

POLITEHNICA University of Bucharest

Doctoral School "Applied Chemistry and Materials Science"



DOCTORAL THESIS

Applications of polysulphonic membranes for the retention of residues of oncological medicinal products

Polysulfone membrane applications for oncology drugs

(Summary of doctoral thesis)

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Bucharest, September 2020

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(corresponding to the doctoral thesis)

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The accelerated development of polluting industries and their impact on the surrounding environment, as well as on the quality of people's lives, have spurred the development of new technologies to combat pollution. Among these technologies can be remembered those that use membranes for the purpose of separating and retaining different pollutants such as medicines, produced with a negative impact on the quality of the environment. These molecules are currently trying to separate and retain them before they are eliminated in the environment. Efforts are also being made to replace old, often highly polluting technologies with new, environmentally friendly technologies.

Classical separation technologies, such as filtration, centrifugation, distillation, extraction, absorption, adsorption, used until recently, have been replaced with new separation and recovery technologies based on the use of membranes. Among these technologies that have applications in different industries can be remembered: micro-, ultra-, hyper- and nano-filtration, electrodialysis and electro-ultrafiltration, pervaporation and pertraction.

The rapid development of these methods was due to the emergence of new materials, but also to the momentum of research in the field of nanomaterials, towards the development of composite and hybrid materials, as well as the discovery of new techniques and technologies.

In this context, research on the development of composite membranes used in the processes of retention of pollutants of an organic nature, present in low concentrations, from different industries, is also intensified.

There are several polymer compounds likely to be used in the preparation of membranes. Among them is polysulphone (PSU). Polysulphone (PSU) possesses physical properties that, as recommended, are suitable for membrane preparation. These properties can be improved if polysulphone impregnation (PSU) with nanoparticles occurs. This process leads to increased hydrophilicity and reduction of the fouling (clogging with organic materials) of membranes in filtration processes.

The membranes thus obtained (by impregnating the membrane with nanoparticles) are considered to be multifunctional compounds because they have both properties specific to nanoparticles and membrane-specific ones, leading to the improvement of the properties of these compounds.

This paper aims to synthesize and characterize new types of polysulphone-based composite membranes for their possible use in the retention of residues of oncological drugs.

The World Health Organization defines the medicinal product as any substance or combination of substances that alters a physiological or pathological process for the benefit of the user or any substance or combination of substances that can be administered to humans or

animals, with a view to establishing a diagnosis or restoration, correction or modification of physiological functions.

Medicines are made up of substances, ingredients or components. [1]

The classification of medicinal products can be done according to several criteria, such as, for example, how they were obtained – herbal products or homeopathic medicines and synthetic drugs, obtained from chemical reactions. Medicines can also be classified according to the active substance contained or according to the conditions treated.

The methods used to treat cancer have changed in recent decades as a result of the identification of new curative treatments for many of the cancers considered fatal, such as testicular cancer, lymphoma or leukemia.

Compounds used in chemotherapy have a varied structure and different mechanisms of action. Among these can be remembered: alkylated agents; analogues of folic acid, pyrimidine or purine, natural products, hormones and a wide variety of agents directed to specific molecular targets.

The beneficial properties of *Madagascar's Periwinkle* or *Catharantus roseus* (also known as *Vinca rosea*), a species of myrtle, have been described in medicinal folklore. Extracts from this plant have attracted interest due to their hypoglycaemic effect in treating diabetes. Purified alkaloids, including vinblastin and vincristine, led to the regression of lymphomas in mice and were among the first used in the treatment of leukemia and testicular cancer. [6]

Vinca alkaloids are asymmetrical dimeric compounds formed by the condensation of vindoline and catharanthine subunits.

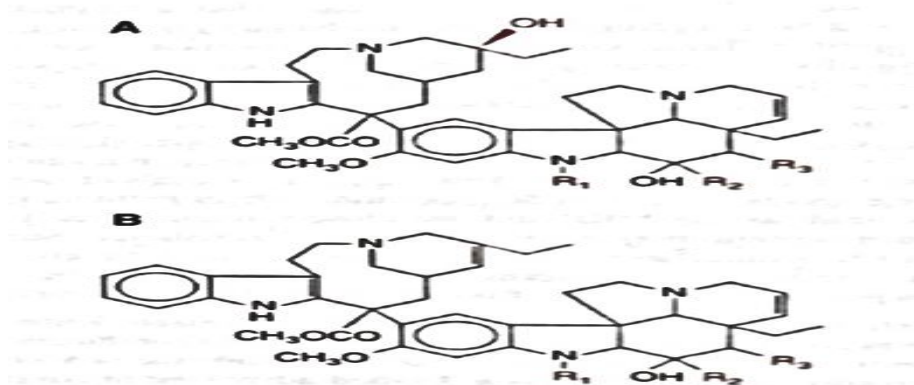


Fig.1 Structure of vinca alkaloids,.

