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SUSTAINED RELEASE OF NYSTATIN FROM POLYURETHANE MEMBRANES FOR BIOMEDICAL APPLICATIONS

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Two types of polyurethanes with concentrations in urethane groups: 1.5 mmoles/g, 2.5 mmoles/g, respectively were prepared. The systems polyurethanes-nystatin was obtained by mixing different amounts of nystatin with polyurethanes and the membrane was prepared by phase inversion method. The structural, thermal and morphological characterization of the obtained systems was performed using ATR-FTIR, DSC and SEM. An *in vitro* technique to determine the release of the nystatin into model biological media was used. The influence of the concentration in urethane group of the polyurethanes on the release of nystatin was studied. It was shown that the mechanism of drug release was Fickian diffusion. The possibility of application of the drug delivery systems as an antifungal drug was shown by biological test.

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1. Introduction

The release of drugs from polymer matrices was gradually developed for therapeutic research because provides a constant concentration of drug over prolonged periods, reduce the toxicity, a high specificity, eliminate the discontinuous therapy and improves the pharmaceutical efficiency [1,2].

The release depends on how the drug is embedded into the polymer and also by the properties of polymers: chemical and morphological structures, glass transition temperature, permeability [3] degree of crystallinity, miscibility [4], the degree of order, biocompatibility [5]. A drug can be dispersed into a polymer to form a mixture or can be dissolved to form a blend with a single glass transition temperature.

Nystatin is a polyene antifungal characterized by a potent broad-spectrum antifungal action including a wide range of pathogenic and non-pathogenic yeasts and fungi [6]. The Nystatin is active against a variety of fungal pathogens including: *Candida*, *Aspergillus*, *Histoplasma*, and *Coccidioides* and has been used for years to treat Candida at the skin [7] and those for the mouth [8]. This information, combined with the facts that the incidence of disseminated fungal infections has risen over the past decade, and that Candida is now the fourth most commonly encountered nosocomial bloodstream pathogen, shows that it is increasingly important to make available new products to fight these alarming trends [9].Various delivery systems have been studied the release of nystatin from natural polymers: chitosan [8], hydroxylmethyl cellulose [10] and synthetic

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polymers like these poly(vinyl acetate) [11], poly(methyl methacrylate) [12], poly(ethylene glycol) [13] and polyurethane [7]. A promising approach for the development of new controlled releasing preparations is the use of polyurethane materials as the basis of drug delivery systems [14].

Polyurethane is a general term used for a class of polymers derived from the condensation of isocyanates and alcohols [15-19]. They are an important and versatile class of polymers that have found many biomedical applications such as artificial heart valve [20], artificial blood vessel [21], fracture fixation [22], injectable products [23], artificial joint [24], controlled release devices [25], on account of their excellent physical properties, relatively good biocompatibility [26-28] and the possibility of changing their properties by varying soft and hard segments from the composition. The polyurethane systems are being used for sustained and controlled delivery of various pharmaceutical agents, including propranolol, caffeine, prostaglandin, and isoniazid [29]. Many of these systems are based on a physical combination of a drug with polymers and the kinetics of drug release is generally controlled by diffusion phenomena through the polymer [29].

In the present study, new polyurethanes with two concentrations in urethane groups (1.5 mmoles/g, 2.5 mmoles/g respectively) were developed in order to obtain membranes with different amounts of nystatin and to evaluate the influence of the chemical and morphological structure of the synthesized polyurethanes on the release of nystatin for antifungal activity. The systems obtained by the phase inversion method were characterized for solid state of polyurethanes and nystatin drug–polymer interaction by ATR-FTIR, Differential Scanning Calorimetry (DSC) and Scanning Electron Microscopy (SEM). Finally the antifungal activity of the systems polyurethane-nystatin was assayed *in vitro*.

2. Experimental

2.1. Materials

Poly (tetramethylene oxide) (PTMO, Mn 2000, Sigma-Aldrich, UK), poly (butylene adipate) diol (PBA, Mn 2000, Sigma-Aldrich, UK), 1,4-butane diol (BD, Sigma-Aldrich, UK) and 4,4'-methylene diphenyl diisocyanate (MDI, Sigma-Aldrich, UK) were used as received. Dimethylformamide (DMF, Sigma-Aldrich, UK) was dried over molecular sieve before use. Nystatin was offered by SC Antibiotice SA Iasi and was used as received. All other chemicals were of analytical reagent grade and used without further purification.

