Selecting medical grade polymers and testing for achieving antibacterial devices tubular prosthetic

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A range of polymers are used for the construction of catheters, including silicone rubber, latex, and thermoplastic elastomers. Polyvinyl chloride is one of the most common choices because it is a material which can assure biocompatibility and mechanical properties necessary for use in medical devices. The device industry has been challenged to produce polymeric biomaterials with built in antimicrobial surface properties that are easily processing and have long term efficacy without leachable. It is intended to obtain plasticized PVC tubing with antimicrobial properties, by a durable, non-leachable antimicrobial treatment that helps inhibit the growth of bacteria to help prolong product life. This paper presents the criteria for selecting of biocompatible materials and some mechanical properties of plastic materials used in the manufacture of medical devices.

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1. Introduction

The healthcare industry continues to evolve, and require technological advances in the field of plastic medical devices and equipment to meet today's healthcare providers and end users (patients) and also to reduce the total cost of care. Most of the using of plastic medical devices is the tubing, such as wells, drains, catheters.

Catheters are tubular medical devices that are designed to eliminate biological fluids from human body or administer a drug. Although medical devices are supplied in packs clean, vacuum and sterilized, after implantation proteins and salts in biological environment are adsorbed on the surface of the catheter, and they forms a layer that adheres planktonic bacteria free circulation. Adsorption is influenced by the hydrophilic character of the surface, roughness, porosity, chemical composition, protein concentration, salts and pH of the biological environment [1 - 5].

Intravascular and urinary catheters are commonly used in hospitals. Numerous studies have shown that the number of infections depends on local conditions, methods of implantation of tubular devices and duration of use. Catheter-associated infections are a source of nosocomial morbidity and mortality [6, 7]. The mechanism by which infection develops is not known, but the phenomenon of bacterial adhesion to the substrate is a critical factor in initiating colonization and subsequent infection. The composition of different biomaterials tubing, include additives and plasticizers that improve their physicochemical properties and biocompatibility. Adhesion of different microorganisms on surfaces and their survival depends on interactions with biomaterial surface of catheters. Some organisms such as coagulase-negative staphylococci may metabolize certain components of plastic catheters in the absence of nutrients and can use them to support growth on the surface of biomaterials [8]. Microbial infection on the surfaces of medical devices is carried out in a phased manner, specific to the plastics used.

Some biomaterials such as for example polyvinyl chloride (PVC) contain many additives, which determine the properties of flexibility so necessary in using catheters. But these additives can be eluted from the catheter in the human or animal body and can be used by microorganisms. These findings require more detailed characterization under clinical investigation in vitro and to define the mechanisms involved in the pathogenesis of infections related to the use of catheters and prosthetic socket, and to design new devices with enhanced features that prevent bacterial adhesion and colonization.

Chemical characteristics are important in initial colonization of a population of microorganisms on the surface, the free migration of pathogens [9]. Hydrophilic surfaces are populated more easily than hydrophobic. Although most organisms have surface charge (gram-positive and gram-negative), they also contain hydrophobic characteristics and may be involved in adhesion to the hydrophobic substrates of medical devices. In reality, however, almost always microbial biofilm depends on adherence of microorganisms forming the surface layer protein, which exhibit special bonding affinity for some places. Proteins that are present in the patient's tissues are rapidly adsorbed after implantation. Therefore, when designing antimicrobial surface, an

important parameter to be considered is the surface adhesion of proteins [10].

There are few methods to prevent biofilm formation. Surface modification of plastic medical devices can be an effective strategy for combating infection. Topological and chemical characteristics of surfaces of medical devices have an important influence on adherence of microorganisms. A perfect surface polished comparative to a rough surface will be unsuitable for habitation by microorganisms as rough surface provides more space and microorganisms can generate a higher adhesive force per area. Inhibition of initial bacterial colonization on the surface is a matter of prime importance in biomaterials science. This can prevent many infections of tubing and biofilm formation.

