológicos durante un año, a tres lotes del granulado. Los resultados mostraron un granulado heterogéneo con olor y sabor característico a setas deshidratadas y color marrón. La humedad residual mostró un ligero aumento (2,85 – 4,70 %), la concentración de fenoles disminuyó un 5 % de la concentración inicial, y el análisis microbiológico no evidenció la presencia de microorganismos patógenos. Los tres lotes evaluados mantuvieron la estabilidad farmacéutica durante el período de estudio.

Palabras clave: estabilidad farmacéutica; granulado; control de calidad; *Pleurotus ostreatus*; hongos.

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Introduction

Once a product has been discovered and demonstrated to possess some form of desirable pharmacological activity, it will remain as a mere curiosity in the absence of a formulation that facilitates its activity. Among the numerous potential formulations for a drug substance, there are a number of reasons for the continued prevalence of the solid dosage forms. From the perspective of the manufacturer, there are several advantages associated with this approach.[(1)]

The technology required is relatively inexpensive, the dosage forms are often highly stable, they are compact, and their appearance can be modified to create brand identification. The simplest form of solid dosage uses granules prepared from the drug and other components in stable aggregates of a size that facilitates precise handling and bulk dispensing. The process of granulation increases the uniformity of drug distribution in the product, improves powder flow rate and flow uniformity, and, if used as a tableting aid, aids compression and binding.[2,3]

The prevalence of health-related issues has increased in recent decades. These include the effects of ageing and the global burden of disease, which comprises a significant number of illnesses, including cancer and a range of non-communicable diseases (e.g. cardiovascular diseases, diabetes, obesity and neurodegenerative disorders).[4] The use of edible-medicinal mushrooms to improve health can be considered an important cultural heritage practice. This is because mushrooms have been used since immemorial time as a food source and as a basis for traditional medicinal treatments.[5] They are now regarded as a promising source of bioactive metabolites, which could potentially be developed for therapeutic applications in both food and pharmaceutical industries.[6]

Recent studies have identified the beneficial role of mushrooms in disease prevention and the modulation of pathogenic processes.[7] *Pleurotus ostreatus* mushroom, belonging to the *Pleurotus* genus, is the second most cultivated species in terms of its economic, dietary and medicinal significance (immunomodulatory and hepatoprotective

effects, antioxidant, antitumor and anti-inflammatory properties). Therefore, it is an excellent candidate for developing functional foods and/or nutraceuticals.[8, 9, 10, 11, 12]

A significant body of scientific evidence validates the assertion that *P. ostreatus* is a valuable dietary component, capable of enhancing human health and wellbeing. Its incorporation into one's daily diet has been shown to promote overall health, improve nutrition, and assist in the management of various diseases.[13] The presence of bioactive compounds was demonstrated in a diverse array of extracts, including alkaloids, reducing sugars, flavonoids, quinones, saponins, among others.[14]

Some authors established the required quality parameters for its utilization as a naturally derived active ingredient. The research demonstrated that the product exhibited favorable organoleptic properties, a nutraceutical composition and an adequate microbiological quality. However, the technological parameters showed inadequate flowability, indicating the need for excipients incorporation to enhance the rheological properties for using in solid dosage forms, such as nutraceuticals and/or biopharmaceuticals, with health benefits.[15]

Preformulating and formulation studies of *Pleurotus ostreatus* granulate were developed for improving the issues identified during the technological assessment of the mushroom derived powdered solid from. The resulting granules exhibited excellent flow properties, thereby corroborating the suitability of the excipients employed in its preparation. Moreover, the active compounds selected as chemical markers (phenols) were present in the formulation, indicating the absence of incompatibilities between the components, and thus, the product suitability as an intermediate for capsule and/or tablet preparation. Additionally, the granules can be used as a solid pharmaceutical form by themselves.

In this context, the assessment of the stability of a properly designed and prepared pharmaceutical granulate allows the establishment of optimal storage conditions and the definition of the product's shelf life. This process enables the observation of the maintenance of formulation potency, purity, organoleptic attributes, and efficacy.