These chemical compounds are commonly found in mixture with other alkaloids in plants. The extracts of Madagascar's Periwinkle contains up to 70 different alkaloids. Due to the presence of nitrogen atom, extracts of these plants can be purified by an acid-base extraction followed by solvent extraction (most often dichloromethane). The separation of the two alkaloids into pure substances was done using chromatographic techniques.



Fig.2 Catharanthus roseus

The two substances have a similar structure the only difference being the carbonyl grouping present in the composition of vincristine compared to a methyl grouping in the same location in the vinblastine structure.

Vinblastine and vincristine are dimeric alkaloids isolated from Madagascar periwinkle (Figure 3) (*Catharanthus roseus*). They exhibit significant cytotoxic activity and are used in antitumor therapy as antineoplastic agents.

A report by United Nation World Water Development shows that in 2050 the decrease in drinking water sources will affect about a quarter of the world's population [19]. Along with the lack of drinking water resources another problem that humanity will face will also contaminate the waters with various pollutants (heavy metals, pharmaceutical compounds, chemical compounds used in agriculture, etc.) constantly increasing. Currently, on an industrial scale, different technologies are used to treat water for drinking or purifying. In general these technologies are relatively expensive with high energy consumption.

Membrane processes have quickly found their applicability in different industrial areas such as: wastewater treatment technologies, medical technologies, different sectors of the chemical industry. The improvement of the techniques of preparation and characterization of membranes has led to a rapid evolution and diversification of these technologies.

They allow the compositions of a complex system, consisting of a solvent in which ionic chemical species, molecules and macromolecules, molecular aggregates and particles are dissolved. Membrany techniques, widely applicable, developed in five directions (microfiltering, ultrafiltration, reverse osmosis, dialysis and electrodialysis). These technologies cover the entire range of particle sizes to be separated, with better results than centrifugal separation.

The development of membrany processes occurs as a result of the action of external factors called the driving force of the process. Thus, depending on the techniques used, the driving force may be different. [24-26].

The main characteristic of polymeric or inorganic membranes, natural or synthetic is their structure. This refers to the texture of the membranes or their morphology. Depending on their texture, membranes are classified into symmetrical membranes, asymmetric membranes or composite membranes.

The homogeneous membranes are prepared from materials that do not lead to the formation of asymmetrical or composite structures. They are intended for applications that use anisotropic membranary morphologies or for which the product flow does not have a high flow. The rules for the selection of membranary materials are mainly influenced by the structure of membranes which play an essential role in the mechanisms of transport and separation.

In the case of nonporous membranes, because their pores are microscopically undetectable, they are considered from the point of view of stucco with a immobile solvent for the molecules subjected to transport. The process of transport through this type of membranes follows through a mechanism of solubility-diffusion, which means that the chemical species dissolve and diffuse inside the membrane under the influence of the concentration and/or pressure gradient. In the case of these membranes, the interaction between the fluid phase and the membrane is very important. As a result of this process, the membrane's inflator in fluid or its complete dissolution may occur.

Reverse osmosis is a physico-mechanical process of separation, framed in the category of filtration techniques before. Because it has as its driving force the pressure difference, reverse osmosis belongs to *the barro-membrane* processes, processes that occupy the first place in the range of industrial applications [45].

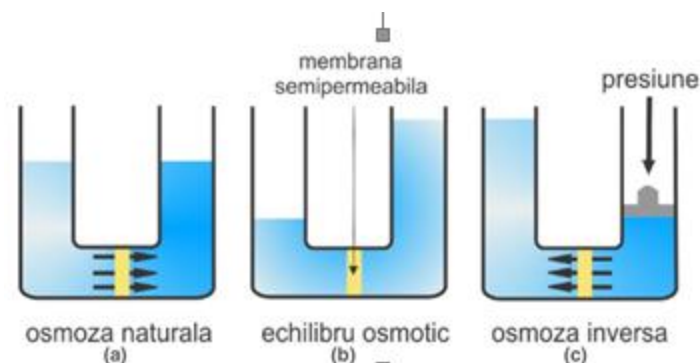


Fig.3 Osmosis process: (a) natural osmosis, (b) osmotic balance or osmotic pressure, (c) reverse osmosis [46].

Osmosis is the process by which the molecules of a solvent pass through a semipermeable membrane from a less concentrated solution into a more concentrated one, the system tending towards equalizing concentrations, according to the second principle of thermodynamics (natural osmosis, fig. 3(a)). Mass transfer results in a pressure difference on the membrane called osmotic **pressure** (fig.3b). Hydrostatic pressure, equal to osmotic pressure,

equals the pressure with which water penetrates through the semipermeable membrane. When more pressure is applied to the concentrated solution than the osmotic pressure, the reverse phenomenon occurs, passing the less concentrated solution through the membrane, taking place the reverse *osmosis* process (fig.3c).

