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POLYVINYLPYRROLIDONE-POLYURETHANE INTERPOLYMER HYDROGEL COATING AS A LOCAL DRUG DELIVERY SYSTEM

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Hydrogels are continuous hydrophilic three-dimensional polymeric networks able to swell large amounts of water or aqueous fluid, without dissolution (1, 2). They are extensively exploited in the field of biomedical applications, since the middle of the twentieth century, when the first synthetic hydrogel poly(2-hydroxyethyl methacrylate) (PHEMA), a material for contact lenses, was reported (3). Then introduced were biological adhesives, soft tissue replacements, wound healing supports, membranes of the drug releasing systems, sophisticated self-assembling "smart" polymers and the most widely used: lubricious coatings for less invasive devices, having the best cost to effect ratio.

Hydrogel coating as a method for solid substrate surface modification, beside advantages like improving material biocompatibility (4), hydrophilization and lubrication (5), brings the additional possibility of the active agent incorporation during the coating process (6, 7).

Thus hydrogel modified surface have an advantage over unmodified one, while it can serve as a drug reservoir for a local drug delivery (8). There are cases when drug dosage time should last at least few hours, but no longer than 3 days. It can be desirable in case of implantation of devices like tracheotomy tubes, when anti-inflammatory active substance should be released at the very beginning to prevent later side effects like tracheal stenosis, but later can not interrupt normal cell divisions in subsequent levels of healing process and epithelium formation. In case of hydrophilic matrix with hydrophobic drug these profile can be easy obtained due to its behavior as the swelling controlled drug release system.

EXPERIMENTAL

The method for coating of medical polymeric devices by water insoluble hydrogel, based on interpolymer of polyurethane (PUR) and polyvinylpyrrolidone (PVP), previously proposed by Micklus (5), was modified and developed to avoid involving diisocyanates, monomers or any polymerization promoters that can be harmful and difficult to remove (9). This dip-coating technique briefly consists of one (one solution of precursors; less stabile) or two steps (each precursor of interpolymer in separate bath), when the solid polymeric substrate, poly(vinyl chloride) (PVC) or polysiloxane (silicone), is immersed for 15 to 60 seconds in solution of each polymer (1-3 wt % in organic solvents) and air-dried.

Materials

High molecular weight (MW = 360 000) 1-ethenyl-2-pyrrolidinone homopolymer (polyvinylpyrrolidone K90, PVP) was purchased from Fluka; the term polyurethane (PUR) refers to ESTANE 5715P; 5-chloro-2-(2,4-dichlorophenoxy)phenol (Irgasan DP 300, triclosan) purchased from Brenntag; poly(iminoimidocarbonyl)iminohexamethylene hydrochloride (polyhexamethylene biguanide, PHMB) was a sample gift from Scunder, Shanghai; tested PVC catheters were a gift of the manufacturer (Galmed, Bydgoszcz); phosphate buffered saline (PBS) was the composition of NaCl (0.8 wt%), KCl (0.02 wt%), KH_2PO_4 (0.02 wt%), $Na_2PO_4 \cdot 12H_2O$ (0.023 wt%) and methanol or ethanol (20 vol%) in distilled H_2O; all solvents and inorganic salts were of analytical grade.

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Obtained hydrogel layers were characterized by means of the Fourier Transform Infra-Red Attenuated Total Reflection (FTIR-ATR) spectroscopy (Nicolet 6700; Smart Orbit diamond ATR accessory; Thermo Scientific), static and kinetic friction factor relative to the uncoated backbone material, against porcine tissue counter-face [according to the method described in (9)] and by the water wettability.

In further investigations the antibacterial triclosan (MW = 289,5) as a model hydrophobic drug was incorporated in two modes: as a component of

Table 1. Compositions of tested coatings (weight %) and rates of drug released per g of polymeric device (i.e. catheter): 1 – first layer; 2 – second layer; i – impregnated in 2-propanol (iPA) or distilled water (w); PUR – polyurethane; PVP – polyvinylpyrrolidone; T – triclosan, P – PHMB; IR – immediate release, SR – sustained release.

	NTi	**HTi**	**HT1**	**HT2**	**NPw**	**HPw**
1	-	1% PUR	1% PUR x% T	1% PUR	-	1% PUR
2	-	3% PVP	3% PVP	3% PVP x% T	-	3% PVP
i	iPA x% T	iPA x% T	-	-	w x% P	w x% P
0.5%	SR 0,001 mg/h	IR	IR	IR	IR	IR
1%	SR 0,001 mg/h	IR	IR	IR	IR	IR
3%	SR 0,004 mg/h	SR 0,2 mg/h	IR	SR 0,7 mg/h	IR	IR
5%	SR 0,006 mg/h	SR 0,2 mg/h	IR	SR 0,7 mg/h	IR	IR
7%	SR 0,010 mg/h	SR 0,2 mg/h	IR	IR	IR	IR

