Activity report

Name of the project: TRANSDERAL PATCH DEVELOPED BY LASER BASED METHODS FOR HYPERTENSIVE HEART DISEASE

First phase: Intermediary phase I/2011 having the objective „Material selection: polymers which shall be laser processed".

Amount awarded from the national budget: 106250 lei.

Introduction:

Mortality due to cardiac diseases dramatically increases with age. The deaths due to heart conditions which appear before the age of 65 are, in general, considered premature and, therefore are of great importance to the area of public health. Arterial hypertension is one of the main causes of heart diseases, and in the last years the mortality rate due to this condition has increased. [D.L. Hoyert *et al.*, Natl. Vital Stat. Rep. **53** 1–48 (2005); J. H. Zhao *et al.* International Journal of Pharmaceutics **337:1-2**, 88-101 (2005)]

Transdermal patches are adhesive patches which contain drugs, and are applied to the skin with the purpose of delivering in a controlled manner the drug for the systemic treatment of the disease. This transdermal therapeutic system is available in pharmacies since 1980. This method of drug administration offers numerous advantages, such as a controlled release of drugs, allows maintaining a balance at the blood level, leading to reduced side effects, and in certain situations to an improved efficacy compared to other dosage forms.

Therefore, the transdermal system has a particular clinical significance for the prevention and prolonged treatment of chronic diseases such as arterial hypertension.

In the particular case of transdermal controlled drug release systems, the main action route is precisely through the controlled release of the drugs from structures with special and controlled properties. Therefore the selection of materials and techniques for the fabrication of controlled drug release systems is very important.

Discussion

In this phase of the project a bibliographic study aiming to the choice of the polymers which are to be deposited as thin films by MAPLE (Matrix Assisted Pulsed Laser Evaporation) and which will include the drug, has been carried out.

The main challenge for the successful fabrication of efficient drug release transdermal systems is the design of the polymer matrix with the following characteristics:

- Biocompatibility;
- Chemical compatibility with the drug to be released;
- To offer an efficient and coherent release of the drug during the product lifetime;
- To be safe. [S. Kandavilli *et al.*, Pharmaceutical Technology (2002)]

In the studies reported in literature there are already therapeutic systems based on nitredipine incorporated in a polyisobutylene matrix using azone as a penetration enhancer [L. P. Ruan *et al.*, J. Controll. Rel. **20**, 231-236 (1992)], as well as patches sensitive to pressure made out of acrylic materials which use as penetration enhancer d-limonene [N. T. Dnyanesh *et al.*, Drug Dev. Ind. Pharm. **29**, 71-78 (2003)].

The studies undertaken in this project lead to the selection of the following polymers:

- Polyisobutylene (PIB);
- Ethylcellulose (EC);
- Hydroxypropyl (methyl)cellulose (HPMC).

The selected polymers and the adjacent materials have been purchased from Sigma Aldrich (in Romania SC Redox SRL).

i) **Polyisobutylene** is one of the polymers of interest (chemical structure in Figura 1) due to the physical and chemical characteristics (saturated hydrocarbon), for ex. Low diffusion coefficient. The physical properties of this polymer change gradually, with the increase of its molecular mass.

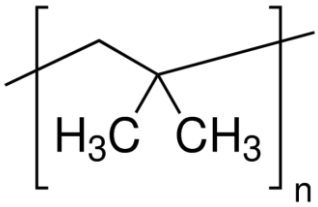

Figure 1 Chemical structure of polyisobutylene (from Sigma Aldrich www.sigmaaldrich.com).

A selection of the properties of polyisobutylene is presented in Table 1.

Molecular mass	**M_n ~200,000 GPC/MALLS**
	M_v ~420,000
	M_w ~500,000
Refractive index	***n*20/D 1.5045**
Transition temperature	**T_g −64 °C**
Density	**0.92 g/mL la 25 °C(lit.)**

Table 1 Properties of PIB (from Sigma Aldrich).

ii) **Ethyl cellulose (EC)**

In Figure 2 the chemical structure of EC polymer is shown, and in the table below the physical and chemical characteristics are presented.