Reverse osmosis or hyperfiltration allows the separation of dissolved substances with molecular dimensions (between 10^{-4} ... 10^{-3} μm and 1 ... 10 \AA). This allows the retention of glucose, sodium chloride, etc. The semipermeable membranes that are used in the reverse osmosis process are obtained from cellulose acetate, nylon and polyamides. Nylon is used in water treatment or treatment processes (being very permeable for chlorides, frequently found in natural or wastewater) or for the concentration of fruit juices. The most used membranes are obtained from cellulose acetate. They have an asymmetrical porous structure consisting of a very thin compact film and a porous one. The principle on which these membranes operate, in the case of water desalination is that of permeability. This is due to the diffusion mechanism of the solution. The motor force of the water diffusion mechanism is given by the pressure gradient, i.e. the flow through the semipermeable membrane. The concentration gradient causes the diffusion of dissolved substances [43].

The increase in oncological diseases in recent decades, in the world's population has led to an increase in the production and consumption of these medicines. As a result, high concentrations of these substances were recorded in the water. Their presence in the water is harm to aquatic organisms and even to human health, due to their mode of action. Their presence in concentrations of up to $100\mu\text{g/l}$ has been detected in hospital effluents. In the absence of a treatment plant of its own, these waters are discharged directly into the sewerage network where their dilution takes place, which leads to a decrease in the concentration of cytostatics in wastewater.

Studies show that some cytostatics, such as citarabine, doxorubicin, etoposide, gemcitabine, IF and vinorelbin at concentrations of up to 15 ng / L in influential/ effluent, are frequently encountered in the waters discharged into the sewerage network, and their concentration in the effluent of classical treatment plants (traditional treatment plant with active sludge, without nitrogen removal unit) is reduced very little.

The effectiveness of the elimination of various cytostatic drugs is dependent on their physico-chemical properties but also on the operating parameters of treatment plants. Advanced use of membrane bioreactor (MBR) systems, operated for a long time in the presence of a diversified microbial community, promotes the biotransformation and mineralization of pharmaceutical products.

Sources of water pollution with oncological medicines are presented in fig.4

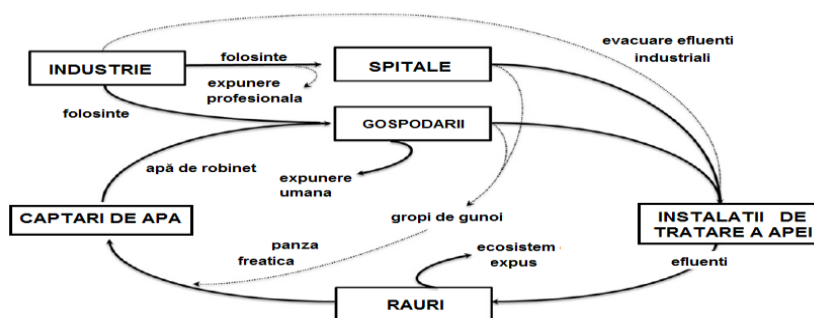


Fig.4 The route of entry and transport of cytostatic medicinal products into the environment. The broken lines indicate uncertain routes.

According to the figure, the following sources of cytostatic pollution can be identified:

[48]

- **Hospitals** – produce large amounts of chemicals and microbiologicals; in general effluents are discharged directly into the sewerage network without prior treatment.
- **Household effluents** – these are produced by patients who receive care at home;
- **Effluents from drug factories** – come from drug factories and represent a mixture of technological waters resulting from the manufacturing of medicines and household waste water. In the case of technological waste water, they may contain pharmaceutical compounds in their intact forms (without being metabolized) which could create additional loads in treatment plants;
- **Disposal as solid waste** – means products that are disposed of as a result of the expiry of the shelf life or the resulting sub-products during the manufacturing process. Although in most countries the disposal of this waste is regulated by law, however, high concentrations of these compounds are recorded, in solid waste or in the levigates of landfills.

Various techniques have been proposed to remove cytostatics from wastewater, which provide for the combination of classical treatment technologies with membrane filtration.

Active coal absorption is an advanced technology for the retention of organic compounds as well as traces of organic pollutants such as nitrogen, sulphide and heavy metals. Before the filtration step on activated charcoal, the water being treated is filtered through filters containing medium granulation material to remove the solid suspensions present in the water.

