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OBTAINING OF TRANSDERMAL PATCHES BY MEANS OF NATURAL ACTIVE PRINCIPLES

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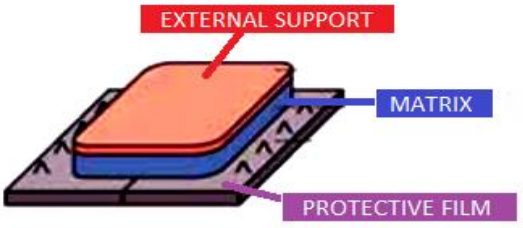
In the present paper the contributions are directed to obtaining transdermal therapeutic patches provided with a functional cotton textile support (acting as a reservoir) which would result in the controlled release of certain natural active principles (propolis and menthol), with .pharmaceutical action on people and children in order to support the treating and preventing of some irritations, wounds, injuries, scratches as well as certain allergic skin conditions in a natural, efficient and comfortable manner which would avoid the classic administration . In order to prove and characterize the inclusion of the active principles (propolis and menthol) into the cavity of the reactive cyclodextrin product grafted on the surface of the biofunctional textile support the following analytical methods were applied: scanning electron microscopy (SEM), energy dispersive X-ray spectroscopy (EDX) and thermogravimetric analysis (TG-DTG).



INTRODUCTION

Various topic system of releasing drugs and cosmetics were applied over time for treating diverse skin conditions playing thus an essential part in the medical field. Thus, in recent years a particular attention has been paid to the application of the drugs with controlled release by means of transdermal administration satisfying the clinical requirements of the people. The transdermal therapeutic patches represents an alternative manner of drug administration in other ways than the classical or common ones (oral, intravenous, intramuscularly). A transdermal patch is defined as a system of a flexible and multilayer pharmaceuticals of variable size containing one or several drug components to be applied on the intact skin for the drug controlled release.[1-4] In order to conceive the textile functional support for the transdermal patches suitable for treating the skin conditions the following elements must be taken into account: intense hydration, achievement of a high comfort on the epidermal level by means of a soft and hydrophilic interface, breathable at the level

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of the microclimate determined by the patches and skin interface, using of some emollients[4,7-9] as well as performing some treatments with various pharmacological agents.[10-15]

The patches of the new generation are small, thin, easily to be applied and have an adhesive matrix. The drug is absorbed through the skin after applying the adhesive layer. The absorbed active component reaches directly the skin capillaries and then the blood flow. By means of this transport the hepatic metabolism is avoided and the interaction of the drugs diminished which would be an advantage to the non-cooperant patients which could easily approach this system. The transdermal patches are increasingly applied in dermatology. Those including the capsaicin as an active component as well as those with anti-aging agents[16,17] are particularly important among them. The highest difficulty in performing the transdermal transport of the active components consists in the penetration of the skin acting as a barrier. The optimization of bioactive component release through the human skin is a major objective of the modern therapy.[10,11,13]

The drugs to be administrated on the transdermal way must be stored in a reservoir, this function being fulfilled by the adhesive in the patches or by a polymer matrix as a gel containing the active component. This matrix can be applied on various types of textile materials (fabrics, knitwear, non-woven materials). The chosen textile materials must be attested for the medical use, must be sterile, hygroscopic, permeable toward air and moisture, absorbing, biocompatible, soft and comfortable when contacted directly with the surface of skin conditions, must show a little contraction and be able to allow the application of a polymer composition on their surface.[12]

The natural active principles are advantageous for their ability of crossing the skin much more efficiently than the chemical compounds since their internal structure is quite similar to that of the natural oils in the skin.[16,17]

The propolis was much investigated for its many pharmacological properties as a miraculous product with antibacterial, healing, antifungal, antioxidant, anti-inflammatory, anticancer, antitumor, antidiabetic properties. It is effective in treating the allergy, bronchial asthma, gastric disturbers, skin wounds, being also approved for clinical studies.[18-20]

The menthol is a natural product extracted from the plant *Mentha piperita* (*Lamiaceae*), being much used in some pharmaceuticals and cosmetics in virtue of the physiological properties acting as a local anesthetic with antiseptic effects.[21,22]