2.2. Polyurethanes synthesis

The polyurethanes were synthesized from PTMO and PBA with Mm 2000, BD and MDI in a solution of DMF according to previously published methods [27]. The polyurethane PU1 was synthesized with 1.5 mmoles urethane/g polymer at the components ratio of PTMO: PBA: MDI: BD = 1:1:3.8:1.008 and another polyurethane PU2 with 2.5 mmoles urethane/g polymer in the ratio PTMO: PBA: MDI: BD = 1:1:8.4:5.6. The polyols PBA and PTMO were dehydrated in vacuum at 120 °C for 2 hrs. The reaction was carried out under stirring with MDI at a temperature of 85°C, in DMF solution and the BD was added at 60°C temperature. The polymerization was stopped at the viscosity of 7000 cP, 7200 cP , respectively at 20°C with a solution of 10 ml ethyl alcohol: DMF 1:1 (v/ v). 35%w/w PU1 and 30%w/w PU2, respectively in DMF solution were obtained. The scheme of synthesis for the two polyurethanes is presented in Fig. 1.

2.2.1 Preparation of polyurethane-nystatin solutions

Different amounts of nystatin were dissolved in the DMF. After complete dissolution of drug, the homogenous solutions were poured in 5 g polyurethane DMF solution. Then the mixture was stirred vigorously for 3 hrs and then poured on Petri-dishes (Ø=110mm). The solutions obtained were left overnight for a given time. Four types of polyurethane-nystatin solutions with different amounts of nystatin were obtained.

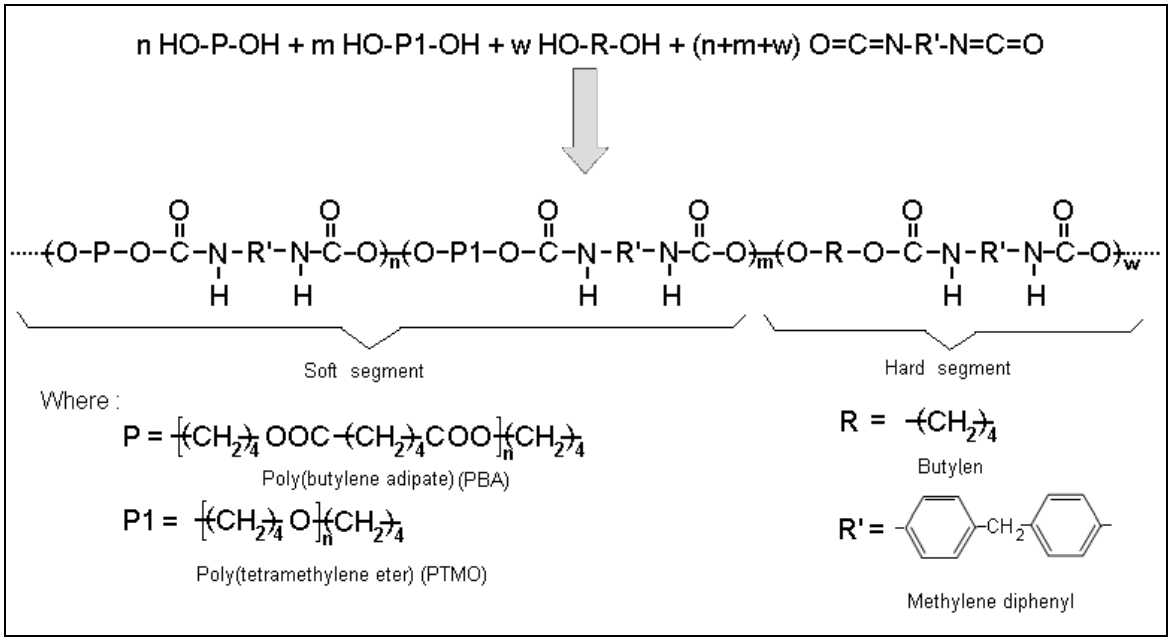

Fig. 1. Synthesis of the polyurethane samples

2.2.2 Preparation of polyurethane-nystatin membranes

Polyurethane solutions with different amounts of nystatin were processed as membranes by using phase inversion method initiated by precipitation in non-solvent [7]. The deionised water at 45 °C was poured over polyurethane- nystatin solution and kept under these conditions until the membrane separated completely from the Petri dish. Then, the membranes were washed in distilled water to remove the solvent traces or the amounts of free nystatin and dried in vacuum oven 25 °C and $2x10^{-1}$ mbar to a constant weight. The percentage of nystatin release from the membranes in distilled water was calculated using the slope and the intercept obtained from the standard curve of nystatin, in distilled water. The proportions of nystatin remained in the membranes, were: 1.6%, 4.1%, 7.9%, 11.9% for PU1 and 1.8%, 4.7%, 9.1%, 13.3% for PU2, respectively.