In advanced wastewater treatment technologies, chemical oxidation processes are used to lower the concentration of ammonium, organic substances as well as to reduce bacterial content

and viruses. Because, when chlorine is used to oxidize pollutants in water, THM (trihalomethane) can be formed alternatives to this method. Thus, chlorine can be replaced with chlorine dioxide (ClO_2) or ozone (O_3). [50]

In the case of waters with high pharmaceutical content, ozone by "*Advanced Oxidation Process*" is used. This process involves the introduction into the treatment water of a mixture of oxygenated water and ozone ($\text{O}_3/\text{H}_2\text{O}_2$) or the Fenton process, which consists in treating water with a mixture consisting of ferrous salts, usually ferrous sulphate and oxygenated water. Starting from these processes, other processes have been developed such as the "*Advanced Oxidation Process*", which involves the use of UV radiation alongside ozone or oxygenated water, or the photo-Fenton process, which uses UV light together with ferrous salts and oxygenated water. [51]

Reverse osmosis is a process in which salts dissolved in water are separated by filtration on semipermeable membranes at higher pressures than osmotic pressure. The membranes currently developed and the equipment used allow the use of working pressures ranging from atmospheric pressure to 6900 kN/m^2 . The advantage of this process is that organic substances are eliminated which are more difficult to eliminate by other technologies. Due to the high operating and maintenance costs, this process is applied less often for wastewater treatment. [52-53]

Another technique used in wastewater treatment processes with high organic content is electro dialysis. By this technique, the ions of the compounds are separated by means of semi-permeable membranes.

The process consists in applying a difference of potential between two electrodes, immersed in the solution to be treated. At the current crossing, the cations will migrate to the negative electrode, and the anions to the positive electrode. In the spaces inside the semipermeable membrane, the concentration grandeur varies. The efficiency of the process is influenced by many factors of which one can remember: water temperature; the intensity of the current used in the process; the type and concentration of ions to be separated; membrane permeability; the encrusting potential of water; flow of the water to be treated.

Environmentally Sound Technologies (TSe) is the basis of the entire transition to a sustainable economy through the more comprehensive whole of economic sectors: waste-free technologies, reducing the impact of pollution, efficient management of natural resources, reducing energy consumption, increasing the competitiveness and number of technological alternatives available and a better quality of life. [66]

The presence of organic pollutants in aqueous systems is due to the intensive use of organic substances worldwide. These substances, which generally have resistance to degradation, discharged into aqueous systems become persistent organic pollutants. It should be noted that many of these compounds are found in low concentrations in surface waters, and their continuous discharge into wastewater treatment plants or directly into natural receptors can pose a potential long-term threat to aquatic and terrestrial ecosystems as well as to the dependent population. For this reason, it is necessary to implement high-performance technologies that allow the degradation/elimination of these pollutants before unloading into the surrounding environment.

Many medicinal substances with different molecular structure have been shown to be photoreactive. They undergo reactions in organic solvents through different ways to light exposure. These reactions can occur through free radical intermediaries, which involve several steps leading to the final products.

The use of photochemical processes in disabling some of the aquatic pollutants is a viable alternative to the purification of industrial waters over the past decade. Direct photolysis of organic pollutants, especially aromatic, is stimulated by light radiation with wavelengths in the range 290-400 nm [73].

In recent years, a number of technologies called Enhanced Oxidation Process (EOP" or Advanced Oxidation Process (AOP) have been developed, capable of converting pollutants into useful chemicals. They are called oxidation processes because they promote reactions that are very similar to a complete oxidation reaction (or mineralization) of pollutants, with the obtaining of CO₂ and a small amount of halogenated acid, with nitrogen or sulfur. Almost all reactions of this type are exergonic and spontaneous; however, they are kinetically slow in the absence of the initiators.

EOP technologies are based on the generation of highly reactive free radicals, such as hydroxyl (OH), that function as initiators. There are three major directions of the EOP currently developed:

- 1) Homogeneous photolysis (UV/H₂O₂ and UV/O₃) – these processes use UV photolysis of oxygenated water and/or O₃ other additives to generate OH⁻ and other radicals in homogeneous solution.
- 2) Heterogeneous photolysis (UV/TiO₂)-here the semiconductor particles of TiO₂ absorb UV light and generate OH radicals⁻ as well as other radicals in heterogeneous reaction to the particle surface.
- 3) Radiolysis – a high ionized energy source (e.g. a linear accelerator) is used to irradiate polluted water. By radiolysis of water are generated oh^{radicals -}, H⁺, hydrated electrons and other

radicals.

In the experimental work, the following materials were used for laboratory scale determinations:

- ✓ Vincristine; (SINDOVIN 1mg; contains 1mg vincristine sulfate; manufacturer TEVA B.V Netherlands);
- ✓ Vinblastine; (VINBLASTINA 1mg; contains 1mg vinblastin sulfate; manufacturer TEVA B.V. Netherlands
- ✓ Visudyne; (VIEDGE 2mg; contains 2mg veterporphyrin; producer Novartis A.G.)
- ✓ Polysulphone (PSf) Type Udel (Aldrich-M = 22000 Yes), used as a basic material for all variants of membranes prepared from solutions of N-methyl pyrrolidone (NMP) (Merck)..

