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Review

Considerations of Nystatin Roll in Oral Candidiasis Scenario and the COVID-19 Pandemic—A Review

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Abstract: Oral candidiasis is an opportunistic infection usually related to predisposing factors. Oral manifestations in patients affected by COVID-19 have been reported, as the oral mucosa is the gateway to this viral infection. Xerostomia, as well as other oral symptoms, are predisposing factors for the emergence of oral candidiasis after the COVID-19 pandemic. It is a common pathology, but fatal if left untreated. Nystatin (NYS) is the drug of first choice in the treatment of oral candidiasis. Herein, we reviewed the epidemiology of oral candidiasis and its treatments, focusing on the mechanism of action, dosage forms, and NYS efficacy. NYS is an effective drug against oral candidiasis and belongs to Class IV of the biopharmaceutical classification system; however, its low solubility and low permeability may compromise its availability in the oral cavity and, consequently, its pharmacological action. Future perspectives to overcome drug limitations were also addressed and discussed in our review.

Keywords: nystatin; oral candidiasis; COVID-19; pharmaceutical dosage forms

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1. Introduction

Candidiasis is a fungal infection caused by the genus *Candida* and may also be known as candidosis. The term moniliasis is older and considered inappropriate since it refers to the archaic denomination *Monilia albicans* [1,2]. Its spectrum is very extensive, from mucosal colonization to invasive systemic conditions [2]. In healthy individuals, the genus *Candida* is found in the oral cavity, belonging to the oral microbiota. *Candida* spp. infection only arises when an opportunity occurs, thus being known as an opportunistic infection [3,4]. Table 1 shows the various clinical forms of candidiasis.

Among the various forms of candidiasis, there is the oral one, the most common fungal oral infection in the oropharyngeal tract, which manifests itself when related to predisposing factors. In general, there are specific and non-specific defense mechanisms present in saliva and oral mucosa, in addition to the presence of the competitive oral microbiota itself, formed by other microorganisms that restrict the growth of *Candida* spp. [3,5]. There are several factors that can cause oral candidiasis, and this pathology is closely linked to other disorders or conditions that are considered risk factors for its emergence [3,6], as depicted in Table 2. Therefore, oral candidiasis may be an indication of problems that affect defense mechanisms, whether local or systemic alteration of the oral microbiota or even neglected oral hygiene [5,6].

To cause infection, *Candida* species have an exceptional ability to adhere to surfaces such as mucosa, teeth, dental fillings, dentures, orthodontic implants, tongue piercings, and even endotracheal tubes present in the oral cavity that are not properly sanitized and have not been replaced [5,6].

Table 1. Clinical forms of candidiasis (adapted from [7]).

Clinical Forms of Candidiasis	Sites/Tissues	Comments
Oral	Oral cavity, oral mucosa	Superficial candidiasis affecting patients with local and systemic changes
Esophageal	Esophageal mucosa	Considered a semi-invasive type of candidiasis
Vulvovaginal	Vulva and vagina	High incidence in women during the fertile period
Urinary	Urinary tract	Frequent candiduria, but not always followed by symptoms
Dialysis-related peritoneal	Peritoneal region	Related to peritoneal dialysis
Postoperative peritoneal	Peritoneal region	It occurs frequently in hospitalized patients and is related to cases of secondary or tertiary peritonitis
Respiratory tract	Respiratory tract	Uncommon and poorly documented clinical manifestation, with a higher incidence in neutropenic patients with hematologic malignancy or undergoing lung transplantation
Hematogenous/Candidemia	Blood	A broad spectrum of episodes, including isolated cases of *Candida* spp. or in conjunction with other *fungi* in the bloodstream that spreads to more organs

Table 2. Predisposing factors for oral candidiasis [2,3,7,8].

