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Antifungal Microcapsules of Ethyl Cellulose by Solvent Evaporation and Their Application to Cotton Fabric

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Abstract
In this study two antifungal pharmaceutical agents, terbinafine and ketoconazole, were microencapsulated by solvent evaporation. Two types of ethyl cellulose with different viscosity values were used. Microcapsules were evaluated by X-ray diffractometry, DSC, FTIR and SEM analysis. Although the characteristic peaks of ketoconazole appeared in the X-ray diffractometry, those of terbinafine disappeared. The same results were observed for DSC analysis. The melting point of ketoconazole existed, while that of terbinafine was not observed. The microcapsules had a spherical shape, however the particle size varied between 5 and 120 μm. The microcapsules were applied to 100% cotton fabric. The washing of fabrics was performed in various washing cycles, and afterwards antifungal tests were performed. The fabrics had antifungal properties against Trichophyton rubrum, which causes mycoses, up to 5 washing cycles.

Key words: *terbinafine, ketoconazole, cotton, ethyl cellulose, microencapsulation.*

Introduction

The encapsulation of liquid or solid agents, such as drugs, proteins, hormones, fertilisers, pesticides, herbicides, dyes, cosmetics and fragrances, by a suitable barrier wall in micron diameters is called microencapsulation. For instance, drying in liquid and the coacervation method as physicochemical techniques, interfacial polymerisation and in situ polymerisation as chemical techniques, and fluidized-bed coating and the spray drying method as mechanical or physical techniques are commonly known. The materials encapsulated are affected for a prolonged period, are isolated from reactive and hostile environments, can be processed more effectively and easily, and are transported safely. The barrier wall can be built using monomers to form polymers or polymers that are polymerised elsewhere, or readymade capsules such as liposome, cyclodextrin derivatives or microorganisms' cells [1 - 3].

The functional finishes can be applied to textiles by padding, coating or master batch mixing. The finishing chemicals should be attached onto textiles by covalent, electrochemical or physical bonds or coated by crosslinking agents and binders. However, traditional techniques can show poor fastness properties. Microencapsulation has appeared to be an alternative way to achieve the functional finishes because of their unique properties, such as controlled release, protection against hazardous and destructive media, as well as providing a higher surface area. Nowadays the application of microencapsulated pharmaceutical agents to textiles has been gaining the interest of researchers. An inclusion complex of miconazole nitrate, a pharmaceutical antifungal agent, and monochlorotriazinyl β-cyclodextrin was applied to cotton fabrics via the impregnation method [4]. Inclusion complexes of ketoconazole, an imidazole based antifungal agent, and monochlorotriazinyl β-cyclodextrin were formed by two methods, kneading and spray drying. Molecularly encapsulated ketoconazole was applied to cotton fabrics by the impregnation method [5]. Molecularly encapsulated terbinafine was also applied to cotton fabric, where antifungal properties were maintained after 15 washing cycles. [6]. The application of melamine-formaldehyde/terbinafine microcapsules saw their attachment onto cotton fabrics using a suitable DMDHEU crosslinking agent. The fabrics were tested to define the antifungal properties against two fungi, *Trichophyton rubrum* and *Aspergillus niger*. [7]. Triclosan loaded poly(L,L-lactide) micro-spheres were applied to viscose nonwoven fabrics. The storage durability of micro-sphere loaded nonwovens at different conditions was investigated. The authors emphasised that higher antibacterial properties were obtained in the case of the higher humidity due to degradation of the poly(L, L-lactide) wall [8].

Terbinafine is an allylamine based novel and newly developed antifungal drug which inhibits squalene epoxidase, the enzyme which catalyses the conver-

sion of squalene to squalene-2,3 epoxide, a precursor of lanosterol, which in turn is a direct precursor of ergosterol. A deficiency of ergosterol is its detrimentality to the integrity of the cell membrane, resulting in a fungistatic effect similar to that seen with azole antifungal compounds. Ketoconazole is an imidazole based antifungal drug which shows a similar effect to terbinafine, but inhibits the course of ergosterol production differently. Both terbinafine and ketoconazole exhibit good antifungal effects against to mycoses and can be used in both oral and transdermal applications [9].

Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydroglucose units joined together by acetal linkages. Ethylcellulose is widely used in oral and topical pharmaceutical formulations, cosmetics and food products. Various methods can be employed for the preparation of microcapsules from ethyl cellulose, such as coacervation, spray drying, phase separation and solvent evaporation, wherein the drug is dissolved, dispersed or emulsifed in an external aqueous or oil phase [10 - 13].

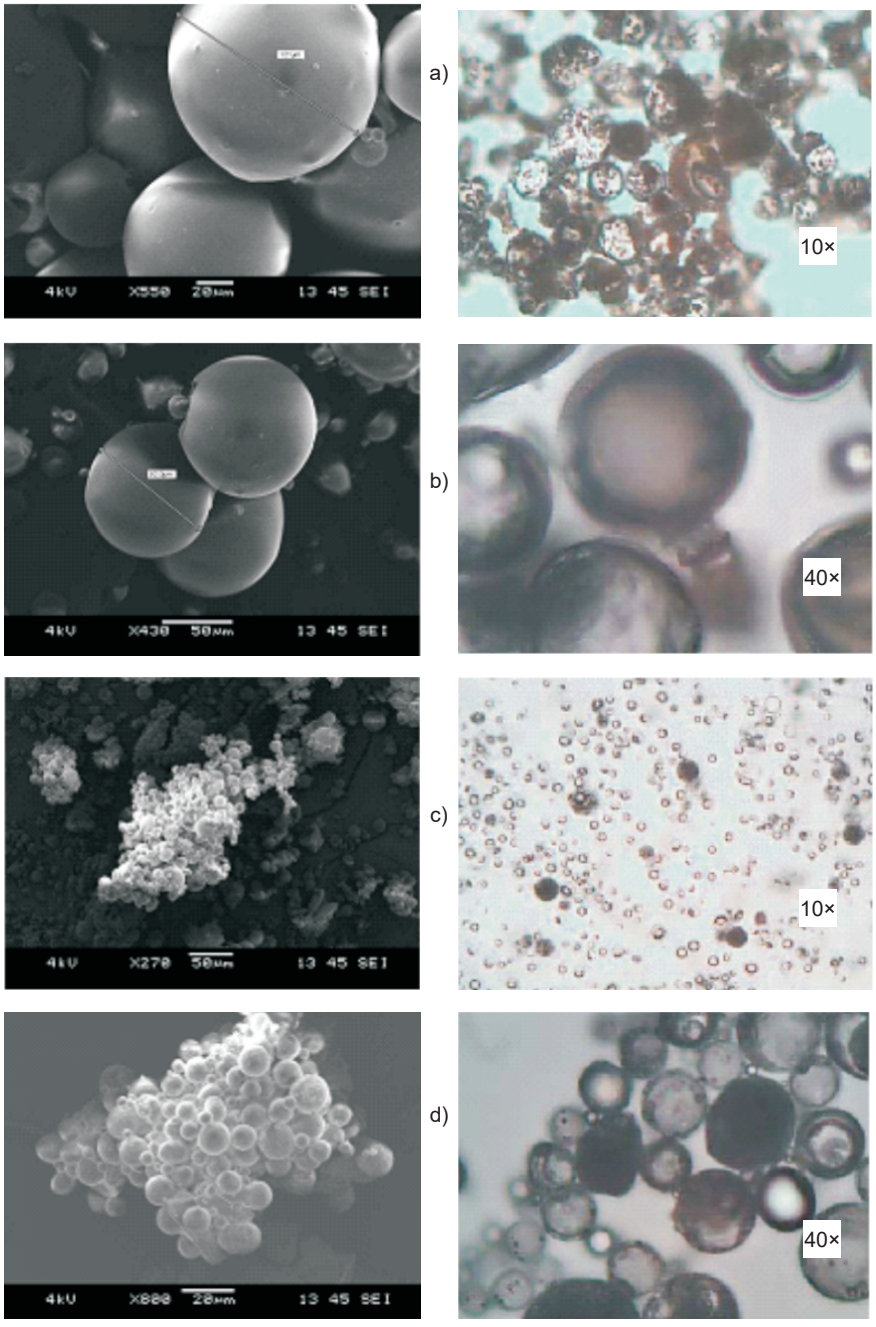

Figure 1. *SEM Micrographs and optical microscope images of ethylcellulose microcapsules: a) ethocell premium 4 KET, b) ethocell premium 7 KET, c) ethocell premium 4 TER, d) ethocell premium 7 TER.*

Mycoses include *Candidiasis, Cryptococcosis, tinea pedis* and *tinea corporis* and *tinea cruris,* causing serious health problems. Also they are very contagious, and easily spread out. The treatment of mycoses needs long term and systematic anti-fungal agent curing. Microencapsulated anti-fungal agents can be applied to textiles. Therefore treatment can be achieved in the long term and systematically.