RESULTS AND DISCUSSION

Components of the transdermal patches

Generally the patches consist of external support sustaining the preparation containing the medicinal compound included into a polymer matrix together with penetration activators, plasticizers and other required excipients. A protective film aimed to protect the pharmaceutical product is placed on and removed subsequently before fixing on the skin.[8,9] The medicinal preparation is placed between the two foils, meaning the active substance, included into a polymer system that assures the controlled release of the active principle (Fig. 1).[8,9]

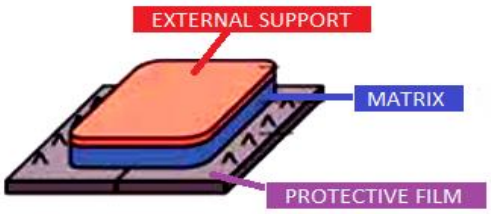


Fig. 1 – The structure of transdermal patch.

In order to perform a transdermal therapeutic patches we made use of some natural active principles known for their therapeutic actions under skin conditions: propolis (bee extract) and menthol (pure compound, main component of the mint volatile oil). These substances included in the cyclodextrin compound grafted on the textile support surface may be released in a controlled manner by a transdermal way under the action of a specific cutaneous stimulus (sweating humidity, specific skin enzymes, friction) in the internal part of the therapeutic patches till the hypoderm level for improving the skin conditions.[23-25]

Bio-functional textile support

In the present paper a textile support of a simple structure of 100 % cotton was advanced (knitwear made in natural cellulose fibers). This choice was taken into account due to the lack of allergy potential, obtaining of textile supports with soft surfaces and good hygienic-physiologic properties such as permeability to air, water vapors and carbon dioxide, thermic conductivity coefficient from a moderate to medium value resulting in a satisfactory skin comfort.

Reactive derivative of monochlorotriazinyl -β-cyclodextrin

The inclusion of the active principles into the surface of the textile bio-functional support was performed by means of a cyclodextrin product, namely the reactive derivative monochlorotriazinyl-β-cyclodextrin able to give inclusion compounds with the drug molecules or other active principles, releasing then gradually the active pharmaceuticals from the bio-functional textile support of the patches to the damaged skin spot.[25-28]

The monochlorotriazinyl-β-cyclodextrin is the first cyclodextrin reactive derivative largely applied in textile finish due to the adequate size of the hydrophobic moiety, reactivity and also due to the rather simple grafting process on the textile support surface.[29-32] The monochlorotriazinyl-β-cyclodextrin (containing 2 or 3 reactive groups per ring) is a reactive product able to be applied on supports containing nucleophile groups such as -OH, -NHR, -SH (*e.g.* cotton, protein fibers, polyamide, viscose).

The active chlorine atoms in the triazine ring can react with the nucleophile groups in the cellulose fibers (-OH) as can be seen in Fig. 2.[12]

The choice of the best method to fix the cyclodextrin on a textile support depends on several factors, mainly the cyclodextrin reactivity till the final application as well the fiber type. The monochlorotriazinyl-β-cylodextrin is the most interesting derivative used on cellulose substrata due to the simple binding process under rather easy conditions.

The monochlorotriazine groups included into the cyclodextrin derivative react by a mechanism of nucleophilic substitution resulting in covalent bonds with hydroxyl groups in cellulose (Fig. 2). The monochlorotriazinyl-β-cyclodextrin is attached to cellulose fibers under alkali conditions and due to the covalent bond between the cellulose chain and monochloro-triazinyl-β-ciclodextrin the durability in the textile products is increased.[12,22,32]

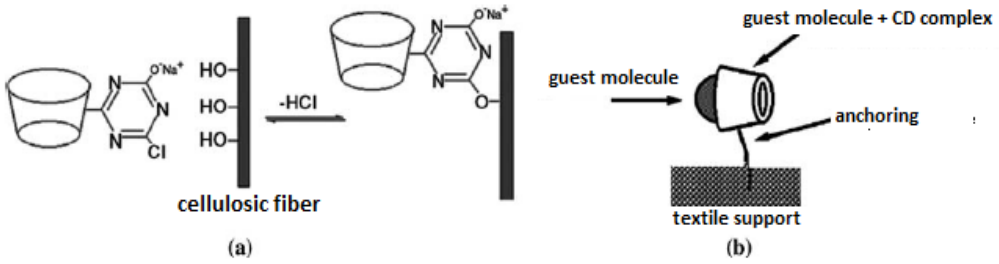


Fig. 2 – a) MCT-β-CD grafting on cellulosic fiber; b) scheme of the formation of the host-guest inclusion complex grafted on the cellulosic support.