2.3. Membranes characterizations

The UV-VIS determinations were performed in triplet with a JENWAY type 6505 spectrophotometer (Bibby Scientific Ltd., England).

FTIR spectra were recorded on thin membrane by ATR method by means of a FT-IR DIGILAB, a Scimitar Series (USA) spectrometer with a resolution of 4 cm^{-1}. A crystal from SeZn with refraction index of 2.4 was used. The spectra were recorded over 600–4000 cm^{-1} domain at room temperature and a resolution of 4 cm^{-1}. The penetration degree was in the range of about 2–3 μm.

Differential scanning calorimeter (DSC) measurements were performed by means of a Pyris Diamond (Perkin Elmer) instrument. The samples mass of 6–8 mg were placed in aluminum foil pans. DSC curves were recorded in nitrogen atmosphere (20 mL/min flow) with a heating rate of 10°C/min from −100 to 80 °C temperature range. The inflexion point of DSC curve was taken as glass transition temperature (*Tg*). Two runs were performed for each sample. As reference, was used high purity (98%) indium, which has melting temperature at 156.68 °C and melting enthalpy of 28.4 J/g.

Surface morphology was examined before and after modifications of PU with nystatin by using a SEM/ESEM FEI Quanta 200 microscope equipped with EDAX Si (Li) X-ray detector and Gatan Alto Cyro stage, operating at 20 kV. Samples were mounted on graphite supports and observed under different degrees of magnifications.

The drug release kinetics of the polyurethane-nystatin membrane was carried out as follows. The experiments were performing in a shaking bath thermostated at 37 °C by immersing 10 mm^2 squared shaped samples (about 0.03 g) of different amounts of polyurethanes-nystatin systems in sealed glass vial containing 15 mL of the phosphate buffer (PB) (pH 7.4). The release was made by changing the phosphate buffer at 24 hours and at certain time intervals, aliquots (1.4 mL) of the sample were withdrawn periodically to determine drug concentration. The released nystatin amount was monitored using a UV-VIS Spectrophotometer with a JENWAY type 6505. The absorbance of nystatin was determined at a wavelength of 305 nm [12]. The amount of nystatin released from the membranes, at a given time, was calculated using the slope and the intercept obtained from the standard curve of nystatin, in phosphate tampon solution pH=7.4, expressed as percentage of total drug content of the investigated membranes. Experiments were performed in triplicate, and the average value was considered.

The kinetics of nystatin release from polyurethane-nystatin membranes was determined by finding the best fit of the release data to Korsmeyer–Peppas plots.

$$M_t/M_\infty = kt^n \quad (1)$$

where: M_t/M_∞ is the fraction of drug release at time t, k is a constant comprising the structural and geometric characteristics of the sustained release system and n, the release exponent, a parameter that depends on the release mechanism and is thus used to characterize it [14]. This n value is used to characterize different release mechanisms and could be obtained from the slope of a plot of log M_t/M_∞ vs. log time [32].

The agar diffusion method [30, 31] was used in the assays against fungi (*Candida albicans-C.albicans*- ATTC 10231*)*, and nystatin as the standard antifungal agent. Antifungal activity was expressed as the average diameter for inhibition zones. Briefly, agar plates prepared with Mueller – Hinton Agar (Difco, USA), were inoculated with organisms to obtain confluent growth after incubation 24 hours at 37 °C. For comparison with the control sample (nystatin, 100µg/ml - in DMSO, on sterile paper discs, 5 mm diameter), the polyurethane-nystatin samples (5 mm diameter) were placed on the inoculated Mueller-Hinton plates, and the plates were incubated at 37 °C for 72 hours. The diameters of the zones of inhibition around each disc were measured. Five samples were measured for every reported data.

All presented results have been expressed as an average of at least three independent determinations, and these mean values were used in plotting the curves. The drug delivery measures are expressed as mean ± standard deviation (SD) from the three independent measurements.