Theoretical background

The term "dosage forms" refers to the product of the technological process that gives medicines the appropriate dosage characteristics, therapeutic efficacy, and stability over time. The most common solid formulations for oral administration are powders, granules, tablets, and capsules. The advantages of solid dosage forms include high physical, chemical and biological stability, accurate dosage, simple and convenient mode of application, and low cost. Furthermore, the versatility in the formulation of solid forms allows for the optimization of the formulation of virtually any active substance.[16]

Granules are products of granulation, i.e., the transformation of crystallized or amorphous powder particles into more or less resistant and porous solid

aggregates. Granules are an intermediate stage in the manufacture of not only tablets, but also other pharmaceutical forms, such as capsules and powders. In the process of developing solid dosage forms, granulation is used to prevent segregation of components during powder mixing, to improve the flow properties of the mixture, to increase the compaction properties of the mixture, to promote the expulsion of interstitial air, to significantly reduce the amount of dust generated during the manufacturing process, to reduce the hygroscopicity of the mixture, to improve the dissolution rate and to increase the density of the product to be compressed.(17)

The quality of the active ingredient and other excipients, as well as, the manufacturing processes, are standardized once the dosage form has been developed. This is the only way to ensure that the quality of the design is reproducible. In addition, the selection and development of appropriate chemical-physical and biological techniques, which correlate well to the biological activity in humans, to determine the quality of the batches and to guarantee the reproducibility of the basic characteristics of the device.(18)

Commonly used parameters in quality control are: (17)

1. Physico-chemical characteristics: organoleptic characteristics (appearance, color, smell and taste), moisture content, etc.
2. Physical-mechanical properties: Granulometric analysis (particle shape, mean particle size), and rheological analysis (compressibility index, Hausner's ratio, angle of repose and flow velocity).
3. Chemical properties: Quantification of active pharmaceutical ingredients.
4. Microbiological tests

Pharmaceutical Stability

Drug stability is the ability of a given formulation to maintain its chemical, physical and microbiological properties within established limits during shelf-life; the major causes of instability are temperature, humidity and light.(19) According to *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH), the purpose of a stability study is to provide evidence of how the quality of a drug substance changes over time under the influence of a range of environmental factors, such

as temperature, humidity and light, and to establish recommended storage conditions, retest periods and half-lives.[20]

Stability studies are carried out on medicinal products taking into account the market for which the product is intended and the climatic zones in which it will be used. For the purposes of global studies, four climatic zones are recognized. In our country, stability studies are developed considering the conditions of zone IV. All pharmaceutical products, regardless of their origin and degree of novelty, must undergo stability studies, varying according to their purpose.[21]

In order to determine the intermediate shelf life and storage conditions, it is necessary to perform an accelerated study and shelf life, or shelf life only. The medicinal product must comply with the *"Resolución No. 34/2000 Requerimientos de los estudios de estabilidad para el registro de productos farmacéuticos nuevos y conocidos, del Centro para el Control Estatal de Medicamentos Equipos y Dispositivos Médicos"* (CECMED, La Habana, Cuba).[21]

Real-time or shelf-life stability studies evaluate the physical, chemical, microbiological and biopharmaceutical properties of a medicinal product during the proposed shelf-life and under the storage conditions, and in the packaging/closure system in which it is proposed to be distributed or in which it is distributed on the market. The results will enable the shelf life and storage conditions to be confirmed or established.[21]

Materials and methods

Raw material and excipients

The raw material employed as the active pharmaceutical ingredient was *Pleurotus ostreatus* CCEBI-3024, a strain cultivated on coffee pulp at the *Centro de Estudios de Biotecnología Industrial* (CEBI) in Santiago de Cuba. The identification was confirmed by specialists from the *Centro Oriental de Ecosistemas y Biodiversidad* (BIOECO, Santiago de Cuba, Cuba).

The excipients employed in this study included colloidal silicon dioxide (Aerosil 200, Evonik Resource Efficiency GmbH, Germany), microcrystalline cellulose (Avicel PH 101, JRS Pharma, Germany), magnesium stearate (Sudeep Pharma Pvt. Ltd, India), polyvinylpyrrolidone (K-25, O-BASF, Germany) and lactose

monohydrate (Molkerei MEGGLE Wasserburg GmbH & Co. KG, Germany), as well as, the pharmaceutical grade materials produced by Evonik Resource Efficiency GmbH (Germany) and JRS Pharma (Germany). The GRAS (Generally Accepted as Safe) excipients were selected on the basis of their multifunctionality in the formulation of pharmaceuticals derived from natural sources.[21] All other chemicals and solutions were of pharmaceutical grade.