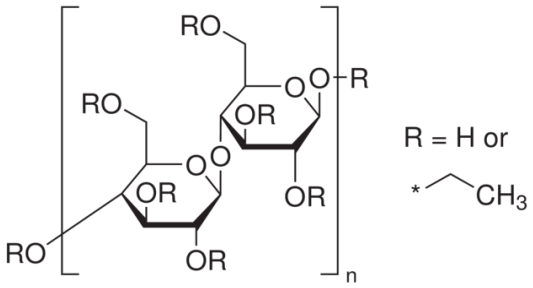

Figure 2 Chemical structure of EC.

Refractive index	***n*20/D 1.47(lit.)**
Viscosity	**4 cP, 5 % in toluene/ethanol 80:20 (lit.)**
Transition temp.	**155 °C**
Density	**1.14 g/mL la 25 °C(lit.)**

Table 2 Proprieties of EC (from http://www.sigmaaldrich.com/catalog/Lookup.do?N5=All&N3=mode+matchpartialmax&N4=ethylcellulose&D7=0&D10=ethylcellulose&N1=S_ID&ST=RS&N25=0&F=PR)

iii) **Hydroxypropyl (methyl) cellulose HPMC**

In Figure 3 the chemical structure of HPMC polymer is presented. One of the most important properties of this polymer is its viscosity of 40-60 cP (2% in water, at 20° C)).

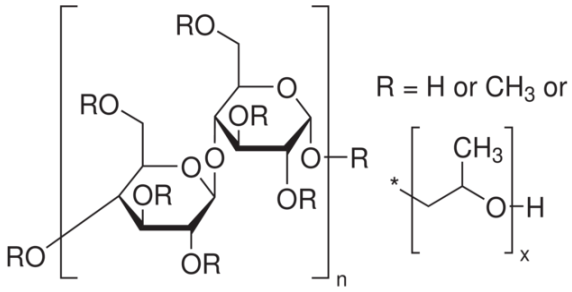

Figure 3 Chemical structure of HPMC (from http://www.sigmaaldrich.com/catalog/ProductDetail.do?lang=es&N4=H8384|SIGMA&N5=SEARCH_CONCAT_PNO|BRAND_KEY&F=SPEC)

The application (incorporation) of a large range of drugs within the transdermal patches is limited by the "obstacles" which are found in the drug's penetration path through the skin. Thereofore, the daily dosage of drugs which can be released by the transdermal patches is of 5-10 mg, limiting the administration method. A significant effort has been focused towards finding a strategy for overcoming the permeability barrier of the human skin. [H. A. E. Benson, Current Drug Delivery **2**, 23-33 (2005)] In this aspect, there are used chemical substances which temporarily reduce the skin barrier and are known as accelerator or enhancers of drug flow. Among these drugs, the most used enhancers of the skin are the terpens. The terpens are mostly found in essential oils and are made of carbon, hydrogen and oxygen atoms, but which are not aromatic. This compounds are mostly used as drugs, as well as flavours or spices. In Figure 4 the chemical structure of a cyclic terpene, limonene is shown.

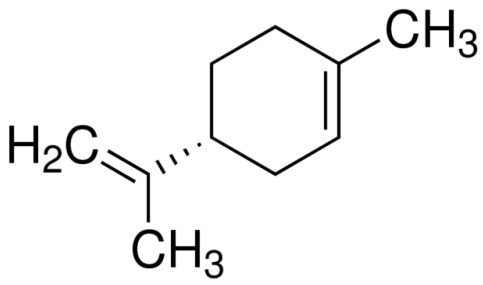

Figure 4 Chemical structure of (R)-(+)-limonene.

Conclusions

The objective of the first phase has been achieved. A spectrophotometer UV-VIS has been purchased to determine the drug concentration in the polymer thin films. In addition, activities for the second phase of the project have been planned:

- MAPLE of the polymers chosen in the first phase I/2011;
- MAPLE of polymer mixtures/polymer-drug;
- morphologic and chemical analysis of the thin films deposited by MAPLE.

Project director

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