Mechanism	Factors
Impaired local defense mechanisms	Low saliva production/xerostomia
	Tabagism
	Oral mucosal diseases
	Topical use of corticoids
	Radiation therapy
Impaired systemic defense mechanisms	Poorly controlled diabetes
	Immunodeficiencies
	Use of immunosuppressors
	Malnutrition
	Neoplasms
	Sarcoidosis
	Cirrhosis
	Sjögren's syndrome
	Hypoparathyroidism
	Hypoadrenalism
Disruption of the oral microbiota	Use of wide-spectrum antibiotics
	High alcohol consumption
	Reflux, low pH
	Carbohydrates-rich diet
Oral hygiene	Dental prosthesis
	Mixed biofilm over nonrenewable surfaces
	Neglected oral hygiene
Groups	Children (immaturity of the immune system)
	Premature newborn
	Lactating
	Elderly

Oral candidiasis is not a lethal disease; however, if not properly treated, it can progress to chronic clinical symptoms, invading other tissues and even causing a systemic infection [8]. More recently, the coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to an increase in cases of oropharyngeal symptoms and oral problems associated with soft tissue and saliva production (dry mouth), even after the recovery from COVID-19. These manifestations in patients who have or had COVID-19 were also predisposing to the onset of oral candidiasis. Case studies have been presented to evaluate the relationship between oral manifestations in patients with a history of COVID-19 [9–12].

Among the species, *Candida albicans* is the main cause of oral candidiasis. Other species can also be pathogenic, such as *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. pseudotropicallis*, *C. guillermondi,* and *C. tropicalis*. However, all *Candida* species can cause mucositis like this infection [5,8,13]. To cause infection, there are fundamental properties for biofilm formation described as virulence factors, such as adhesion to host surfaces, morphological transformation, more invasive forms (hyphae), and the production of enzymes in the extracellular environment [6,13]. Oral candidiasis is seen in several different clinical findings, acute or chronic, and in a wide spectrum of severity, which makes its diagnosis difficult. Among them, we can mention pseudomembranous candidiasis, atrophic erythematous candidiasis, chronic hyperplastic candidiasis, angular cheilitis, and central papillary atrophy, among others [8,14].

Patients with oral candidiasis may be asymptomatic or manifest various symptoms, depending on their clinical form (Table 3). In general, burning sensations, the presence of metallic taste, pain, and dysphagia are reported [5,8,14].

Table 3. Clinical manifestations of oral candidiasis (adapted from [8]).

Clinical Manifestation	Finding	Symptomatology	Site	Observances
Pseudomembranous	White, creamy, and easy to remove plaques	Burning sensation	Palate, tongue, and jugal mucosa	Related to antibiotics and immunosuppressor therapy
Erythematous	Red spots	Burning sensation	Jugal mucosa, tongue, and hard palate (posterior region)	Related to antibiotics, xerostomia, and immunosuppressor therapy
Central papillary atrophy	Red and atrophic regions on mucosa	Asymptomatic	Buccal mucosa and tongue's dorsum	Related to immunosuppression
Chronic Multifocal	Red regions with easily removed patches	Burning sensation or asymptomatic	Palate (posterior region), tongue's dorsum, and commissures of the mouth	Related to immunosuppression
Angular cheilitis	Red fissured patches	Local wound sensation	One or both commissures of the mouth	Related to immunosuppression
Denture stomatitis (chronic atrophy)	Red regions	Asymptomatic	Localized erythema of the oral mucosa under dentures	Positive culture on the denture, but not on the mucosa
Hyperplastic (Candidal leukoplakia)	White patches	Asymptomatic	Jugal mucosa	Related to immunosuppression
Mucocutaneus	White plaques and red regions	Asymptomatic	Jugal mucosa, palato, and tongue	Rare, hereditary
endocrine candidosis syndrome	White plaques (non-removable)	Asymptomatic	Jugal mucosa, palate, and tongue	Rare, related to endocrine disorder

2. Oral Candidiasis

2.1. Pseudomembranous Candidiasis

The form of pseudomembranous oral candidiasis is popularly recognized as "thrush" and usually presents in the form of yellow or white plaques adhering to the oral mucosa, with an inflammatory basis. The plaques are easily removable by scraping with a tongue depressor or gauze pad and are characterized by a disordered set of hyphae, yeasts, epithelial cells, and fragments of necrotic tissue, distributed in the jugal mucosa (cheek region), palate, dorsum of the tongue, the gums, and the oral floor [2,5,15]. After the removal of the plaques, the region has an erythematous, ulcerated, and sensitive surface [14].