Characterization of the obtained patches

SEM analysis

In Fig. 3 the presence of micro-deposits (as spherical form) on the textile support surface due to the grafting of the reactive cyclodextrin product is made evident in Fig. 3a. The fact can also be noticed that the fibers did not degrade following the fixation treatment of cyclodextrin at 160° C keeping their shape and size.

As regards the inclusion of the active principles the fact deserves mention that the surfaces of the textile supports grafted and treated with propolis (Fig. 3b) and menthol (Fig. 3c) appear much cleaner due to the effect of ethanol that cleanse the cellulose surface.

a b c

Fig. 3 – a) SEM analysis for the sample grafted with monochlorotriazinyl-β-cyclodextrin;
b) SEM analysis for the sample grafted with monochlorotriazinyl-β-cyclodextrin and treated with propolis;
c) SEM analysis for the sample grafted with monochlorotriazinyl-β-cyclodextrin and treated with menthol.

EDX analysis

For the study by EDX spectroscopy a standard sample (grafted with monochlorotriazinyl- **(**β-cyclodextrin) was taken along with the samples grafted with monochlorotriazinyl-β-cyclodextrin and treated with active principles (propolis and menthol) of 5 × 5 mm size. The EDX elemental analysis made evident the elemental composition of both standard sample and those grafted and treated with menthol and propolis. The obtained results are illustrated by the pictures in Figs. 4–6.

The nitrogen presence is made evident to be caused by the fixation of the triazine derivative. The nitrogen mass percent found in the sample grafted with monochlorotriazinyl-β-cyclo-dextrin is higher (9.62%) than in the samples treated with the active principles, namely propolis (7.73%) and menthol (8.88%), respectively. The decrease in the nitrogen mass percent for the treated samples is indicative of the inclusion compounds formed between monochlorotriazinyl-β-cyclodextrin and active principles.

The presence of some bands characteristic of the host or guest species in the spectra of the samples treated with active principles which are shifted in comparison with the bands of the standard sample could be taken as a prove of the inclusion compound formation.

The opposite situation is not always true since the absence of a band characteristic of the guest molecule does not really mean that the inclusion compound was not formed. Sometimes overlaps can be noticed between the bands of the guest and host species.[12]

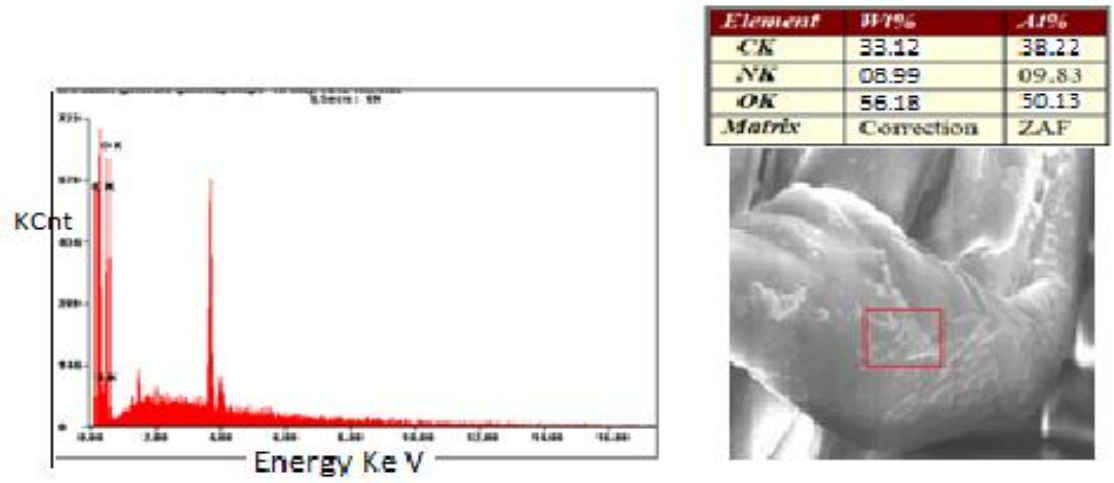


Fig. 4 – EDX spectroscopy for the sample grafted with monochlorotriazinyl-(β-cyclodextrin.