The aim of this study is to make a pharmaceutical fabric. Antifungal pharmaceutical agents were microencapsulated by the solvent evaporation technique. The preparations were applied to 100% cotton fabric. X-ray diffractometry, thermal analyses, FTIR, imaging techniques and antifungal tests were also applied.

Material and method

Materials

Terbinafine (TER-Nobel Ilaç Sanayi; Turkey) and ketoconazole (KET-Sandoz; Turkey) were used as core material. Ethylcellulose, Ethocell Premium 4 and 7 were kindly supplied by Dow Chemical (Turkey). Arabic Gum (Sigma, Germany) was used as a protective colloid. Ethylene dichloride (Fluka, HPLC degree 100%) was used as an organic solvent. Ethanol (Fluka, Germany), methanol (Fluka) and deionized water were used to wash the microcapsule slurry. All chemicals were used without any purification.

Preparation of microcapsules

The preparation of microcapsules was carried out by using solvent evaporation. Firstly Arabic gum was dissolved in deionised water at 2000 r.p.m., and 3 g ethylcellulose and 1 g antifungal agent were dissolved in ethylene dichloride, which were well mixed to produce an organic phase. After that the organic phase was added to an aqua phase. The system was vigorously stirred using a Eurostar Digital mixer (IKA, Germany) at 20 °C and 2000 r.p.m., and microencapsulation was completed after 1.5 hours. Then the solution was filtered to obtain a microcapsule slurry, which was then washed with a water/ethanol/methanol mixture (1/1/1) and then dried at room temperature and in an oven at 105 °C for 4 hours [11, 14].

Application to textiles

Ethylcellulose microcapsules were applied to cotton fibres by using a suitable crosslinking agent (KNITTEX®