The pseudomembranous form can manifest itself in patients who make use of broad-spectrum antibiotics, which leads to a decrease in the competing bacteria present in the oral cavity. It can also affect immunosuppressed patients, either through diseases such as carriers of the human immunodeficiency virus (HIV) and leukemias or by using immunosuppressive drugs [1,2,15]. Young children up to 2 years old can be affected due to their poorly developed immune systems [2,15,16]. The symptoms are burning sensation and burning, itching, taste alteration, being described as bitter or salty, and even dysphagia (difficulty swallowing) [2,8,15].

2.2. Erythematosus Candidiasis

This form is related to the use of medications (corticosteroids and broad-spectrum antibiotics), prolonged use of removable prostheses, and xerostomia [2,14]. It commonly appears as red spots with the absence of white plaques, affecting the dorsum of the tongue, palate, or any superficial part of the oral mucosa [2,8].

Erythematous candidiasis is the most common oral candidiasis; however, in many cases, it is clinically neglected. It can be found in several different forms, depending on the cause or location [2,14]. According to Gianni and Shetty (2011) [2], erythematous candidiasis is categorized into some subtypes, such as acute atrophic, chronic atrophic, angular cheilitis, median rhomboid glossitis (also known as central papillary atrophy), and chronic multifocal.

Central papillary atrophy is clinically presented with a well-defined erythematous region in the midline of the posterior region of the lingual dorsum, which is due to the loss of filiform papillae. It is presented in the form of a red or red-whitish spot and is flat or raised [2,14]. Some carriers may also present the infection in other parts of the oral cavity, and thus this type of candidiasis is called chronic multifocal. In this case, in addition to the dorsum of the tongue, they may arise at the junction between the hard palate and the soft palate and the labial commissures [2,6,8]. The lesion in the labial commissures, recognized as angular cheilitis, is characterized by erythema, pain, fissures, and desquamation, which may be associated with chronic multifocal candidiasis or arise alone. In these cases of cheilitis, saliva usually accumulates in the commissures, which leads to a moist region that favors fungal growth. This occurs in patients who have decreased vertical occlusion dimension and accentuated grooves and who also make use of dental prostheses [2,17]. In unusual conditions, habits such as licking the lips or sucking the fingers can create a pattern of moistening of the perioral skin, causing cheilocandidiasis [18].

Acute atrophic candidiasis, also known as "antibiotic sore mouth," is clearly caused by antibiotic use and in cases of uncontrolled diabetes. Its clinical presentation occurs in the form of erythema, involving atrophy of the papillae of the dorsum of the tongue. Patients complain of burning sensations in the mouth due to the diffuse loss of the filiform papillae of the dorsal region of the tongue. Pruritus, xerostomia, and taste changes are also reported [2,8].

Finally, chronic atrophic candidiasis is commonly referred to as prosthetic stomatitis and is related to the prolonged use of removable prostheses or in cases that are poorly fitted, of inadequate design, or have poor oral and denture hygiene [2,8,19]. Prothesis hygiene must be carried out to remove microorganisms, including *Candida* spp. The involved methods are chemical cleaners and/or mechanical removal. It has been reported that biofilm formation depends on the types of denture resin, the kind of cleanser, and, also, the cleanser concentration. Furthermore, the prothesis roughness can lead to microbial colonization [19]. Patients are usually asymptomatic, and clinically, they can present with erythema and hemorrhagic petechiae. Clinical manifestations occur in the palate near the prosthesis, where the salivary flow is restricted [2,8].

2.3. Hyperplastic Candidiasis

Hyperplastic candidiasis is known as chronic hyperplastic candidiasis or *Candida* leukoplakia and presents as non-removable white or red plaques with elevated lesions ranging in size from small to nodular to palpable [2,8]. The frequent localization is on the surface of the dorsum of the tongue, the palate, and the jugal mucosa. This is the rarest type of oral candidiasis, but its malignant transformation potential is still controversial [8,20].

2.4. Mucocutaneous Candidiasis

Mucocutaneous candidiasis is a chronic, persistent form and is considered the most severe form of the disease. In this scenario, a systemic distribution and the most extensive degree of impairment of the host's immune system are seen. It initially presents in pseudomembranous or hyperplastic form but then involves the skin, esophageal mucosa,

and nails [2,8,21]. It is also associated with various endocrinopathies, such as Addison's syndrome, hypothyroidism, hypoparathyroidism, and diabetes mellitus [2,22]. Often, endocrine disruption occurs months or years after *Candida* spp. infection [2].