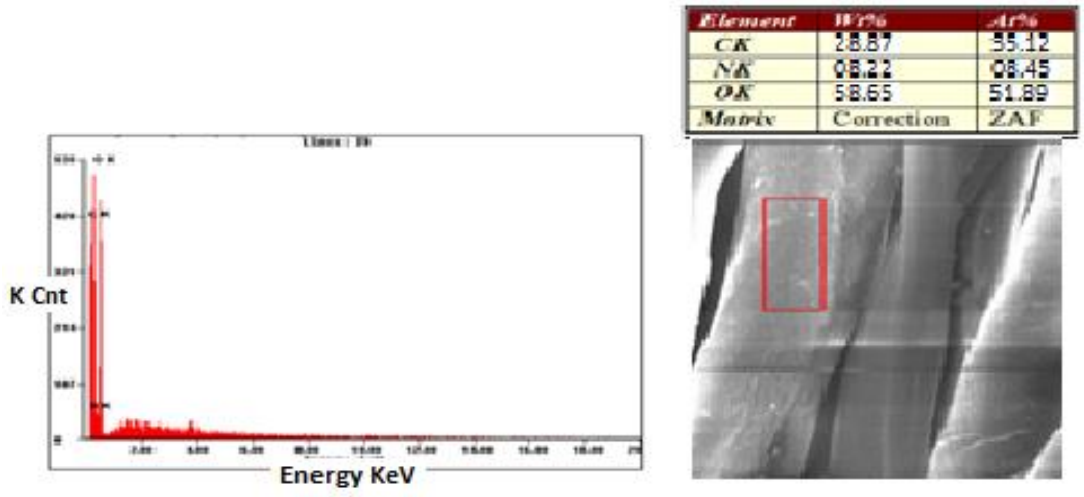


Fig. 5 – EDX spectroscopy for the sample grafted with monochlorotriazinyl-β-cyclodextrin and treated with propolis.

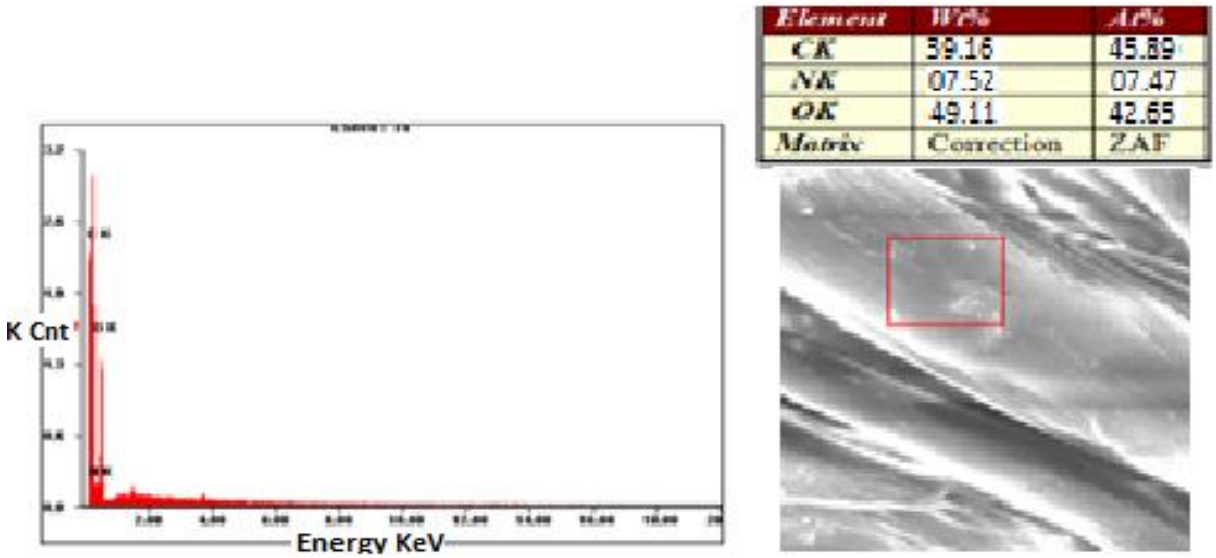


Fig. 6 – EDX spectroscopy for the sample grafted with monochlorotriazinyl-β-cyclodextrin and treated with menthol.