3. Results and discussions

Linear segmented polyurethanes comprised from soft, amorphous PTMO and PBA-based segments, and hard, crystalline MDI-BD based segments with different concentrations in urethane groups (1.5 mmoles/g and 2.5 mmoles/g) have been synthesised. At the 2.5 mmoles/g concentrations this segments conduct to phase separated morphology [27] and it is well known that a better microphase separation is obtained by lowering the competitive hydrogen bonding between hard and soft segments [28]. On the other hand, nystatin is a polyene which exhibits relative numerous hydroxyl functional groups active in hydrogen bonding.

An important aspect related to the applicability of the polyurethane blends with nystatin content is to establish the influence of the concentration in urethane groups in the release behaviour of nystatin. In this respect, we have chosen two representative concentrations in urethane groups 1.5 mmoles/g and 2.5 mmoles/g, respectively for their structural, morphological influence and physical interactions on the kinetics release of nystatin.

3.1. ATR-FTIR analysis

The representative ATR–FTIR absorbance bands observed in spectra of PU1 and PU2, their blends polyurethanes-nystatin with different concentrations of nystatin and the nystatin powder are shown in Fig.2.

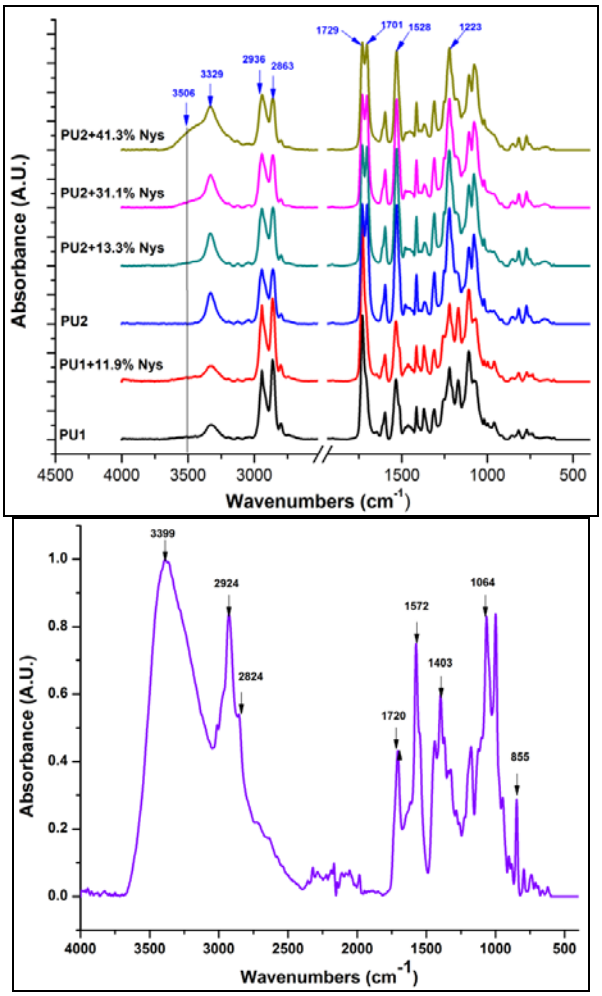

Fig. 2. The spectra of PU1, PU2, blends with different proportion of nystatin (left) and nystatin (right)

The characteristic bands of aromatic poly (ester-ether) urethane are found at about the same number of waves in both polyurethanes PU1 and PU2. The main difference between both of them is in the ratio of absorbance $A_{C=O\ bond}/A_{C=O\ free}$ in the range of 1800-1628 cm^{-1}. If at the PU1 the absorbance band of the carbonyl bond is not well defined at 1712 cm^{-1}, this became peak at the 1701 cm^{-1} in PU2, due to the increase in the molar concentrations of urethane group from 1.5 mmoles/g to 2.5 mmoles/g and due to the amorphous/crystalline phase separation [27, 33].

The ATR-FTIR spectrum of PU1 and PU2 displays a broad intense absorption bands with the maximum at 3326, 3329 cm^{-1} respectively, assigned to ν(N-H) stretching bounding [22], and the peaks at 2939, 2858 and 2936,2863 cm^{-1}, respectively, are the asymmetric and symmetric stretching vibration $\nu(CH_2)$ [34, 35].