Bacterial infection coming from long lasting use of medical devices is a major problem which can cause high medical costs, and even leading to death. One way to prevent infection is the incorporation of antimicrobial agents into the bulk material or as a surface coating is considered a viable alternative to systemic administration of antibiotics to the patient. Antimicrobial agents are designed to obtain non-vegetative materials, in order to impede the protein adsorption and subsequently the microbial adhesion.

Manufacture of plastics antimicrobial medical devices allows manufacturers to create new products active against bacteria biocompatible surfaces that help reduce the risk of infection. Hospitals and doctors increasingly prescribe more antimicrobials using plastic devices for patient.

Lately, it has resorted to the application of silver nanoparticles on the surface of medical devices to prevent sticking bacteria and subsequent biofilm formation. Nanoparticles are either stored directly on the device or used in a surface coating polymer. Silver is released slowly from the surface, thus destroying bacteria present near the surface. In the last decade numerous studies have been conducted that demonstrating the character antimicrobial of silver nanoparticles that can be applied to a wide range of different medical devices. Ions and silver salts have a low toxic effect in vivo. Catheters coatings containing silver nanoparticles could be a real option to reduce the rate of infection and the risk of thrombosis.

The use of tubular prosthetic devices with silver coatings may prove to be a real advantage for hospitals, leading to decrease the number of infections related to medical devices. Nature of silver particles and how they are incorporated in the coating will determine the effectiveness of such modified medical devices [11].

This paper present the preparation of a medical recipe based on plasticized poly(vinyl chloride) (PVC) and material characterization in terms of physicochemical properties, mechanical, biocompatibility and analysis by spectrometric methods, to treat with antimicrobial silver ions as additives for limiting or even preventing biofilm formation on urinary catheters surfaces.

2. Experimental part

2.1. Material and methods

Selecting polymers for medical devices depend on the time of contact with biological fluids and tissues internal or external. Polymers suited for medical devices must meet the requirements for design, processing and operational performance. Requirements specific to medical devices involves: biocompatibility, absence or limitation loss of plasticizers together with the unreacted monomers, impurities, additives and catalysts trace, barrier properties to oxygen and moisture, optical clarity, ability to connect medical device components, UV stable, chemical stability, biostability, feasibility functional, sterilizability, environmentally friendly, storage under normal conditions.

Among the plastic materials used to make medical devices, the most common are rigid and plasticized PVC, polyethylene (PE), polyurethane (PU), silicone rubber, polystyrene (PS), polyamide (nylon), acrylonitrile butadiene styrene (ABS) [12].

About 25% of medical devices are made of plasticized PVC, according to the marketing analysis. The main reason for using PVC is low cost price, and easy processing followed by adaptability to a wide range of applications.

Among the many medical applications of PVC it can enumerate: blood collection bags, tubing (drains and catheters), dialysis equipment, face masks, oxygen administration equipment, laboratory equipment and packaging.

PVC medical grade is compounded together with stabilizers based on barium, zinc and calcium-zinc which protect them at the processing temperatures, the temperature of the autoclaving and ambient temperatures during storage.

PVC medical devices can be sterilized by autoclaving, ethylene oxide or gamma irradiation. Although plasticized PVC can present T_g less than 40^{o}C though it can be sterilized by autoclaving at 121^{o}C.

PVC medical products have passed the toxicological tests, biological and physiological. In short, PVC is a material that can be used in medical devices due to reduced cost and operating properties [13].

To achieve medical devices urinary catheters it was proposed to prepare a biomedical recipe based on plasticized PVC. It were selected the following materials: medical grade PVC S 170,100 and compounding additives such as plasticizers, stabilizers, lubricants, as shown in Table 1.

Table 1. The recipe used to produce plasticized PVC granules.

Components	**Parts by weight, p**
PVC S70	72 p
Di -2-ethyl- hexyl- phtalate (DOF)	25 p
Stabilizer (Baerostab 170)	1 p
soybean oil epoxidized (LSA)	2 p

Raw material characterization is presented in the following tables.