Thermal analysis (thermogravimetry)

Three samples were taken for the thermogravimetric analysis: a standard sample (textile support) (1), a sample with a textile support of monochlorotriazinyl-β-ciclodextrin (2) and the third with a textile support grafted with monochlorotriazinyl-β-ciclodextrin and treated with a menthol alcoholic solution (3).

In Figs. 7a, b, c the TGA-DTG thermograms obtained by the DTG analysis represent the first derivative (curve) of the mass versus temperature.

The TG curves obtained for the samples under investigation are indicative of mass losses proceeding into three stages (where mass modifications happen) and of the processes overlapping (by DTG).[33-35]

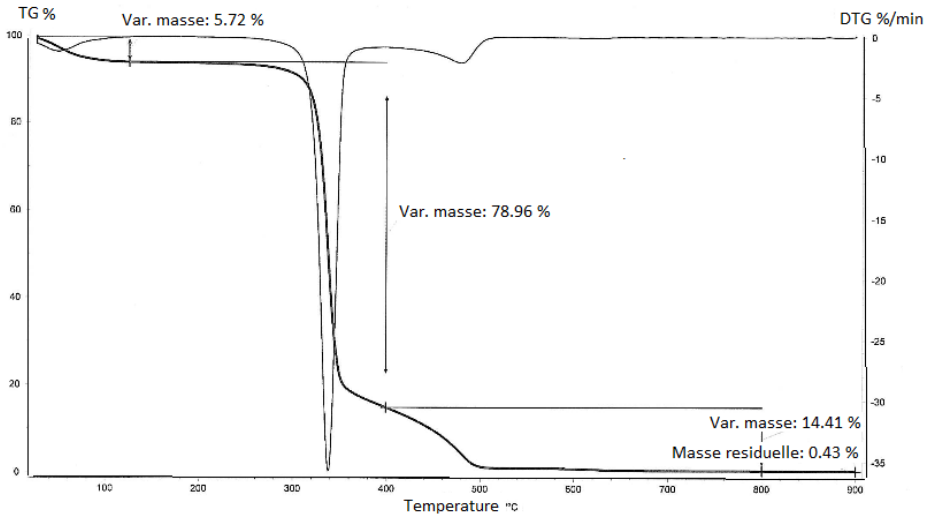
The values of the weight losses in the three stages versus temperature are listed in Table 1.

Table 1

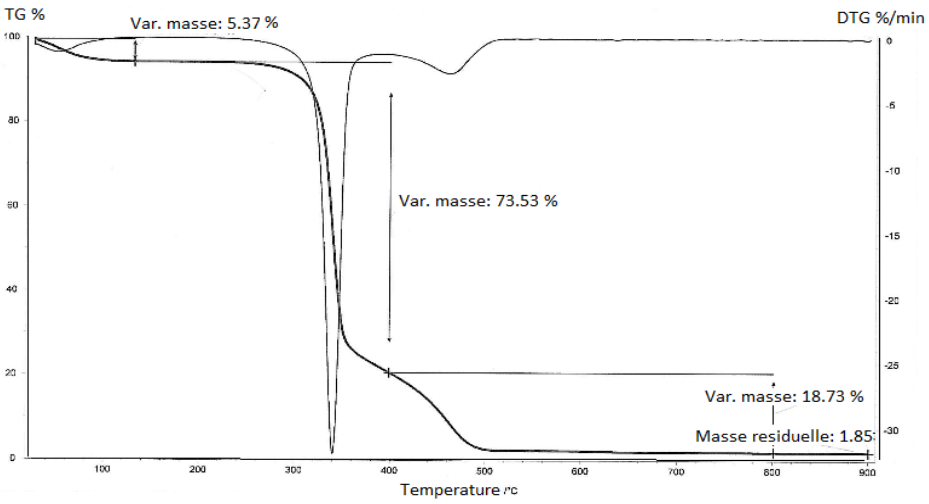
Thermogravimetric characteristics for the samples