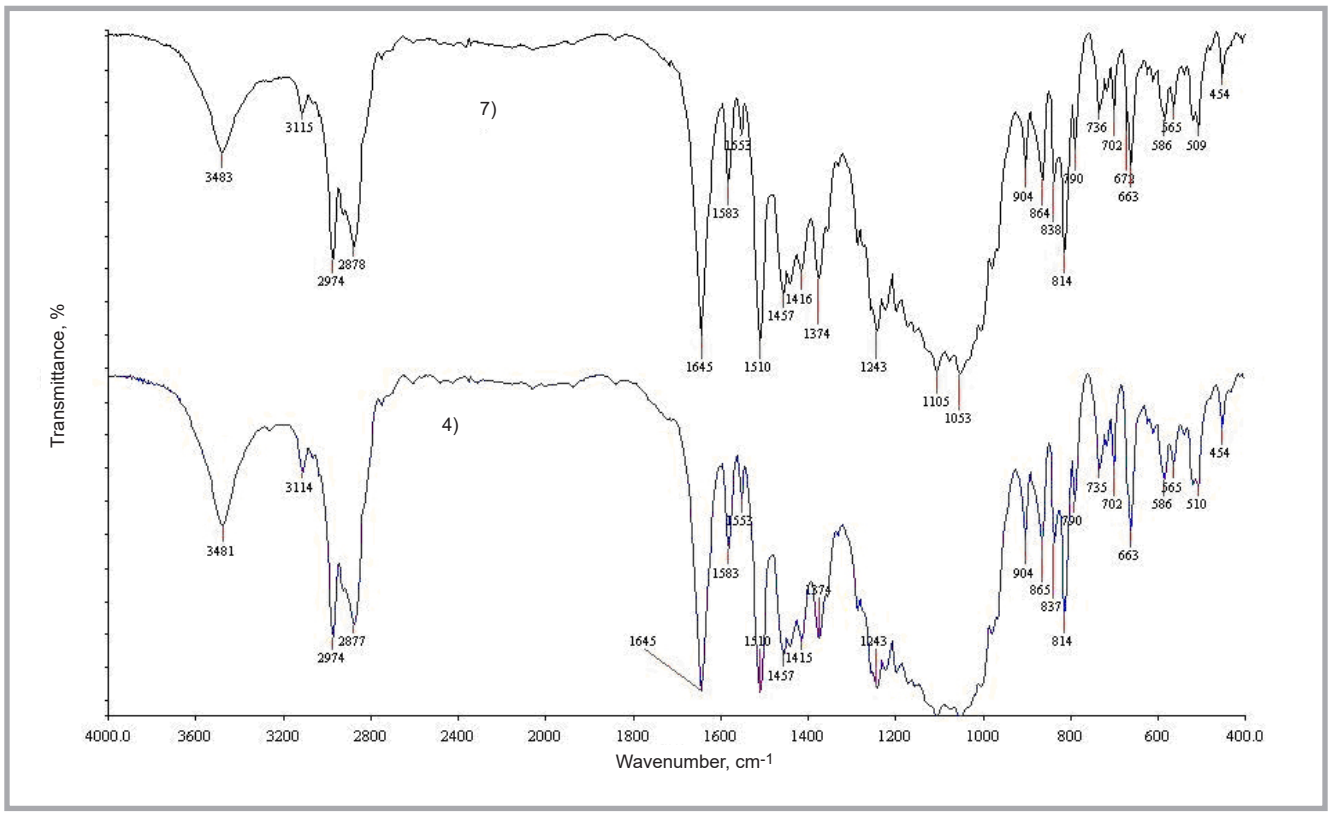

Figure 2. *FTIR spectra of KET microcapsules: 4) ethocell premium 4, 7) ethocell premium 7.*