Oyster mushroom granules

Three batches of granules (200 g) were made using a vertical granulator (Collette Model GRAL 75, Belgium). The best combination of excipients was used, which included five raw materials and four response variables. This allowed the evaluation of the flowability and compressibility of the powdered solid obtained from fruiting bodies of *Pleurotus ostreatus* and used as the active ingredient of the formulation.

All powders were first sieved through a 177 µm mesh (TSS-200, Utrecht, Germany). Prior to granulation, the *Pleurotus ostreatus* powder was mixed with the other excipients in a horizontal laboratory mixer (Eureka AR-400, USA). The granules were prepared using water as a diluent. The wet mass was dried in a vacuum dryer (Sartorius, Germany) at 40°C for 14 hours. The dry mass was crushed and dried in a vacuum oven (Sartorius, Germany). The dry mass was ground in a blade mill and sieved through a 350 µm mesh.

Shelf stability study

The stability study of the *Pleurotus ostreatus* granules was conducted in accordance with *Resolution No. 34/2000* of CECMED, which establishes the requirements for stability studies for the registration of new and known pharmaceutical products. The granules were packaged in 120 mL white, wide-mouth polyethylene terephthalate (PET) plastic bottles with lids. The samples were stored at a temperature of 30 ± 2°C and a relative humidity of 70 ± 5%. The physical, chemical and microbiological stability indicators were evaluated over a period of one year, at intervals of 0, 3, 6, 9 and 12 months.

Organoleptic characteristics

The granulate was assessed for color, appearance, smell and taste.[18]

Moisture content

Moisture content was assessed using an infrared gravimetric method with a thermogravimetric balance (model MB-110, MRC, Germany).[12]

Total phenolic content

Phenolic content was determined by the Folin-Ciocalteu method, with slight modifications. A sample of *Pleurotus ostreatus* granules was taken, 1.5 mL of Folin-Ciocalteu reagent (10 %) was added, leaving five minutes at room temperature. Then 2 mL of Na_2CO_3 solution was added and after one hour in the dark, the absorbance at 765 nm was recorded in the UV-Visible spectrophotometer (Genesis 10S, Thermo Fisher Scientific, Waltham, MA, USA). A calibration curve made with gallic acid at concentrations of 6.25, 12.5, 25.0, 50.0 and 100.0 µg/mL was used. The results were expressed as mg of gallic acid per 100 g of dehydrated *Pleurotus ostreatus* powder.[22]

Microbiological tests

The microbiological control of *Pleurotus ostreatus* granules was conducted in accordance with the methodology outlined in INS 01.148 T of the Laboratorio Farmacéutico Oriente (LBF, BioCubaFarma, Santiago de Cuba), to determine the presence of aerobic microorganisms, filamentous fungi and yeasts, as well as, specific bacterial strains, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacteriaceae* and *Candida albicans*. The results were evaluated against the established acceptance criteria for the microbiological quality of non-sterile pharmaceutical forms.[23]

Statistical analysis

Microsoft Excel and Statgraphics Centurion XV were used for the maths and statistics. For the stability study at 0, 3, 6, 9 and 12 months, the residual moisture content and the concentration of total phenols were expressed as the mean ± standard deviation of each batch. Their medians were compared using

the Kruskal-Wallis test and the standard deviation through Cochran's variance test, considering a 95 % confidence level.

Results and discussion

The quality of a pharmaceutical product is dependent of a number of factors, one of which is the stability, which must be evaluated during the development of a dosage form to prevent or address potential stability issues. If such problems are identified, the use of technological resources can extend the dosage form's shelf life, ensuring its continued utility. [17] Between its initial manufacture and its subsequent use, a dosage form's physical characteristics may change, affecting the bioavailability of the active ingredient. These changes involve a modification of the biopharmaceutical characteristics of the product, although they do not necessarily result in the degradation of the drug.