Sample	Stage	T_{onset} °C	T_{peak} °C	T_{endset} °C	W%	Residue
1	I	91	110	320	5.72	0.43
	II	320	340	400	78.98	
	III	400	500	800	14,41	
2	I	62	141	328	5.37	1.85
	II	328	360	400	73.53	
	III	400	495	800	18.73	
3	I	78	138	325	4.42	0.59
	II	325	345	400	77.31	
	III	400	480	800	17.15	

Tonset (ºC) – the initial degradation start temperature for each stage,
Tendset (ºC) – the final temperature of each degradation stage,
Tpeak (ºC) – specific temperature to the maximum degradation rate,
W (%)- weight loss.



a)



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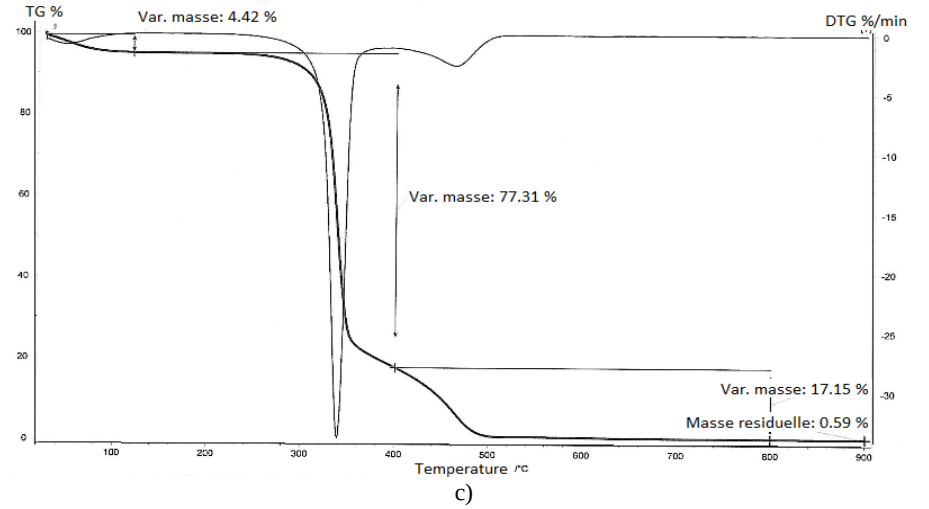

c)

Fig. 7 – a) TG and DTG curves for textile support sample; b) textile support of monochlorotriazinyl-β-ciclodextrin; c) textile support grafted with monochlorotriazinyl-β-ciclodextrin and treated with a menthol.

The values of the mass losses for the three samples under study are generally close to one another. The most significant loss was noticed in the IInd stage at 320–400°C.

The TGA-DTG reveal that the decomposition temperature of the monochloro-triazinyl-β-cyclo-dextrin/menthol inclusion complex did not modify significantly compared to the standard sample. In the complex thermograms no variation is noticed in the degradation zone of the sample treated with the active principle which would indicate a different state acquired relative to the standard sample proving thus the presence of an inclusion compound.

EXPERIMENTAL

Grafting of the cyclodextrin reactive product on textile support

The textile support taken for grafting with monochlorotriazinyl-β-ciclodextrin is the cotton knit alkali treated and bleached. The monochlorotriazinyl-β-cyclodextrin (supplied by the Wacker Chemie, Germany company) was chosen as a host compound taken as a support while the antiallergic active principles (propolis and menthol) were the guest. The fixation of the cyclodextrin derivative on he textile material was performed by the semi-continuous process-padding and thermal treatment (T_{term}).