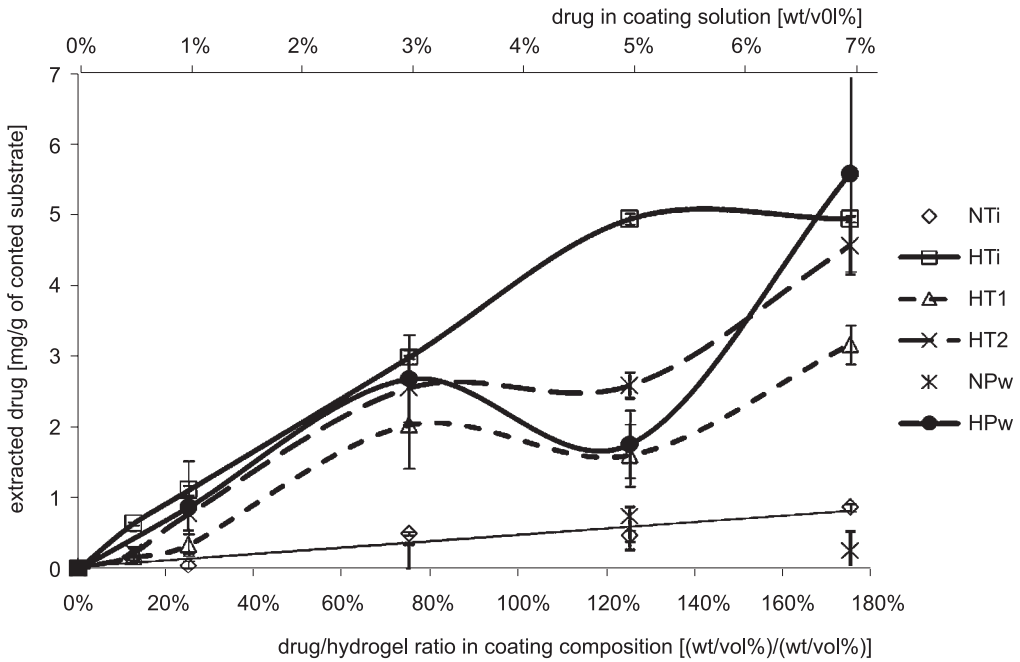

Figure 1. Total amount of loaded drug in dependency on drug concentration and incorporation mode: N – uncoated substrate; H – hydrogel coated substrate; T – triclosan (hydrophobic drug); P – PHMB (hydrophilic drug); i – impregnated with drug in 2-propanol; 1 – drug in first layer solution; 2 – drug in second layer solution; w – impregnated with drug in distilled water.

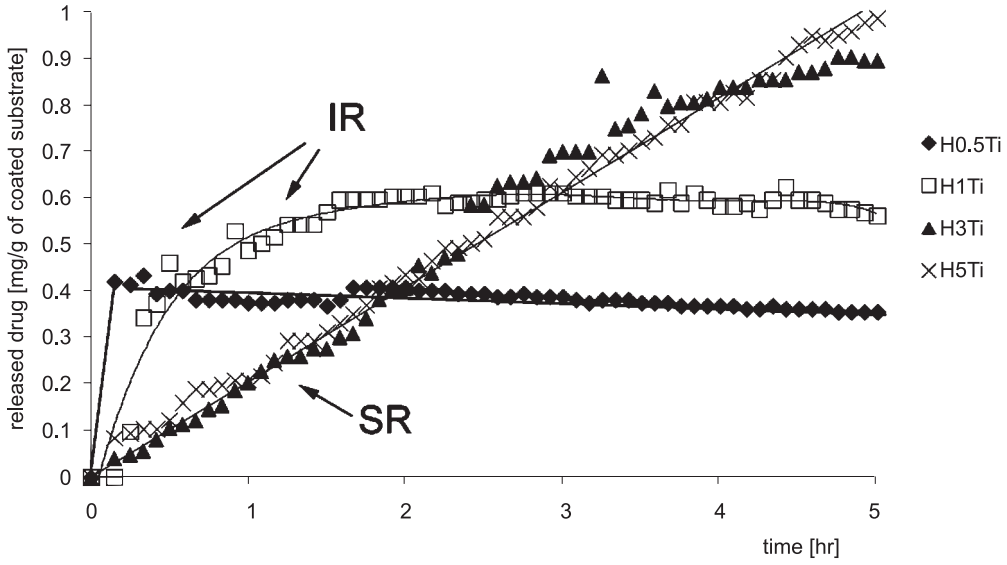

Figure 2. Drug release profiles: immediate release (IR) – H0.5Ti and H1Ti, sustained release (SR) – H3Ti and H5Ti; hydrogel (H) coating (1 wt% PUR, 3 wt% PVP) impregnated with triclosan (0.5, 1, 3 or 5 wt%) (T) in 2-propanol (i).

the solution in any step of the coating formation or through the additional impregnation bath. Hydrophilic active agent, PHMB, was incorporated just in impregnation mode, from water solution. Tested compositions are presented in Table 1. Prepared this way, coated and uncoated samples were compared due to the active substance incorporation capacity, measured as the amount extracted to the methanol or water, or a mass of the total released drug, evaluated to the unit mass of the substrate.