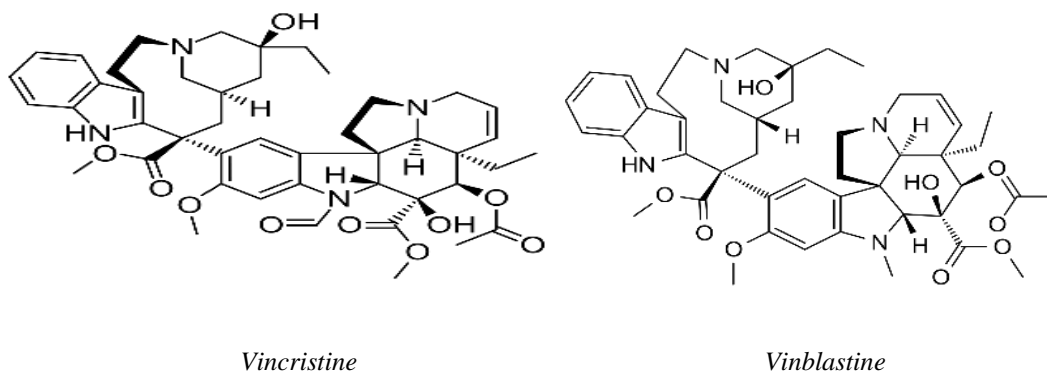


Fig.5 Structures of VB and VC

In the laboratory tests, magnetite samples were prepared, with particles with average diameters of about 10 nm, by chemical coprecipitation from chloride, ferric and ferros solution, and the precipitation agent used was sodium hydroxide.

The method of preparation was as follows: in a flask with three necks of 100 ml, anhydrous ferric chloride (FeCl_3) dissolved in 12.5 ml distilled water and then bubbling argon for 30 minutes. Ferrous chloride was added ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), also under argon atmosphere. In a 500 ml three-necked flask, we dissolved NaOH in 125 ml of distilled water to show concentration $[\text{OH}^-]$. We heated the NaOH solution in the thermostatic water bath until it reached the reaction temperature, then added the drip iron salt solution to the basic solution. Immediately a black precipitate formed. The reaction solution was mixed vigorously for 30 minutes (from the moment the iron salt solution was added). At the end of the 30 minutes, we removed the reaction balloon from the water bath and, using a permanent magnet, separated the magnetite particles from the rest of the solution. After washing with distilled water and then with about 100 ml of 0.01M solution of HCl, for neutralization, the separate particles were filtered and the precipitate dried in the exicator with CaCl_2 . In order to obtain maghemite particles ($\alpha\text{-Fe}_2\text{O}_3$), we continued the process because the reverse spinel structure of magnetite

([Fe³⁺]tetra[Fe³⁺Fe²⁺]octaO₄) is prone to oxidation, so it can be transformed by a process of total oxidation up to α -Fe₂O₃ which has the same structure, but possesses only one third of places with octahedral holidays. Magnetite particles were treated with nitric acid.

Temperature impacts particle morphology. The spherical shape is the desired one because the polyedric forms can create over-tensioned areas in composite structures. Although when the samples were prepared, the particles were dispersed by means of a surfactant and by sonication, they still tend to agglomerate.

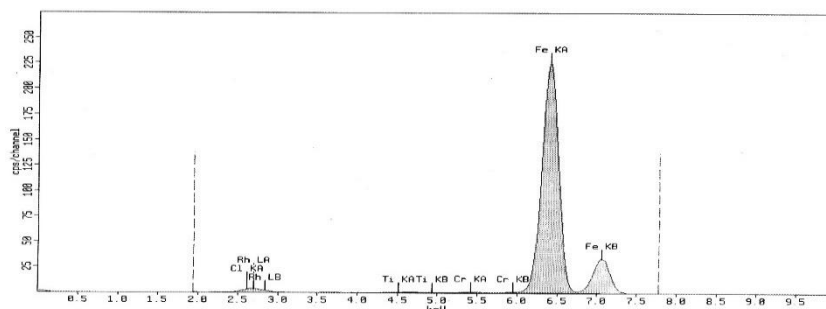


Fig.6 X-ray fluorescence of magnetite

By *X-ray diffraction*, we have demonstrated that the iron oxide particles in the resulting composite are nanocrystalline with mixed phases, being present both α -Fe₂O₃ and Fe₃O₄.

The average size of the magnetite particles Fe₃O₄ was around 35 nm and they showed a tendency to crowd that increased with the temperature of heat treatment, resulting in clusters of particles with average dimensions of up to 100 nm and even up to about 120 nm. When the temperature of the heat treatment increased above 350 °C, the reverse oxidation reaction of the magnetite occurred, with the reformation of the phase α -Fe₂O₃ or α -Fe₂O₃. The presence of the phases α -Fe₂O₃ and Fe₃O₄ determined the magnetic behavior of the powders obtained.