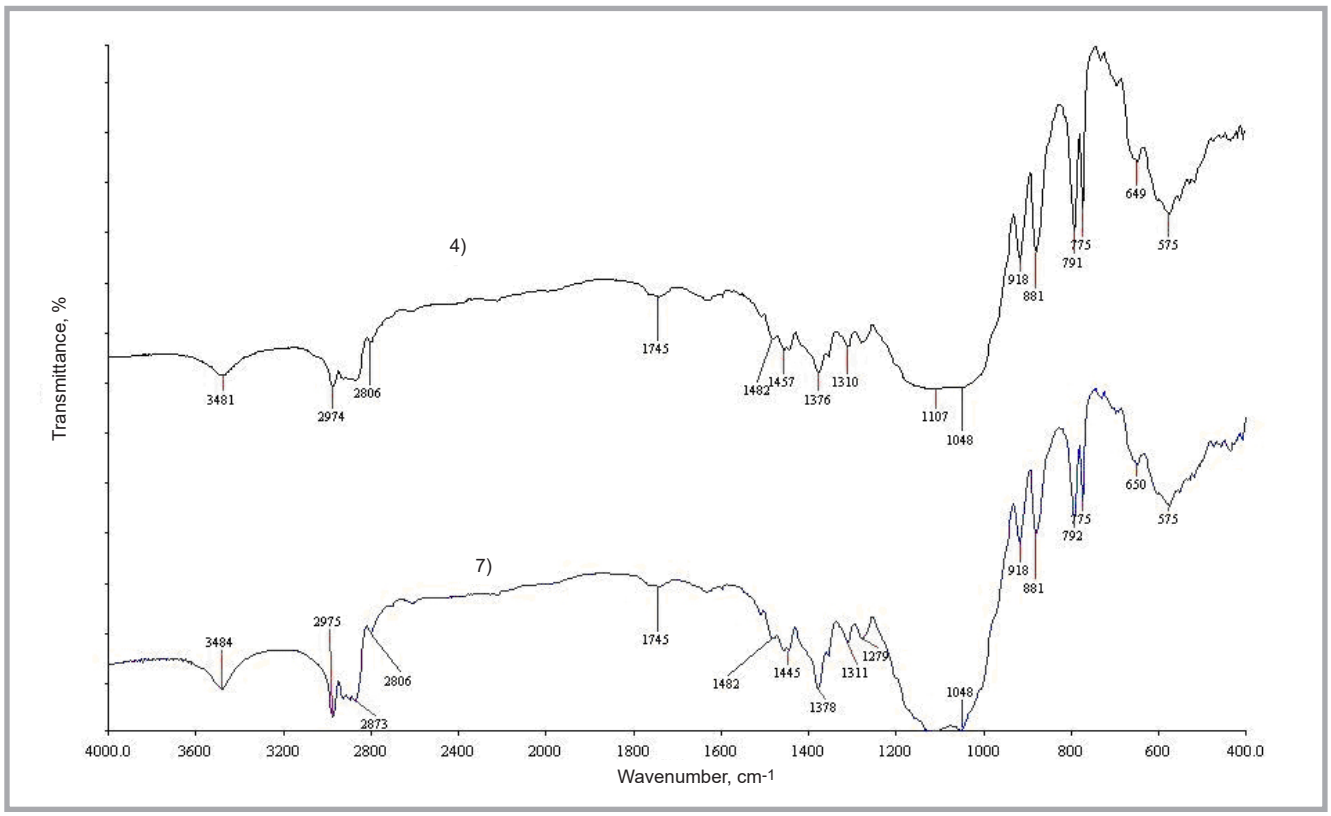

Figure 3. *FTIR spectra of TER microcapsules: 4) ethocell premium 4, 7) ethocell premium 7.*

FFRC - Huntsmann) which consisted of modified dihydroxyethylene urea. The first preparations were dissolved in water and then 150 g/l of the crosslinking agent KNITTEX® FFRC was added. The pH of the solution was adjusted to pH 5 by acetic acid (Merck, Germany). The application was conducted according to the impregnating method at 80% pickup. Drying was carried out at 130 °C and curing performed at 130 °C for 3 minutes [14].

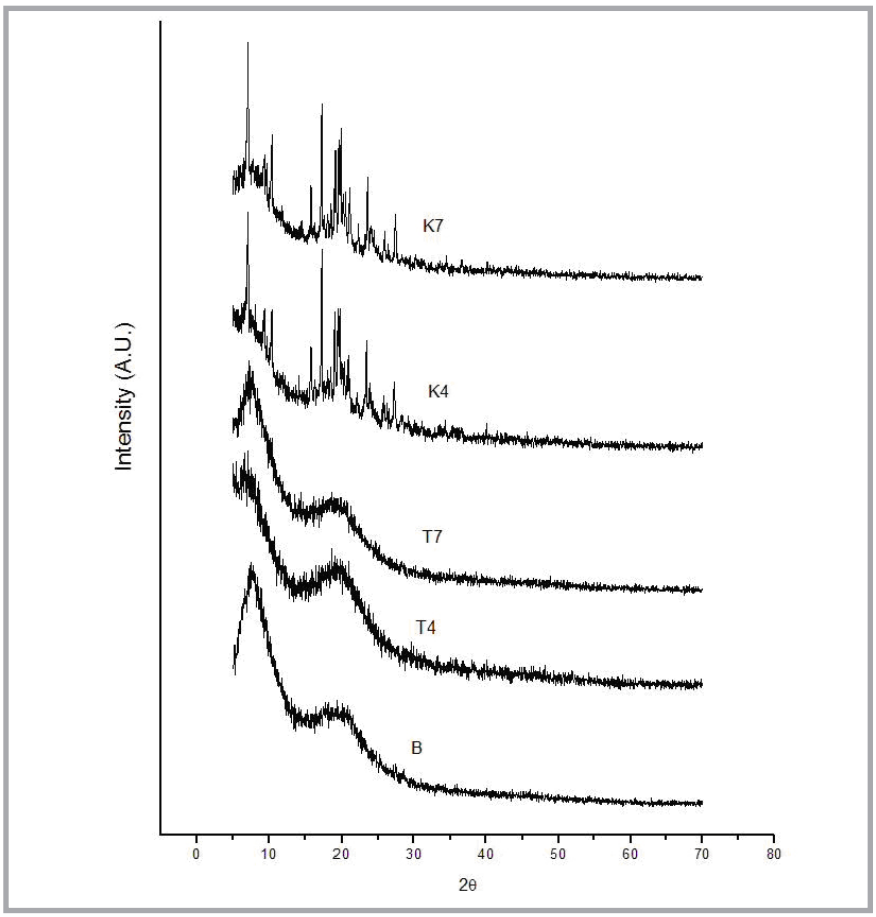

Figure 4. *XRD patterns of microcapsules: B) blank microcapsule, T4) ethocell premium 4 TER, T7) ethocell premium 7 TER, K4) ethocell premium 4 KET, K7) ethocell premium 7 KET.*