The characteristic stretching vibration peaks at 1727 and 1729 cm^{-1} belong to carbonyl groups of polyester chain and free urethane and the peaks at the 1712 and 1701 cm^{-1}, respectively, belong to the stretching vibrations of bonding carbonyl groups of urethane structure [34, 36-39]. The peaks at the 1595 cm^{-1} belong to the stretching vibrations ν(C=C) of the aromatic cycles and

the peaks at the 1530, 1222 and 1528, 1223 cm^{-1} respectively, have a complex structure and consist mainly from the deformation vibrations δ (N-H) and stretching vibrations ν(C-N) [34, 40].

This bands overlap with the absorption bands of polyurethane PU1 and PU2, which have the same type of groups and vibrate at the same wavelength. The absorption bands at 3506 cm^{-1} (usually related to free hydrogen of –NH-COO-, and –OH,-COOH from nystatin) is very well defined in spectra associated with PU2-nystatin blends in the concentrations of 30% and 40%, as an indication that the hydrogen free from the spectra PU1-nystatin and PU2-nystatin blends were hydrogen bonded to polar groups such as carbonyl in ester, urethane or ether bond at the lower concentrations, phenomenon that emphasizes the compatibility of the two compounds.

The typical ATR-FTIR absorbance bands in spectrum of nystatin displays a broad intense absorption bands with the maximum at: 3399 cm^{-1} – due to the stretching vibration of hydrogen bonded; 2924 and 2824 cm^{-1} – due to asymmetric and symmetric stretching vibration CH_2 group, 1720 cm^{-1} - due to the stretching vibration of carbonyl from ester and carboxylic acids, 1572, 866 cm^{-1}- due to the double bonds CH=CH, 1403 cm^{-1}- due to the bending vibration ν(-CH), 1064 cm^{-1}- due to hydroxyl groups from nystatin [41-44].

3.2. DSC analysis

The Fig. 3 shows the DSC curves of PU1, PU2 respectively, with their blends and the values of *Tg*. It is known that the secondary interactions, as hydrogen bonds between drug and polymers lead to increase the *Tg* [44], the phenomenon called antiplasticization [45]. *Tg* indicates some physical interactions between the polyurethane chains and nystatin.

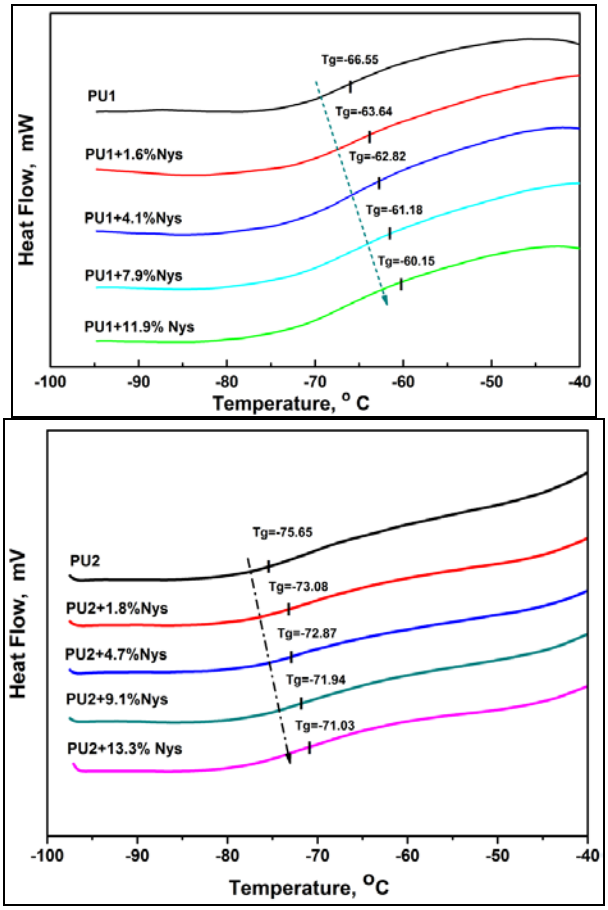

Fig. 3. DSC curves of PU1and PU2 and their blends with different proportion of nystatin

Glass transition temperature of the PU2 is lower by comparison to the PU1 series because the PU2 contains 2.5 urethane mmoles/g compared with 1.5 urethane mmoles/g for PU1. This fact is due to the crystalline-amorphous phase separation that is specific to polyurethanes, when the concentration in urethane groups it is more than 2 mmoles/g [27]. It is known that this phenomenon is more pronounced at polyether urethane [21]. Also, the increases of *Tg* with the proportion of nystatin in the polymeric matrix, in both series of polyurethanes, shows that nystatin produce the structuring of polyurethanes macromolecules. This effect may be, especially, due to the interactions hydrogen bonds between nystatin and urethane groups, so that macromolecular chains modify their conformation, and the polyurethane-nystatin matrix becomes more rigid with the increases of nystatin concentration.