In some patients with this manifestation, candidiasis has been related to mutations in the autoimmunity regulatory gene, leading to the formation of antibodies against the host's own tissues. Normally, the immune disorder is evident early in the life of patients who have oral candidiasis, nails, skin, and other mucous membranes [2,7]. Patients may still develop endocrine abnormalities such as endocrine-candidiasis syndrome and autoimmune polyendocrinopathy-candidiasis dystrophy syndrome (APECED) [2,23].

2.5. The Genus Candida

Of the fungi of medical interest, the genus *Candida* is the most important due to its high frequency of colonization and infecting the human host [7,13]. The oral prevalence of this fungus is variable, but, according to Colombo et al. (2013) [7], it is found between 20 and 40% in the gastrointestinal tract of healthy adults, and approximately 20 to 30% of women have colonization by *Candida* spp. in the vaginal tract. In immunocompromised patients, *Candida* spp. colonization can reach 60% of cases [24]. These microorganisms are considered commensal and become pathogenic when changes in the host's defense mechanism occur, secondary anatomical barriers are compromised, or invasive medical processes are made. Hence the clinical interest in *Candida* spp. infection, more specifically oral candidiasis, due to the significant number of complications that intersect the various medical specialties [7,13].

The morphology of the genus *Candida* is the autochthonous form of yeasts that colonize the oral cavity and the gastrointestinal tract, belonging to the microbiota. Among the approximately 20 *Candida* species of medical interest, *Candida albicans* has the highest prevalence in the oral cavity. If there is a disruption of local defense mechanisms, metabolic dysfunction, or even the presence of diseases associated with immunosuppression, colonization can lead to infection and pathology [7]. Thus, oral candidiasis is the most common opportunistic infection found in patients with acquired immunodeficiency syndrome (AIDS) and is considered a marker of the progression of immune deterioration in these patients [3].

The genus *Candida* can also be seen in the form of pseudohyphae and hyphae, in addition to the form of yeasts. This characteristic is recognized as dimorphism and is associated with the virulence of this microorganism because, in this form, it becomes invasive, penetrating the tissue, which leads to an infectious picture. The pseudohyphae and hyphae are the morphological forms that adhere to the oral cavity surface for the colonization of *Candida* species, resulting in biofilm development and penetration into the tissue. *Candida* spp. and bacteria can be found in the biofilm [13]. Such interaction occurs through commensalism; however, studies are necessary to investigate the complex interactions between fungi and bacteria [25]. At the site, a state of hypersensitivity and the production of toxins occur [3,13].

Candida albicans exhibits different forms of growth and can reproduce by multilateral budding in the form of yeast [7,13]. However, they can also be found in elongated and filamentous forms, called pseudohyphae and hyphae [13].

2.6. Oral Candidiasis and COVID-19

COVID-19 is a recent infection, and there is not enough information to relate directly to oral candidiasis. Although oral candidiasis in patients with COVID-19 was reported [10,11,26–29]. The issue is that the presence of *Candida* species in the oral cavity can be a reservoir for infection in other parts of the body [13].

COVID-19 patients can experience oral manifestations like lesions, ulcers, erythematous plaque, dysgeusia, and dysphagia. It is not clear whether these manifestations are caused by a viral infection, opportunist infections (e.g., oral candidiasis), immunosuppression, or COVID-19 agonist treatment [11,27,29,30]. There are some cases in which

RT-PCR was performed on patients confirming a diagnosis of COVID-19; however, the oral candidiasis was confirmed only by a clinical diagnosis [11,27–29]. In fact, the diagnosis of all oral candidiasis manifestations is substantially clinical and is based on the observation of lesions without performing a biopsy (except in cases of candida leukoplakia) [8].

Common risk factors for COVID-19 (for example, immunosuppression, steroid and antibiotic therapies, oral manifestations, and salivary gland damage) can lead to the development of oral candidiasis [3,9–11,27,29,30]. In patients with COVID-19, the SARS-CoV-2 virus compromises the immune response since the virus can affect the production, decrease, or release of some mediators: interleukin-6, tumor necrosis factor, interleukin-1α, and interleukin-1β. One of them, salivary histatin-5, is damaged, which inhibits *Candida albicans* [9].