The padding (impregnation-squeezing) of the textile material (on the Benz laboratory foulard) was performed at a squeezing degree of 135% with a solution containing 100 g/L mono-chlorotriazinyl-β-ciclodextrin and 20 g/L Na_2CO_3. The drying was performed at 80 °C for 10 min (on Mesdan Lab Dryer); the thermal fixation was made at 160 °C for 7 min (on Mesdan Lab Dryer) for achieving the chemical fixation of the reactive cyclodextrin product on the textile support. The reaction products were removed by worm (at 90 ºC) and cold (20 ºC) repeated washings till pH = 6.5 – 7; the final drying was made at room temperature (22 °C) for 72 h.

Inclusion of the active principles into the cyclodextrin reactive product grafted on textile support

The cotton knit was alkali treated, bleached and grafted with monochlorotriazinyl-β-cyclodextrin and then used as a support for the inclusion of the two natural active principles: propolis and menthol. Alcoholic solutions of propolis (30% w/v) and menthol (10% w/v) were used.

For the initial conception of the transdermal patches four knit bands of 1 × 45 × 60 cm. size were taken into account. Thus, in order to apply the active principles on every knit strip the optimum amount of active principle was divided into 4 parts and added into 60 mL alcoholic solution. The natural active principles were then sprayed under laboratory conditions by means of an Einhart ET-185 (Germany) spraying system.

Following the spraying treatment the samples of textile support treated with the active principles were dried at room temperature (22 °C) for 24 h. In order to fix the active principles on the textile support grafted with the cyclodextrin reactive product (monochlorotriazinyl-β-cyclo-dextrin) the textile samples were finally dried in a Venticell 55 oven at 40 °C for 5 h since this temperature does not cause the product degradations.

Characterization of the obtained patches

SEM analysis

The investigation was carried out on a scanning electronic microscope of the LEO type (Leica Electron Optics) at an acceleration voltage of 15 kV and an working distance (sample-scan head distance) of 22 mm.

The four samples of textile material were fixed on aluminum plates by means of a double tape. For improving the quality of microscopic images the textile samples were covered with a thin layer of gold in rarefied argon (20 Pa) by means of an Emitech K550 Sputter Coate spray, with a current of 20 mA for 80 seconds.

EDX analysis

The Fourier transform infrared spectroscopic analysis (FTIR) was carried out on a Thermo Nicolet Nexus spectrometer by attenuated total reflection – ATR with Smart Endurance accessory over the 1650 – 550 cm^{-1} domain. This analysis represents a surface analysis necessary for the solid materials with an investigation depth between 10 and 0.1 μm, when the radiation suffers multiple reflex on the surface under investigation prior to measuring. The ATR is a good tool for investigating the uniformity, thickness and coverage being able to analyze the thin layers of textile supports or other materials by means of infrared beam.

Thermogravimetric analysis

The thermogravimetic analysis was carried out on a Netzsch TG 209 thermograph. The Netzsch thermographs are of a compact structure and are provided with a digital high resolution microbalance. The vertical arrangement affords a facile performing and a direct temperature level. The thermographs are well sealed and allow under vacuum the measurement of mass changes under a defined atmosphere (inert, oxidative, reducing, static). The optional extension for the DTA signal gives crucial information on exothermal or endothermal processes in the sample, even these phenomena are not connected with the mass changes. Due to the vertical design of the Netzsch thermogravimeters the gas capture after measurements is much easier performed through thermostatic adapters. The samples submitted to analysis were of about 10 mg mass and the air acted as a purge gas.

CONCLUSIONS

In order to conceive the transdermal patches a textile support made of cotton fibers was chosen due to the high physiological properties. In addition to that, the two preparatory operations (alkaline treatment and bleaching) resulted in the improvement of the biocompatibility of the textile support with epiderma, namely it becomes aseptic, hydrophilic, soft, non-toxic showing also a good chemical reactivity for the finishing/treating operations.

The active principles were included into the surface of the bio-functional textile support by means of cyclodextrin product (monochlorotriazinyl-β-cyclodextrin) able to form inclusion compounds with the active principles under study (propolis and menthol) releasing then the pharmaceutically

active compounds gradually and as a controlled form from the patches textile support.

The experimental results reported on the selection, preparation and treating of the textile support, characterization of the natural active principles and of the bio-functional textile support by means of the chemical analyses represent the necessary steps for conceiving the transdermal therapeutic patches.

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