For the preparation of the membranes used to make this thesis, it was used:

- ✓ polysulphone – polysulphonic resin (PSf), pellets, nominal M.W. 75000; density: 1.24 g/cm³;
- ✓ 1-Methyl-2-pyrrolidone (N-methylpyrrolidone-NMP): C₅H₉NO –Merck (NMP); content: 99%; molecular mass: 99.13 g/mol; density at 20 °C: 1.03 g/ml; water solubility: 1000 g/l at 25 °C; boiling temperature: 202 °C.

Preparation of polysulphone solution. The required amount of solvent is inserted into an Erlenmeyer glass and under magnetic shaking gradually add the purified polymer until the desired concentration is reached. (15% polysulphone in mixture of NMP:aniline solvents = 95:5). If reprecipitated and dry polymer is used, the polymer solution is obtained in about 4h. Before the solution is used, it is de-released into a vacuumed exicatorator for 30 minutes.

Dispersal of nanospecies. The dispersion of magnetic particles, which were prepared by a variant of the Massart method, in the polymeric solution of casting PSf /NMP-A in concentration of 10% polymer face is carried out by ultrasonic, for 4 hours in the Branson 1510 ultrasonic bath. In fine, a dark brown dispersion with a concentration of 2-5% nanoparticles is obtained in the polymeric solution.

Membrane formation. . Take about 5ml of the prepared solution and place on a spectral glass holder. With the help of a chromatographic crayfish, the solution is spread to a standard thickness of 250 μm . The film thus deposited on the glass holder is then immersed in a coagulation bath. (distilled water and iso-propanol, 50%), specially prepared. The membrane was made within 15 min. The appearance of the membranes is shown in Figure 7.

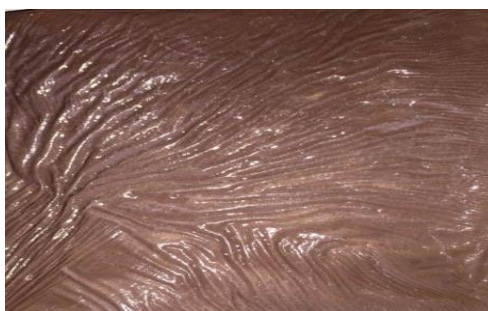


Fig.7 NMP-magnetite polysulphone composite membranes

In laboratory experiments, composite membranes from the polysulphone disperssystem – magnetic nanoparticles / NMP / isopropanol were synthesized.

The solution of the composite membrane was obtained after the addition of 0.87 g of nanocomposite material into a solution of 20% Psf in DMF (80ml) in the autoclave of the colloidal mill (Retsch PM 100) equipped with a quantum grinding device, with a diameter of 1 mm

To obtain the composite membrane solution, 0.87g of dispersed nano composite material was added to a 20% Psf solution in DMF (80ml) in the autoclave of the colloidal mill (Retsch PM 100) equipped with a 1 mm diameter quantum grinding device.

The resulting mixture was mixed for 3 hours at 300rpm. A small portion of the nano composite membrane solution was deposited on a spectral glass and with the help of a scraper was stretched to a standard thickness of 250 μm .

The nano composite membrane, brown-blackish in color was immersed in the coagulation bath, at a temperature of 25°C. After 30 minutes the membrane was washed with distilled water in order to separate traces of coagulant and solvent.



Fig.8 Experimental drug retention plant



Fig. 9 The appearance of the membrane before the passage of medicines (without magnetite (left) and with magnetite (right))

The separation of molecules by membranes and membrenary processes is mainly aimed at preventing pollution of the environment with dangerous substances, such as medicines, but also their separation and recovery before their discharge into waters. It also aims to improve the technologies currently used with less polluting technologies.

The use of magnetic nanoparticles (MNP), and especially magnetite (Fe_3O_4), is an important and interesting technological alternative in the field of separations. Magnetite is widely used in chemical analyses by taking into account its main advantages:

1. the synthesis is simple, cheap and runs with high efficiency;
2. has a high sorption capacity due to the large area;
3. toxicity is low and has strong magnetic properties;
4. these particles are superparamagnetic and provide rapid extraction and easy separation from the sample treated by the use of an external magnetic field;
5. is biocompatible and easy to modify.

The irradiation experiment was performed in a reaction vessel using a polychromatic lamp with medium pressure Hg. Samples of 2 ml of the drug solution were collected at different irradiation times (from 1 to 45 min) in the cube of the cube and then the entire contents of each vat were analyzed. In addition to the permanent decrease of THE NB absorbents, new compounds appear, detellable by UV-Vis and FTIR.



Fig.10 Experimental irradiation plant

Different membrane filters (PSF) were tested in this paper. Responses obtained for cytostatic compounds from the analysis of these samples were then compared with those obtained from the analysis of the same water samples with the tip of the compounds at the same concentration level, but after the filtration stage. Prior to analysis, all samples were diluted 1: 1 (v/v) with HPLC purity water to reduce the effects of the potential matrix. The results on the retention of target cytostatics showed differences depending on the filter material and matrix and no difference depending on the size of the pores, cellulose being the most recommended filter for these compounds.