Other factors also involve the relationship between oral candidiasis and COVID-19. The angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 receptors, proteins that mediate the SARS-CoV-2 virus entry in the host cells, and the spike protein of the SARS-CoV-2 virus are present in the oral mucosa. This suggests the emergence of oral manifestations [29,31].

Virág et al. (2021) [32] investigated the effect of antivirals against the SARS-CoV-2 virus by testing them in Vero E6 cell-based cytopathic assays on Wuhan and British mutant strains. The mechanism of this effect involves the binding of nystatin to cholesterol found in the plasma membrane of the cell host. The viral envelope fusion with the plasma membrane of the cell host occurs for the entry of the virus. Therefore, in the post-pandemic scenario where novel strains of the SARS-CoV-2 virus have been reported, NYS should be investigated as an alternative use [32].

3. Nystatin (NYS)

NYS was discovered in the 1950s by Hazen and Brown [32–35]. In therapeutics, NYS has been employed for many years, demonstrating its safety and efficacy with good pharmacological action; however, few relevant adverse effects are reported. More recently, NYS has been used more frequently due to the increase in the number of cases of candidiasis in patients with neoplasms, HV, and other systemic disorders, including COVID-19 [9,36–38]. Figure 1 shows the chemical structure of NYS.

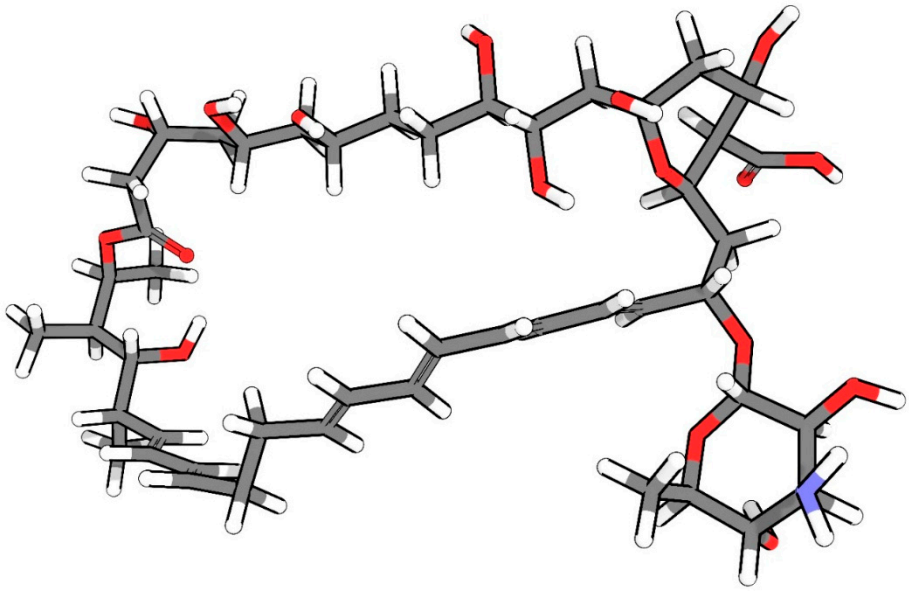

Figure 1. Chemical structure of NYS in 3D (carbon atoms are in gray, hydrogen atoms in white, oxygen atoms in red, and nitrogen atoms in blue)

3.1. Physicochemical Characteristics

From a chemical point of view, NYS is considered a polyene, that is, belonging to the group of substances formed by carbon atoms with several double bonds. In fact, NYS is a tetraene, which, more specifically, are polyenes that have four unsaturated double bonds in sequence [34,39]. It is still considered a macrolide; that is, it has a large cyclic chain. These chemical characteristics are usually associated with its low permeability, which prevents it from crossing intestinal cells when administered orally. Finally, this molecule has carboxylic and amino groups, which leads to pKa: 3.62 (acidic) and 9.11 (basic) [32,40–42].

NYS is considered practically insoluble in water, chloroform, ethyl ether, and ethanol; poorly soluble in methanol; and easily soluble in dimethylformamide and dimethylsufoxide. This drug presents as a hygroscopic powder, yellow, fine, and has a characteristic odor, often reported as cereals (and with an extremely unpleasant taste, according to Souza et al., 2023 [33]). In addition, NYS has sensitivity to heat, light, and the presence of oxygen [32,39].