Table 2. Characteristics of PVC S 170100 provided from EST CARDINAL SRL.

Characteristics	Analysis method	Results
Appearance, color, aqueous extract	EUROPEAN PHARMACOPOEIA, edition 6	Clear, transparent liquid
Reducing substances, ml $Na_2S_2O_3$ 0,01M	EUROPEAN PHARMACOPOEIA, edition 6	0,41
Value K-WERT	SR EN ISO 1628- 1, 2/2003	70,36
Moisture and volatile substances, %	ASTM D 3030/2000	0,052
Residue on sieve of 0,250mm, %	SR EN ISO 4610/2003	0,2
Residue on sieve of 0,063mm, %	SR EN ISO 4610/2003	97,1
Waste from calcinations at T= 850^0 C	SR EN ISO 3451- 5/2003	0,0075

Table 3. Characteristics of DOP provided from S.C. PRODPLAST S.A.

Characteristics	Analysis method	Results
Aspect	Visually	Colorless, opaque liquid
Density, g/cm^3	STAS 35:1981	0,982
Refractive index	SR 7573:1995	1,484
Oxidizable materials	ST 51/2007 (pt 4.7)	0,07

Table 4. Characteristics of LSA provided from S.C. PRODPLAST S.A.

Characteristics	Analysis method	Results
Aspect	STAS 12335-1985, Pt. 4.2	Oily liquid, clear, slightly opalescent
Density, g/cm^3	STAS 12335-1985, Pt. 4.4	0,990
Acidity index, mg KOH/g	STAS 12335-1985, Pt. 4.5	1,2
Iodine index, g/100 g	STAS 12335-1985, Pt. 4.6	9
Epoxy groups, %	STAS 12335-1985, Pt. 4.7	14
Volatiles, %	STAS 12335-1985, Pt. 4.8	0,5
Flammability point, ^{0}C	STAS 12335-1985, Pt. 4.9	240

Table 5. Characteristics of stabilizer type Baerostab 170 V provided from S.C. PRODPLAST S.A.

Characteristics	Analysis method	Results
Aspect	Visually	Emulsion paste with fatty and milky aspect
Colour	Visually	White- mate
Odor	Organoleptic	Weak odour

Preparation of recipe.

Machines on it were obtained PVC granules were:
- dry blend mixer of 5 l capacity;
- granulator KO-46 from PR BUSS BUSS AG company, Bassel SCHWEIZ, with 2 extruders.

a) ko-kneter (transport)
b) granulating extruder - ASV 46

On leaving the granulator, the granules are pneumatically transported and taken from a cyclone, that provides cooling granules and prevent sticking together.

Temperatures scheduled areas (° C) to obtain pellets of plasticized PVC in extruder ASV 46, were:
- zone I 105 ^{0}C
- zone II 135 ^{0}C
- zone III 145 ^{0}C

Preparation of samples for laboratory analysis

For testing physical and mechanical properties of plasticized PVC recipe it have performed two types of samples, namely:

Smooth films obtained by deposition on a substrate of plasticized PVC in cyclohexanone solution. In order to achieve smooth films it used equipment with magnetic stirrer called AREC. Plasticized PVC granules were dissolved in cyclohexanone by stirring at a temperature of 100^{o}C, speed 600 rpm for 5 h. The resulting solution was cast on glass substrate. After drying it were obtained thin films with thickness up 0.1 mm (Fig. 1).

Flat plates, obtained by pressing plasticized PVC granules (Fig. 2), using press Brabender Polystat T 200.

Fig. 1. Film from PVC plastified.

Fig. 2. Plate from PVC plastified.

Plasticized PVC granules were pressed in the press Brabender laboratory under processing conditions provided in Table 2.

Table 6. Pressing parameters.