Modifications may be made to a range of physical characteristics, including organoleptic properties and moisture content. Such alterations have the potential to influence the release of the active ingredient, subsequently impacting its bioavailability. In this regard, the results demonstrated that the physical parameters (organoleptic characteristics and moisture content) exhibited stability throughout the shelf life of *Pleurotus ostreatus* granules. This was observed under packaging conditions utilizing 120 mL white PET (polyethylene terephthalate) plastic bottles with wide mouths. The product showed a characteristic odor and taste of the active ingredient, a pale amber color, and a coarse heterogeneous solid appearance for nine of the twelve months studied. From the ninth month ahead, slight changes began to be noticed, such as darkening of the color.

Despite the absence of a reported study examining the organoleptic analysis of *Pleurotus ostreatus* granules for solid pharmaceutical formulations, the findings aligned with one study aimed to the fortification of cereal flours with *Pleurotus ostreatus* flours, in which the mushroom flour exhibited a brown coloration, accompanied by a distinctive mushroom odor and granular appearance.[24]

The stability of certain substances in a solid phase is influenced by the presence of moisture. The residual moisture values of the *Pleurotus ostreatus* granules throughout the stability study are illustrated in table 1. The moisture

values were maintained at a level between 2.8 and 4.7%. The statistical evaluation of each batch over the course of the study showed no significant differences ($p < 0,05$).

Although, upon initial observation, no significant difference between the batches is seeming, it is essential to consider the potential experimental variations that could influence the observed discrepancy in the results. These may include variables related to the analyst; the calibration of the equipment used for the measurement; the precise drying time; the humidity of the environment, which may vary between the days of the test, and others. It is noteworthy that the distance between the data points does not exceed one unit.[25]

Furthermore, the role of a binding agent in a granule must be recognized, as the use of water as a diluting agent resulted in a significantly lower average water percentage, which could potentially impact the granule's properties. This could lead to an increased susceptibility to breakage, cracking and disintegration during compression, ultimately affecting the quality of the tablets produced.[26]

Table 1- Residual moisture behavior of the three batches of *Pleurotus ostreatus* granules during the shelf-life stability study.

Batches	Residual moisture (%)				
	t = 0	t = 3	t = 6	t = 9	t = 12
1	3,79 ± 0,76	3,76 ± 0,68	3,80 ± 0,72	4,13 ± 0,59	4,20 ± 0,26
2	3,39 ± 0,45	3,54 ± 0,22	3,63 ± 0,14	3,96 ± 0,36	4,05 ± 0,29
3	4,08 ± 0,44	4,10 ± 0,42	4,14 ± 0,40	4,22 ± 0,52	4,27 ± 0,40
Kruskal-Wallis (*P-value*)			0,44		
Cochran's C (*P-value*)			0,65		

However, an examination of the initial powder samples showed that *Pleurotus ostreatus* powder is hygroscopic, a quality that is incompatible with the production of pharmaceutical products, particularly on an industrial scale. This requires the utilization of special conditions to prevent moisture absorption by the powder from the surrounding environment, thereby reducing costs and enhancing the product's utility. Consequently, the incorporation of a moisture-absorbing agent, specifically colloidal silicon dioxide, represents a critical element in the formulation of the desired granulate.[26]

The evaluation of chemical stability of the *Pleurotus ostreatus* granulate was undertaken with consideration of the total phenol content (figure 1). The Folin-Ciocalteu method was employed for the quantification of these secondary metabolites. The selection of these compounds was based on the high content of phenolic compounds reported for the *Pleurotus ostreatus* species, [22, 24-29] as well as, the numerous therapeutic properties associated with these compounds.[30]

The experiments were conducted at 0, 3, 6, 9 and 12 months. The results obtained allowed the determination of whether the concentration of phenols, as an active pharmaceutical ingredient, was below 90 % of the initial concentration, which would serve as an indicator for the period of validity of the formulation. The same pattern was observed in all cases, indicating that no factors affecting the degradation of phenolic compounds were identified up to six months of study. Thereafter, a decrease of 5 % in phenolic concentration was observed. A comparison of medians using the Kruskal-Wallis test (P-value = 0,00) showed significant differences, associated with the decrease in concentration during months nine and twelve.