3.3. Surface morphology

By SEM images was observed some change in the surface membrane aspect, reflected in the total pores surface. The blank PU1, PU2, respectively, shows macroporous aspect in section. The nystatin affects the size of pores by changing the parameters of the mass transfer solvent-water in polymer matrix in the formation phase of membrane. The SEM images were analyzed using the software Image J version 1.43u (available from the National Institute of Health, USA) to obtain the average size of pores and their distributions. Image J is an image processing software for determining edges of features that are of interest, calculating their area, proportion and other useful measurements. Fig. 4 present comparatively the SEM image of PU samples used in this study. In corner of each image it is represented the average diameter distribution of pores. From the diagram distribution it is observed that more than 60% of the membrane pores have average diameter less than 10 μm and 12.5 μm, in case of PU1 and respectively PU2, without nystatin and less than 17.05 μm and 17.9 μm in case of PU1 and respectively PU2, with nystatin. This shows the good distribution of pores in the polyurethane membranes formed, which present high porosity and interconnected structure. In both cases nystatin have an effect of increasing the average pore diameter about of 40-70%. We can say that the release is controlled mainly by the influence of the concentration in urethane groups of polymers, but also of membrane pores size. The PU1 with a concentration in urethane groups 1.5 mmoles/g determines a faster release of nystatin.