The dissolution tests were carried out in sealed vials to the 3 mL PBS containing 20% low MW aliphatic alcohols (methanol or ethanol to improve solubility of hydrophobic drugs) from sliced catheter samples (2 mm thick; diameter 5 mm; drug released only by outer surface approximately 30 mm^2) and evaluated by UV-Vis spectroscopy (Helios Gamma Thermo Scientific). The measurements were taken every 5 min; all vials were shaken between each scan. The concentrations in mg/L of were evaluated from the subsequent equations:

$$\text{triclosan } c_T = A[283nm]/0.015$$

$$\text{PHMB } c_P = A[270nm]/0.00228$$

RESULTS AND DISCUSSION

IR spectra confirmed the presence of the coating layer. Strong peak around 1650 cm^{-1} indicates the C=O bond of PVP (amide II), not visible in uncoated substrate spectrum; wide band about 3390 cm^{-1} are related to amides, N-H and O-H hydrogen bonds; a presence of PHMB can be identified by a band near 1549 cm^{-1} (NH_2, amide I) and 2172 cm^{-1} (C=N stretch); triclosan at wave number 1593 cm^{-1}. Comparison of the spectra of triclosan powder, hydrogel coating and hydrogel coating with triclosan content shows molecular interactions between hydrogel polymers and the drug (appearance of the new wide band at about 3100 cm^{-1}, with simultaneous decrease of the hydrogel peak at 3410 cm^{-1}).

Wetting angle and tribological tests confirmed changes in surface properties, super-hydrophilicity and enormous lubricity in hydrated state. In wet state observed water wetting angles shifted from about 80 deg for uncoated surface to nearby 0 deg. In case of urethral poly(vinyl chloride) catheters with hydrogel coated inner surface, the capillary action phenomenon was observed (inner diameter 3 mm; capillary elevation in uncoated catheter = 0 mm, hydrogel coated = 5 mm), proving high affinity between coating and water molecules.

Hydrogel coated catheters revealed even 10-fold friction factor reduction, for typical example silicone tube coated in two steps, immersed for 45 s in each step: static friction coefficient equal to 11%, kinetic friction coefficient equal to 13% in comparison to 100% for the uncoated substrate, both measured on the tissue counter-face samples.

Drug extraction experiment confirmed a capacity of the coating to absorption much higher amounts of the drug than uncoated substrate (Fig. 1). The dependence of the total amount of extracted drug on the drug content in the coating or impregnating solution, which can be calculated to the proportion of drug mass to the dry mass of the hydrogel forming polymers, PUR and PVP (both scales at Figure 1), is surprisingly not linear (multiple experiments eliminates the risk of human error), the only exceptions are uncoated substrates impregnated with the drug and hydrogel coated substrates impregnated with hydrophobic triclosan in 2-propanol. In all other cases, namely hydrophobic drug incorporated to the first (with PUR) or second (with PVP) layer of the coating, and hydrophilic drug incorporated to the hydrogel coated substrate in the mode of impregnation from water solution, the function shows a minimum between 100% and 150% of the drug in relation to the hydrogel forming polymers (5 wt/vol % of the drug). This can be due to the irreversible complexing of the drug in hydrogel matrix at this special proportion of hydrogel composition PUR : PVP : drug 1 : 3 : 5, when the drug became a part of the hydrogel matrix and cannot be extracted or, oppositely, molecular interactions in the coating and impregnating solutions prevent incorporation of the drug to the coating layer.

The results obtained from dissolution tests are presented in Table 1, according to the composition of each tested sample. Generally, they can be differenced due to the mode of drug release: IR – immediate release and SR – sustained release with zero order kinetics; examples of such release profiles are presented in Figure 2. As it can be seen in Table 1 with results, the mode and rate of drug release are dependent on the drug properties (hydrophobic or hydrophilic), concentration in process solution and the mode of incorporation. Thus we can obtain a rapid release of high dose or controlled dosage, when needed.

CONCLUSION

Hydrogel coating on the polymeric substrate has the ability to absorb and complex much higher amount of the drug than uncoated device. The drug will start release in the presence of body liquids in two possible modes: immediately, during first 15 min to 1 h after implantation (useful in local sterilization and anesthesia), or with constant rate, dependent on the coating process parameters.

Combination of the hydrophilic matrix and the hydrophobic drug seems to be especially promising. During hydrogel swelling an interesting "spraying effect" can be observed, when solid microparticles of the solubilized drug are precipitaded out of the coating layer to the surrounding solution. This phenomenon can be utilized in design of drug release systems, reacting on water content increase as the start signal.

Moreover, the impregnation mode allows for modification of devices like silicone catheters or polyglycolic acid resorbable sutures without polymeric coating step, in cases where polymer backbone is a good solvent for incorporated active substance [like a silicone for triclosan (10)] or has a complexing capacity.

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