Pressing emperature (^{0}C)	Pressing time (minutes)	Pressure (barr)
160	15	250

It were obtained plates with thickness of 1 mm, from which the specimens standardized were punched for testing in terms of physical and mechanical properties and surface roughness of the material by determining the contact angle.

Characterization of recipe samples

Mechanical properties. Determination of tensile strength and elongation at break were performed on the machine FP 10/1.

Measurements to determine the contact angle between the surface and water plasticized PVC plate were performed at room temperature droplet method ("Sessile drop method") at 20°C within 30 seconds after placing liquid drops of 5 μ L plate surface. This time is long enough that the contact angle of the droplet to reach equilibrium value and short enough to evaporation losses are negligible.

It was measured the base diameter (d) and drop height (h) using a cathetometer with a magnifying power of 20X. Contact angle was determined by the relationship:

$$tg\frac{\theta}{2}=\frac{2h}{d} \quad (1)$$

Depending on the angle of contact the following situations are possible:

a) $\theta = 180^0$, $\cos\theta = -1$, that means the wetting is zero;

b) $\theta = 0^0$, $\cos\theta = 1$, results in a complete array of fluid, i.e. a perfect wetting of the surface;

c) case intermediate: θ > 90^{0}C; corresponds to a poor wetting.

θ < 90^{0}C corresponds to a good wetting, but not total.

It was used the equipment CAM 101 equipped with digital camera C200-HS type KSV Finland to record the drop image.

UV-VIS and DSC spectroscopy. In order to determine the absorbance it was prepared an aqueous extract obtained according to the European Pharmacopoeia Ed 6/2008. Absorbance was detected on equipment Helios Alpha spectrophotometer UV / VIS in the λ = 200-400 nm, using the blank double distilled water, autoclaved under the same conditions as samples analyzed.

To obtain the aqueous extract was used EURONDA E5 autoclave under the following conditions: temperature: 121 ± 20 W and pressure: 1.2 barr.

PVC thermal analysis of samples was performed by METTLER-TOLEDO equipment DSC-823 under the following conditions: temperature range: 25 to 350 ^{0}C, heating rate: 100C/min, standard aluminum crucible with 40 ml pine.

3. Results and discussions

Testing of the mechanical physical and chemical analyses it is of the great interest, since the values offer important information especially about biocompatibility and flexibility so necessary in medical device using. It were performed analyses of the physical and mechanical properties of the granules and plates from the recipe of plasticized PVC.

In Table 7 presents the results obtained from the recipe characterization of plasticized PVC granules.

Table 7. Physico-chemical characterization of plasticized PVC granules.

Characteristics	Results
Aspect, shape, colour	The granules are consistent-looking, cylindrical shape, with no metal or non-metallic impurities
Dimensions (∅×h), mm	3,5×3
Density relative, g/cm^3	1,240
Aspect of aqueous extract	Clear liquid transparent, colorless
Reducing substances, ml $Na_2S_2O_3$ 0,01M	0,15
pH sample- pH witness, T= 20^{0}C pH sample pH witness	0,12 7,70 7,62
Acidity, ml NaOH 0,01 mol/l	0,95
Alcalinity, ml HCl 0,01 mol/l	0,71
The evaporation residue,%	0,007

The results presented in table 7 are in accordance with EUROPEAN PHARMACOPOEIA , ED. 6/2008 [14]. The values show that the recipe does not release harmful substances in the aqueous extract.

In Table 8 are presented the results obtained from physical-mechanical characterization of the recipe of plasticized PVC plates.

Table 8. Physical-mechanical characterization of plasticized PVC plates.

Characteristics	Results
Hardness Shore A, (^{0}Sh A)	88
Tensile strength, daN/cm^2	160
Elongation at break, %	220
Thermal stability at 180^{0}C, minutes	35

Mechanical properties of the experimental recipe are very close to PVC plasticized. The hardness Shore and elongation at break indicate that this material is flexible and appropriate to use in medical devices type tubing that require flexural resistance. The tensile strength value of flexible PVC is up to 150 kg/cm^2, which is low because of presence of plasticizers in the formulation [15].