In order to accelerate and make the degradation of these medicines from waste water discharges more efficient, photosensitized processes can also be used to which these drug solutions are subjected, by using porphyrin sensitizers.

Visudyne, the drug containing verteporfin active substance, is a derivative of benzoporphirin, recognized as a drug on the pharmaceutical market (approved), with the action of a photosensitizer agent in photodynamic therapy. Since this medicine is extremely photosensitive, it is necessary to separate the photodegraded forms of this medicine, and in this paper we aim to address a new method of separating them by using polysulphone-N-methylpyrrolidone composite membrane membrane (PSf-NMP) polymer membranes. The results provided by various spectral techniques (UV-Vis absorption spectrophotometry, optical microscopy) on these ionized forms of Visudyn and the separation of ionized forms by passing over polysulphone membranes (Psf) with N-methyl-pyrrolidone (NMP) and magnetite are presented.

Verteporfin is the active substance of the drug Visudyn (basic porphyrinic form of the drug), approved and in use in ophthalmological tumor disorders and forms.

Verteporfin (Visudyne, BPD) (Vys) is a derivative of benzoporphirin. The chemical structure is shown in fig.11. The molecular formula of this compound is $C_{41}H_{42}N_4O_8$, and the molecular mass is 718.8.

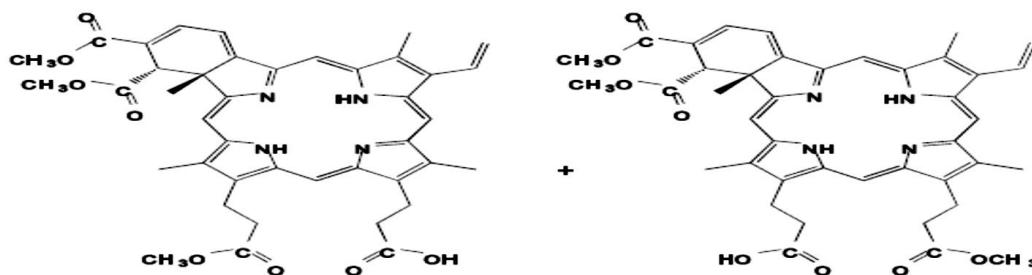
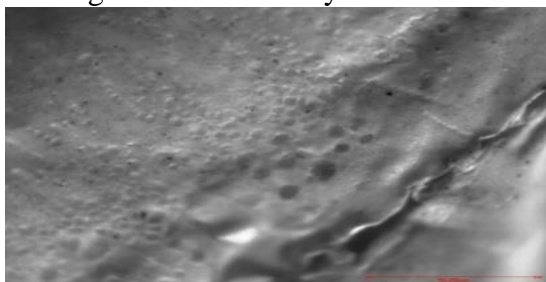
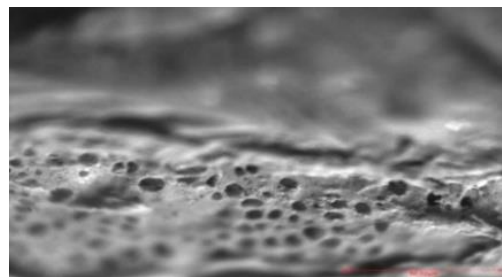


Fig.11 Structure of the isomer forms of Verteporfin (1:1)

Analyzed by optical microscopy, the membranes are different in porosity and integrity and after passing the photodegradation products of Visudyne (fig.12), the pores become larger and not evenly distributed. Basically, the membranes look like a sieve with a large number of pores and very fragile, easy to break, which can be explained by the acidic structure of the final photodegraded forms of Vys.



Before crossing Vys photodegraded



After passing Vys

Fig.12 Optical microscopy of the membrane, before (left) and after passage (right) Vys photodegraded

The most important advantages of using PMR with suspended photocatalyst are represented by:

- Easy advanced separation of catalyst particles from the treated solution;
- Possibility of recovering the photocatalyst and reusing this in future treatment cycles with the corresponding reduction of operating costs by decreasing the consumption of fresh TiO_2 and implicitly the storage spaces of the spent photocatalyst;
- Decrease in water treatment costs in particular due to decreased energy consumption (no further coagulation – flocculation – sedimentation) and space needs are required.

In this case, the membrane is subjected to direct irradiation with light and is exposed to oxidizing agents produced by photocatalytic reaction. The proposed technological flow is based on the application of a heterogeneous photocatalysis hybrid process – membrane process

(membrane photocatalytic reactor – PMR with suspended photocatalyst) and is composed of two main stages:

- Heterogeneous photocatalysis under the following conditions:
 - pH=6,5;
 - $[\text{TiO}_2]= 200 \text{ mg/L}$ (cycle 1), adaus of TiO_2 for cycles 2-5;
 - $t = 90 \text{ min}$;
- Separation and then reuse of the photocatalyst by ultrafiltration using a 12% polysulphone polymer membrane under the following conditions:
 - Pressure = 2 bar;
 - Concentration ratio = 1/2.