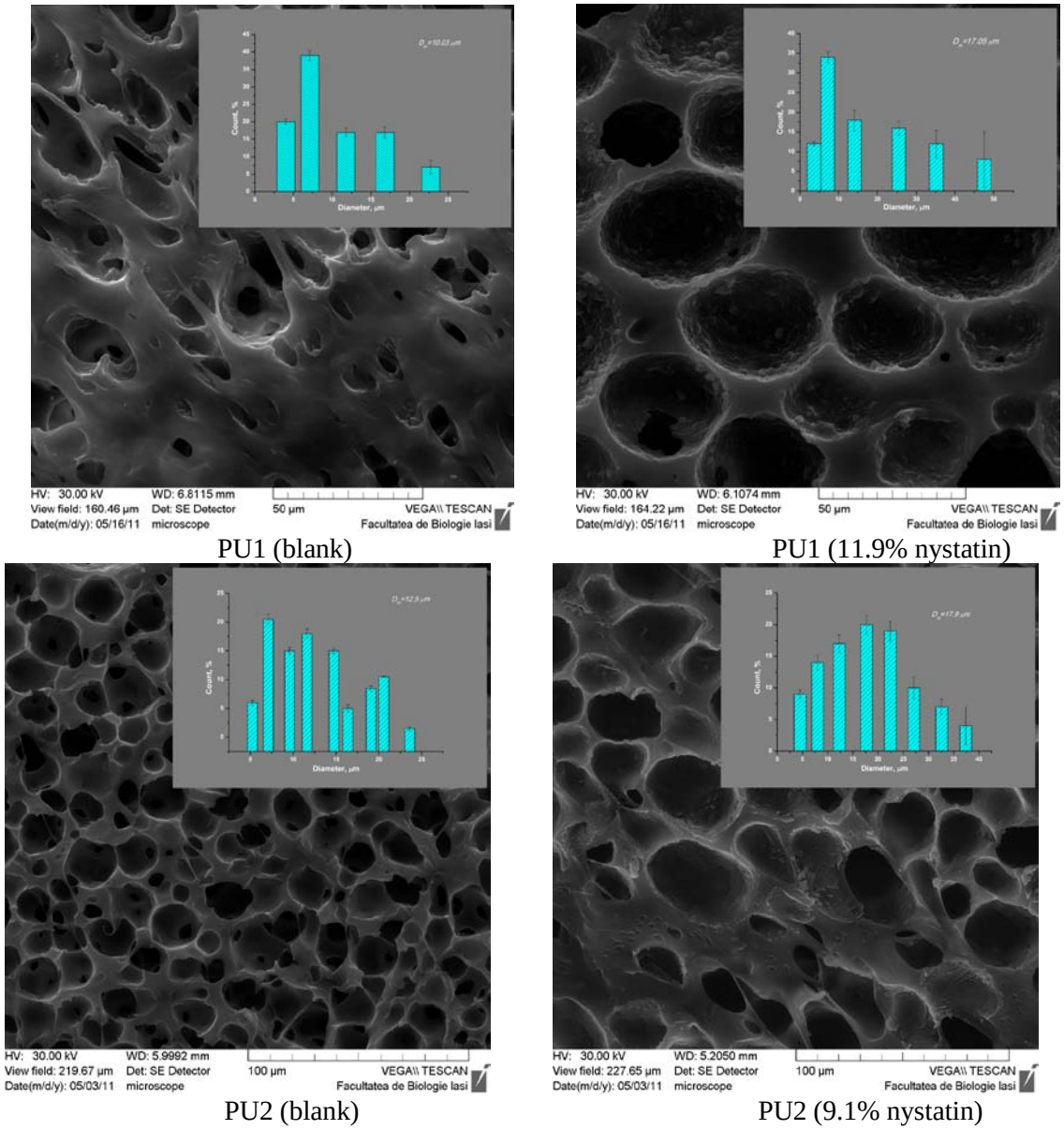

Fig. 4. SEM images and distribution of pores (corner); D_m – average diameter

3.4 In vitro release study

One of the main characteristics of drug delivery systems is the way of drug release to the organism [29]. In our study, the release behaviour of nystatin from polyurethane membranes was studied by immersing polymeric samples into phosphate buffered solution at 37 °C. Fig. 5 shows the release of nystatin for 216 hrs in PU1 and PU2, respectively. In both cases, the release rate of nystatin increased because of the high concentration in nystatin. Similarly, drug release profile of both formulations exhibits an initial burst release and then a sustained release driven by diffusion of the nystatin through polyurethane membranes. The nystatin release is strongly dependent by the concentration of urethane group: for the polyurethane-nystatin system PU1 is significantly higher than that from the polyurethane-nystatin system PU2 (Table 1). The same behaviour of the released rate, in function of the urethane concentration was observed by Basak [46]. For example, the polyurethane-nystatin system (PU1, 16.09 µg/mg initial concentration of nystatin), releases 10.53µg/mg of drug and the system polyurethane-nystatin PU2 for 18.08µg/mg initial concentration of nystatin releases only 5.85 µg/mg. The slower rate of release found in the case of

system PU2 is because of the strong interaction of hydrogen bond between the drug and the polyurethane than that found in the case of system PU1, where the concentration in urethane groups is with 40% lower than in the system PU2. This suggests that a high concentration of urethane groups in the polyurethane matrix does not favour the quick release of nystatin from polyurethane-nystatin system.

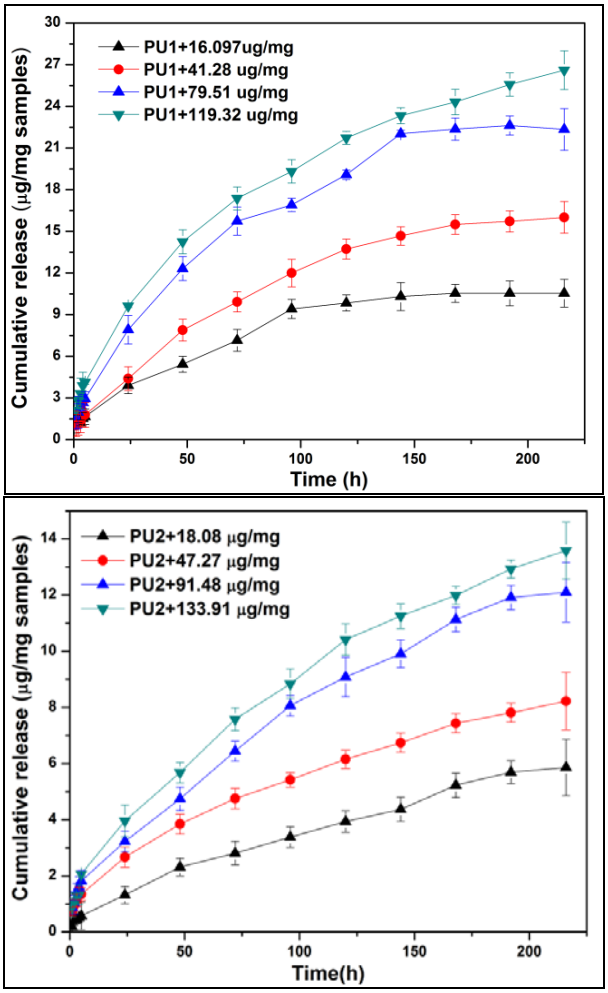

Fig. 5. Nystatin released in function of time from PU1and PU2 membranes, for different initial proportions of drug (pH=7.4)