The plasticizer forms links with polymer molecules and acts as spacer between molecules of the polymer. Due to this linkage plasticizer has great effects on the mechanical properties of the polymer [16].

The value of contact angle for surface plasticized PVC recipe, is shown in Table 5.

Table 5. Contact angle.

Code recipe	Contact angle, ^{0}
PVC plastified	86,68

It is noted that the value of contact angle value is relatively low, which indicates that the recipe of PVC plasticized is of hydrophobic nature.

The results obtained from spectrometric analyzes are presented in the following figures.

According to the European Pharmacopoeia in the case of medical devices made from PVC, the absorbance in the domain of λ = 220-360 nm should be less than 0.3%. As shown in Fig. 3, for plasticized PVC sample, the absorbance is 0.275% that it is in accordance with the European Pharmacopoeia requirements for the use of PVC in the medical field.

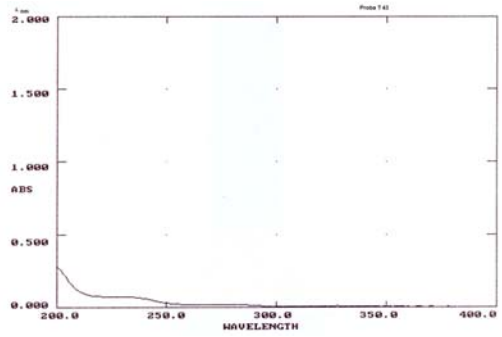

Fig. 3. Absorbance of PVC plastified sample.

The analysis of Fig. 4 show that in the variation in temperature from 300 to 350^{o}C for plasticized PVC sample, it shows exothermic peaks, which indicates that the polymer shows no changes in the morphology of the surface material.

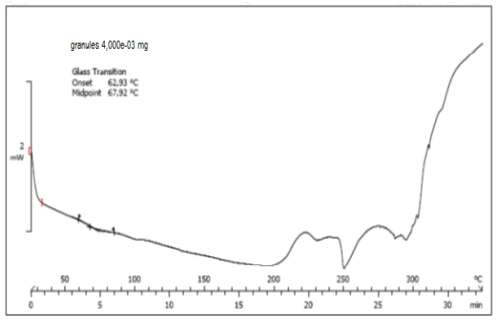

Fig. 4. The thermogram DSC for PVC plastified.

5. Conclusions

Polymeric materials play an important role in medical therapy and device quality. They provide safety and efficiency, design flexibility, easy processability and sterilization capacity. For a good selection of materials at specific medical need to take into account functional requirements, design, manufacturing and performance. Due to the material composition and surface imperfections at medical device in contact with the body for a longer period may occur catheter adhesion phenomena of microorganisms and biological environment and salts of infections due to biofilm formation. Since the most effective way to control this infection is to prevent intractable bacterial adhesion and subsequent biofilm formation on the catheter, the catheter material importance and coverage antibacterial substances can not be underestimated.

The strategy of selecting a suitable material for medical devices must take into account functional requirements on product design, processing and performance. The material selected must be compatible with one of the methods of sterilization: autoclaving, ethylene oxide or irradiation.

From the polymeric materials used to produce medical devices, PVC prominently because of its physical, sterilization and biocompatibility. This material meets the requirements regarding functionality, integrity, processability and low cost price.

The paper presented the raw materials and method of obtaining recipe of plasticized PVC granules, whose physico-mechanical, chemical and biocompatibility properties meet the requirements for use in the manufacture of medical devices tubing type catheter.

The results obtained from physico-chemical and mechanical testing shows that the experimental material meets the requirements of the European Pharmacopoeia, and can be used in the manufacture of tubular prosthetic medical devices, and to prevent biofilm formation on the

inside surface can be used for subsequent embedding type antibacterial agents such as silver ions.

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