NYS is defined as a substance or a mixture of two or more substances. This complexity occurs due to its production process. NYS is obtained by fermentation, and three biologically active compounds are produced: NYS A1, NYS A2, and NYS A3 [32,43].

The main component is NYS A1, which has D-mycosamine bound to carbon 19 oxygen. NYS A2 also has D-mycosamine, bound to the same carbon. However, this compound has differences in the stereochemistry of the hydroxyl, methyl, and D-mycosamine groups. And yet, it does not have a hydroxyl on carbon 10, and it has a hydroxyl on carbon 16 (instead of carbonyl). NYS A3 also has the sugar D-mycosamine on carbon 19, but another sugar is found, L-digitoxose on carbon 35. It also presents variations in the stereochemistry in the groups of hydroxyl, methyl, and D-mycosamine groups [32,43].

3.2. Mechanism of Action and Pharmacological Aspects

This antifungal is classified as Class IV of the biopharmaceutical classification system (BCS), presenting low solubility and low permeability. Due to its low permeability, it is weakly absorbed by the skin, mucous membranes, or gastrointestinal tract, and its therapeutic use is restricted to the treatment of fungal infections topically. When administered orally, most of it is found in the stool unchanged [32,44–46]. Due to its low aqueous solubility, NYS offers difficulties in the preparation of medications, besides being less available to exert its action topically, especially in the treatment of oral candidiasis, since the oral mucosa is bathed in saliva [44,46].

The NYS molecule has much similarity to amphotericin B, another antifungal polyene, and both have the same mechanism of action. However, amphotericin B is used for the treatment of systemic and local infections, and NYS is restricted to topical application, used in the prophylaxis and treatment of superficial candidiasis of the skin and mucous membranes, as it is effective against most infections caused by *Candida* species [41,45].

The mechanism of antifungal action of NYS occurs through its interaction with ergosterol, a sterol present in the plasma membrane of fungal cells, causing disorganization in the plastic membrane of the fungus since channels are formed, which leads to a loss of selective permeability [34,47]. Through these channels occurs the outflow of water and ions, essential for cell survival, which culminates in cell damage and then in death [35,36,39,41,47]. Some authors propose a sequence of three events for the action of NYS:

(A) the binding of an antifungal monomer with the plasma membrane of the fungus;
(B) the formation of an oligomonomer;
(C) and its insertion in the lipid bilayer, generating a pore through which the passive flow of molecules through the membrane occurs. Although this explanation is still controversial [32,39,47].

NYS also binds weakly to cholesterol, a sterol present in the plasma membrane of mammalian cells. It is this link that explains its adverse and toxic effects, and therefore NYS should not be administered parenterally [34,41,45]. When administered by this route, it can cause hemolysis, necrosis, and cold abscesses at the injection sites due to its immediate binding with the plasma membranes of red blood cells, interfering with their

structure [32,35] Thus, when NYS is administered orally, the desired effect is a superficial effect on the oral mucosa that lines the gastrointestinal tract [45].

In the American and Canadian markets, NYS in the form of liposomes is found for the treatment of invasive intravenous infections. In this case, NYS is not restricted to the treatment of candidiasis but can also be employed to combat *Aspergillus* spp. infections. This liposomal form of NYS can be used intravenously since it does not present the adverse effects of NYS in the conventional form. This is explained by the presence of lipids in the composition of liposomes, which have a higher affinity for NYS than cholesterol, but NYS's affinity for ergosterol still remains higher [32,34,39,48].

When administered topically, the adverse effects of NYS are uncommon, and episodes of nausea, vomiting, and diarrhea may occur, as well as allergic reactions [49]. In many cases, nausea is caused by the extremely unpleasant taste of the drug, which can compromise compliance to treatment [49].

3.3. Pharmaceutical Preparations Containing NYS

NYS can be found in several pharmaceutical forms, intended for cutaneous, vaginal, and oral administration, and is found in the national and international markets for the treatment of vaginal, oral, esophageal, intestinal, and cutaneous candidiasis [7,32]. Therefore, NYS can be found in the following pharmaceutical forms: powder, tablets, creams, ointments, pastilles, and suspensions. The type of pharmaceutical form used will depend on the type of candidiasis to be treated [39–42]. Table 4 presents pharmaceutical forms of NYS.

Table 4. Dosage forms containing nystatin (NYS) for the treatment of fungal infections and type and site of administration [39–42].

