Ecole Doctorale des Sciences Fondamentales

Title of the thesis: Fluorination of PVC-made medical devices to prevent plasticizers migration into the human body

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Summary :

Polyvinyl chloride (PVC) is widely used in medical devices (MDs), especially in infusion tubing and extracorporeal circulation lines (eg dialysis). A high content (up to 40% by weight) of plasticizers (TOTM, DEHT, DINCH, DINP) is added to PVC in order to improve its flexibility. However, these compounds migrate from the MDs to infused solutions or blood and thus come into contact with the patient. To date, migration studies have shown that any plasticizer commonly integrated into MDs migrates in varying amounts depending on its chemical nature. This exposes the patient to a toxic risk which varies according to the nature of the plasticizer and the quantity released, as none of these chemical compounds has demonstrated complete safety. Some are cytotoxic, in particular after metabolism (hydrolysis upon contact with blood) and / or exhibit endocrine disrupting effects. The MPS team has demonstrated the migration of plasticizers from infusion MDs or extracorporeal circulation lines and shown the exposure of patients in intensive care and cardiac surgery units. Hence, metabolites of all plasticizers present in MDs were found in the urine of patients at concentrations sometimes exceeding acceptable limits (data being published).

Therefore, it is necessary to find solutions for limiting and / or preventing the migration of plasticizers from PVC tubings. The proposed solutions must allow a barrier effect to the release of plasticizers while preserving the isofunctionality of the MD, its biocompatibility and the absence of interactions with drugs in the context of infusions. To date, none of the tested solutions meets all of these objectives. The coextrusion of PVC with an internal polyethylene layer does not constitute an effective barrier against the migration of plasticizers. The functionalization of the PVC surface by physical processes such as plasma or UV irradiation allows only partial limitation of migration. A surface treatment by gaseous fluorine seems to advantageously offer PVC the necessary barrier properties to plasticizers. The

reaction of a great majority of the most common polymers, including PVC, with molecular fluorine F_2 is spontaneous at room temperature. As a heterogeneous gas/solid process, it requires no solvent and allows the processing of parts of any shape. Furthermore, no interface is created with the risk of a loss of adhesion, unlike when a film is deposited on the polymer. Indeed, fluorination modifies the material at the surface level only, creating a continuum. Stable covalent C-F bonds are formed, resulting in a long lasting and irreversible treatment. Only the outer thickness (0.01 to 10 μm depth) of the polymer thus treated is chemically modified while its bulk properties remain unchanged. The fluorination of polymers or membranes has already proved efficient in blocking the diffusion of small molecules (O_2, CO_2). The permeability toward large dimension polyatomic molecules is even more decreased than that of small ones. The fluorination treatment notably allowed the selective separation of H_2/CH_4 and He/CH_4 gas mixtures.

The new MPS team at ICCF will bring its experience on plasticizers migration in real clinical situation to the project. The team has developed *ex vivo* models to assess the latter phenomenon during drug infusion, dialysis and other extracorporeal circulation modes, such as ECMO. These models can now be used to test fluorinated PVC-made MDs. The MPS team is also able to assess the biological risks of the new materials to be tested (biocompatibility studies according to the applications of the MD).
The F_2 group of the Inorganic Materials team at ICCF has a recognized experience in the synthesis and characterization of fluorinated materials. This group has developed a gas/solid fluorination experimental set up, unique in France. Indeed, reactors from 1 to 50 L in volume make possible the fluorination of large dimension parts of any shape, including tubes and pipes of variable diameters. The team's know-how in terms of risk management and evolution of the treatment conditions (F_2/N_2 dilution rate, static or dynamic fluorination modes, control of the fluorine addition level, use of catalytic conditions… etc.) and its high performance instrumentation dedicated to the characterization of fluorinated interfaces (XPS, solid state NMR, IR spectroscopy …) are serious assets in the success of the project.