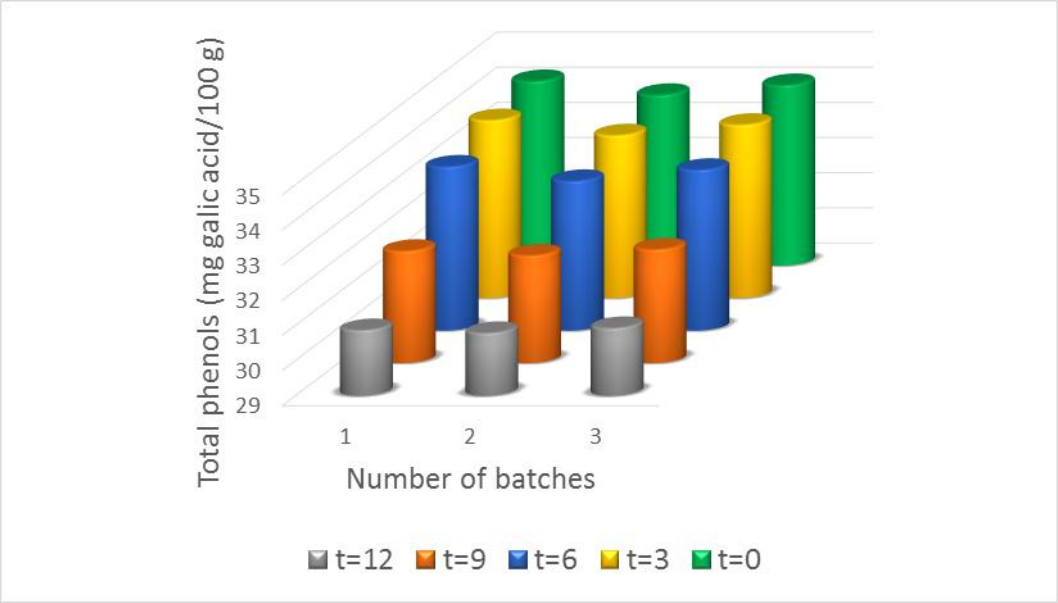

Fig. 1- Phenol concentration in the three batches of *Pleurotus ostreatus* granules during 12 months of shelf stability study

The pharmacological activity of *Pleurotus ostreatus* has been the subject of several studies, which have demonstrated the presence of phenolic compounds

in extracts with antibacterial properties and the capacity to combat oxidative stress. These findings suggest the potential use of this mushroom as a nutritional supplement or ingredient in food formulas such as yoghurt, biscuits and flour, which may be suitable for preparations with a short shelf life. [21] The microbiological stability of the three batches of *Pleurotus ostreatus* granules, which was maintained throughout the study, is illustrated in table 2.

No pathogenic microorganisms that could compromise the quality of the product (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, or other) were isolated. The results were in agreement with the limits established in the literature for the determination of microorganisms in solid formulations. A number of studies have documented the antimicrobial properties of the *Pleurotus ostreatus* species.[31, 32, 33] The microbiological quality of the granules remained unaltered during the course of the study.

Table 2. Microbiological stability tests of *Pleurotus ostreatus* granules for 12 months.

ENSAYOS	LIMIT [23]	time (months)				
		0	3	6	9	12
Total bacterial count	≤10^3 ufc/mL	≤10ufc/mL				
Total count of fungi and yeasts	≤10^2 ufc/mL	≤10ufc/mL				
Pseudomonas aeruginosa	Absence	Absence				
Sthaphylococcus aureus	Absence	Absence				
Enterobacterias	Absence	Absence				
Candida albicans	Absence	Absence				

To estimate a pharmaceutical product's stability, it is necessary to consider all the criteria derived from the previous studies. The three batches stored in the final container remained stable. All the physical, chemical and microbiological parameters were within the quality limits for solid formulations. The concentration of phenols was above 90 %, but decreasing, so the response of these metabolites should be studied further.

Conclusion

The study showed that *Pleurotus ostreatus* granules remained unchanged in taste and appearance. There was a slight increase in residual moisture (2.85 –

4,70 %), while a decrease of 5 % in phenolic concentration was observed (33,85 – 34,24 mg GA/100 g). There were no signs of any harmful bacteria or fungi. The three batches of the product remained stable for the full 12 months in the shelf life study, which represent an advantage for the further development of nutraceutical and/or pharmaceutical preparations.

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Conflict of interests

Authors declare no conflict of interest in the submitted manuscript.

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