Applying the proposed flow ensures the removal of TCS (>93%) and reducing consumption of fresh photocatalyst (52%).

Compared to photocatalytic reactors for which TiO_2 consumption is $80 \text{ mg} \times 5 \text{ cycles} = 400 \text{ mg/treatment sequence}$, the use of PMR results in a reduction of $192 \text{ mg/treatment sequence}$ (five cycles) which represents a 52% reduction in photocatalyst consumption compared to classical photocatalytic reactors.

The configuration chosen was that of photocatalytic membrane reactor with suspended catalyst having the following advantages compared to photocatalytic membranary reactors with photocatalyst immobilized on / in the membrane:

- Possibility of reuse of the photocatalyst compared to the classical processes of heterogeneous photocatalysis. Reduced photocatalyst consumption by 52%;
- The decrease in treatment costs mainly due to the reduction in the consumption of Fresh TiO_2 but also the decrease in energy consumption due to the fact that no further steps of photocatalyst separation are needed.

The proposed treatment flow consists of two main stages: a first stage of heterogeneous photocatalysis followed by the separation of the photocatalyst using a polymer membrane and its reuse in the next treatment cycle together with the addition of a fresh photocatalyst.

Studies have shown that this treatment cycle can be repeated five times without the removal of oncological drugs from the system falling below 93%. Degradation efficiencies ranged from 99.72% (cycle 1) to 93.52% (cycle 5). The fact that degradation efficiencies are for all higher treatment cycles after passing through the membrane module compared to the output from heterogeneous photocatalysis demonstrates that the membrane plays a double role in both photocatalyst separation and pollutant removal.

As regards membrane flows in the process of photocatalyst separation they fall within the specific range of ultrafiltering, decreasing by 25% from the maximum flow in the 5th separation cycle. Membrane clogging was calculated on the basis of average flows of distilled water before and after the passage of photocatalyst suspensions through the membrane, resulting in a degree of clogging of 16.2%.

In conclusion, it can be said that laboratory tests on real aqueous systems have confirmed that the use of membranary photocatalytic reactors is a promising alternative for the treatment of waste water containing organic pollutants.

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Abbreviations used in the drafting of the thesis

<i>Vb</i>	<i>Vinblastine</i>
<i>Vc</i>	<i>Vincristine</i>
<i>Sheep</i>	<i>Reverse osmosis</i>
<i>Md</i>	<i>Average concentration</i>
<i>Mbr</i>	<i>Membrane bioreactor</i>
<i>THM</i>	<i>Trihalomethanes</i>
<i>BOD₅</i>	<i>Biochemical oxygen consumption at five days</i>
<i>Code</i>	<i>Chemical oxygen consumption</i>
<i>Hc</i>	<i>Compact Hexagonal</i>
<i>Cc</i>	<i>Compact cubic</i>
<i>Eop</i>	<i>Enhanced Oxidation Process</i>
<i>Aop</i>	<i>Advanced Oxidation Process</i>
<i>Uv</i>	<i>Ultraviolet</i>
<i>UV-Viz</i>	<i>Ultraviolet — Visible</i>
<i>Ms</i>	<i>Dynamic Light Scattering</i>
<i>Pcs</i>	<i>Photon Correlation Spectroscopy</i>
<i>Sls</i>	<i>Static Light Scattering</i>
<i>Psf</i>	<i>Polysulfone</i>
<i>NMP</i>	<i>N-methylpyrrolidone</i>
<i>FTIR</i>	<i>Fourier transformed IR spectrometry</i>
<i>Afm</i>	<i>Atomic Force Microscope</i>
<i>Sem</i>	<i>Scanning electron microscopy</i>
<i>Edx</i>	<i>Energy dispersion X-ray spectroscopy</i>
<i>Cf</i>	<i>Cyclophosphamide</i>
<i>IF</i>	<i>Isophosphamide</i>
<i>SMPR</i>	<i>Photoreactor with separate membrane</i>
<i>IMPR</i>	<i>Photoreactor with integrated membrane</i>
<i>HPD</i>	<i>hematoporphyrin</i>
<i>Dhe</i>	<i>dihematoporphyrin ether</i>
<i>CiAl-TSPc</i>	<i>aluminum sulfonated phthalocyanine</i>
<i>BPD-MA</i>	<i>benzoporphyrin monoacid derivative</i>
<i>Ptd</i>	<i>Photodynamic therapy of cancer</i>
<i>Pnm</i>	<i>Photo-nano medicine</i>
<i>Vys</i>	<i>Vysudine BPD</i>

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