3.5 Mechanism of drug release

The release data were analyzed with the Korsmeyer–Peppas equation. The release rate *k* and the diffusion coefficient *n* of each system were calculated by linear regression analysis. The coefficients of correlation (r^2) were used to evaluate the accuracy of the fit. The *k* and *n* values are given in Table 1. The corresponding plot (log cumulative percent drug release vs. time) for the Korsmeyer–Peppas equation indicated a good linearity ($\boldsymbol{r^2}$ = 0.9919, 0.9945 respectively). In some formulation the value of *n* ranged between 0.51 and 0.57, which indicate that the mechanism was close to the Fickian one [15]. In our study the average of the release exponent *n* was 0.5257, 0.5275, respectively, which appears to indicate a Fickian diffusion mechanism for drug release in both systems PU1, PU2. The values of the correlation coefficient are very close to 1, for PU1 is 0.9919 and for PU2 is 0.9945, respectively. The release is controlled mainly by the influence of the concentration in urethane groups of polymers. The weaker interaction, such as hydrogen bonds, who occurs in the PU1 (with a concentration in urethane groups 1.5 mmoles/g) determines a faster release of nystatin for 216 hours.

Tabel 1. In vitro drug release amount (after 216 hrs) in pH=7.4 buffer, for the systems based on Korsmeyer-Peppas equation PU1 and PU2

Sample	Amount of nystatin, µg /mg	Released of nystatin pH 7.4, 216 hrs		Drug release kinetics with the Korsmeyer-Peppas equations	
		µg /mg	%	n	k
PU1	16.0976	10.53±1.00	65.44±0.99	0.5257	0.0668
	41.2813	16.00±1.14	38.77±1.20		
	79.5186	22.34±1.50	28.10±1.15		
	119.3217	26.60±1.40	22.29±1.17		
PU2	18.0899	5.85±1.00	32.40±1.25	0.5275	0.0660
	47.2706	8.22±1.50	17.39±1.24		
	91.4805	12.10±1.06	13.23±1.02		
	133.9153	13.58±1.01	10.30±1.01		

3.6 In vitro antibacterial activity

Antifungal activity of the polyurethane – nystatin systems has been evaluated against *C. albicans* which is known to cause dermal and mucosal infections, beside other infections in humans. All materials studied in this work show antifungal activity, with inhibition zone ranging from 12 to 25 mm (Table 2).

Table 2. Antifungal activity of the polyurethane – nystatin by the agar diffusion method

Sample (µg nystatin/mg sample released after 72 hrs)	Inhibition zone, mm ±SD
PU2 (2.8 µg /mg)	12.2±0.4
PU2 (4.75 µg /mg)	15.4±0.5
PU2 (6.44 µg /mg)	23.5±0.2
PU2 (7.58 µg /mg)	25.3±1.0
Nystatin (100µg/ml)	28.1±0.2
DMSO	-

However, the compounds differ significantly in their activity against test microorganism; by increasing the concentration of nystatin in material the inhibition zone increased too. Nevertheless, the variation of the antifungal activity is not increasing linear with nystatin concentration in polyurethane because of some interactions between polymer and drug.

4. Conclusion

This work present the preparation and characterization of two polyurethanes with different concentrations in urethane group and some formulations polyurethane-nystatin systems for evaluate their influence in the release of nystatin. The presence of the physic interaction between nystatin and the polymer (proved by DSC and ATR-FTIR) was evidence as well. The study revealed that drug release is strongly dependent by the amount of nystatin in the systems and the concentration in urethane groups. The high concentration of urethane in the polyurethane membrane decreases the release of nystatin from polyurethane-nystatin system. Drug release follows a Fickian diffusion for both type of systems polyurethanes-nystatin. Moreover, the proposed polyurethane-nystatin systems PU2 exhibited an antibacterial efficacy against *C.albicanus* (proved for a period of 72 hrs). The nystatin-polyurethane systems could be advantageously adapted in applications in which a sustained release of this antifungal is valuable to prevent or reduce infections. The obtained membranes have promising potential in drug delivery application as wound dressing material.

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