Dosage Forms for NYS	Type/Site of Administration	Types of Candidiasis
Powder	Topical/skin	Cutaneal
Cream	Topical/vaginal	Vaginal
Suspension	Topical/oral	Oral, oropharyngeal, and esopharyndeal
Tablets	Topical/oral	Oral and oropharyngeal
Pills	Topical/oral	Oral and oropharyngeal
Ointments	Topical/skin	Cutaneal
Liposomal	Systemic/parenteral	Intravenous fungal infections

The NYS aqueous oral suspension is used in the treatment of oral candidiasis, whose concentration is 100,000 IU/mL. The patient is instructed to apply 5 mL of the drug 3 to 4 times a day, performing mouthwash for 5 min, with subsequent swallowing of the product. Treatment lasts from 7 to 14 days [50]. In the Brazilian market, only this pharmaceutical form of NYS is found for the treatment of oral and oropharyngeal candidiasis. However, in other countries, NYS is available in the pharmaceutical form of medicated lozenges and oral tablets. Each tablet contains 200,000 IU of NYS and should be administered 1 to 2 units, 4 to 5 times a day, for 10 to 14 days. Each tablet has 500,000 IU, which should be applied 3 times a day for 7 to 14 days [40]. Nystatin oral suspension is usually administered for mild to moderate conditions, and swallowing the suspension can impact the liver's function [38].

Aguiar et al. (2010) [51] described a preliminary clinical study with 14 patients who were diagnosed with oral candidiasis. The subjects were divided into 2 groups, where the first received the treatment with the use of 1 NYS oral tablet containing 500,000 IU, 4 times a day, for 7 days. The second group was treated with 5 mL of NYS oral suspension (total dose of 500,000 IU), applied 4 times a day, also for 7 days. The treatment performed with oral tablets proved to be more effective, eradicating the infection more quickly. This data suggest that the increased contact between the drug and the oral mucosa led to a more pronounced therapeutic effect. Thus, the use of dosage forms that allow intimate

contact with the mucosa and have higher residual power may provide a more prominent pharmacological action. NYS is known for its remarkable post-antifungal effect (a delay in fungal regrowth that persists after a brief exposure to an antifungal agent). For that reason, a topical pastille of NYS was developed. The benefits of using those in substitution for oral NYS suspension are controversial; however, the combination of the two therapies appears to be more effective in treating oral candidiasis [52].

Topical therapy using NYS is the backbone for oral candidiasis treatment. The main reasons are its increased efficacy, low cost, and fewer side effects when compared with triazoles and echinocandins. To improve nystatin action, pharmaceutical systems have been developed to increase its aqueous solubility [32,34]. Another interesting treatment with high efficacy is photodynamic therapy; however, its high cost reduces its accessibility. For denture stomatitis, NYS suspensions of 100,000 IU and six sessions of photodynamic therapy showed the same results [39]. Regarding the COVID-19 patients, the overconsumption of corticosteroids and antimicrobial therapy was associated with multiple *Candida* strains; however, NYS suspensions showed good outcomes as treatment [53].

4. Conclusions

Oral candidiasis is an opportunistic fungal infection that requires an early diagnosis for better treatment and outcomes. The diagnosis is commonly performed by observing lesions in the oral cavity. The COVID-19 pandemic brought a new predisposing factor, contributing to the prevalence of the disease. The mainstay of therapy is NYS. The protocol of the NYS suspension of 1,000,000 IU is an effective drug against oral candidiasis, despite its low solubility and low permeability, which affect its availability in the oral cavity. Other pharmaceutical forms for the improvement of nystatin solubility seem to be an interesting alternative. However, the risk-benefit ratio for the patient must be discussed, especially in an acute COVID-19 scenario. The NYS binding to membrane sterols, specifically cholesterol in human cells, impairs the SAR-CoV-2 virus budding process; however, it cannot be used as an antiviral drug to treat COVID-19. Nonetheless, NYS can be considered a disinfectant for the gastrointestinal tract against the SAR-CoV-2 virus; thus, pharmaceutical technologies that are relevant to improving the aqueous medium solubility/dispersibility to deliver NYS must be studied. Finally, investigation is still needed to better understand the relationship between NYS, COVID-19, and oral candidiasis.

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