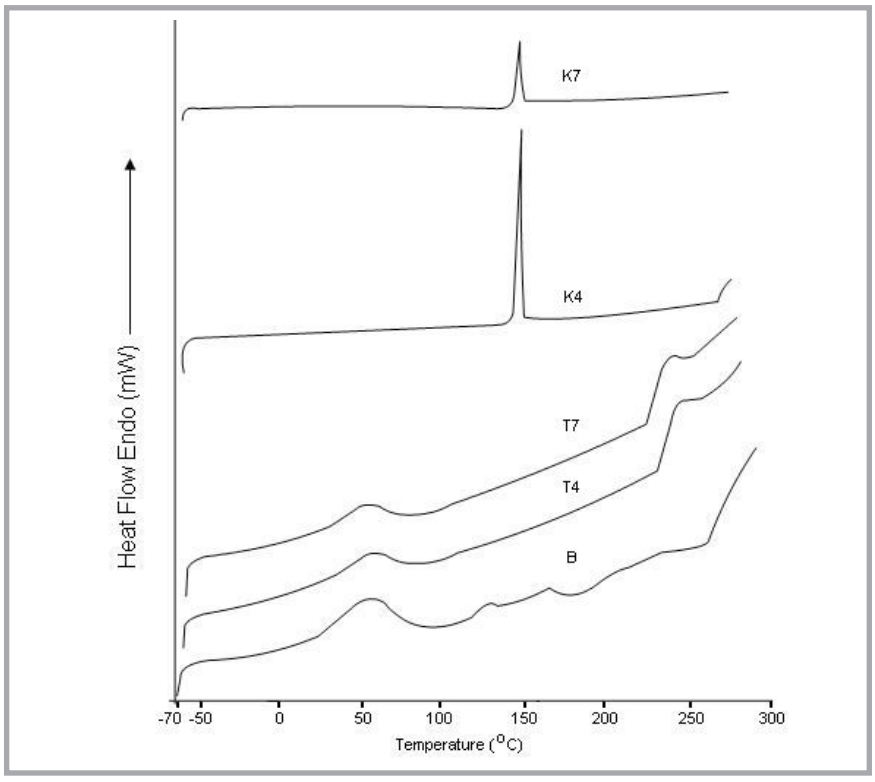

Figure 5. *DSC thermographs of microcapsules: B) nlank microcapsule, T4) ethocell premium 4 TER, T7) ethocell premium 7 TER, K4) ethocell premium 4 KET, K7) ethocell premium 7 KET.*

Characterisation

Differential scanning calorimeter (DSC)

Measurements of the melting point and melting heat of the microcapsules obtained were performed in a differential scanning calorimeter (DSC) - Perkin Elmer DSC apparatus (USA). The samples were compared with Al pan at nitrogen flow. The measurements were performed varying the temperature in the range from 20 to 250 °C with a heating rate of 10 °C/min under a nitrogen atmosphere.

X-ray diffraction (XRD)

XRD patterns of the samples were obtained using an D/Max-2200/PC X-ray diffractometer (Rigaku, Japan). A copper source was employed. Observations were carried out at 2° θ.

Scanning electron microscope (SEM)

Microstructural features of the capsules prepared were analysed by scanning electron microscopy (SEM) using a JSM–6060 JEOL microscope (Japan). Before imagining, the samples were coated by Au-Pd.

Optical microscope

Optical microscope images were captured using an Olympus CX21 microscope, which is equipped with a CCD video camera (Olympus, USA).

Resistance to washing

The resistance of the cotton fabrics to washing was established using Atlas Linitest apparatus (USA) according to TS EN ISO 105 C06 Test for colour fastness- Part C06: Color fastness to domestic and commercial laundering 2001.

Fourier transform infrared (FT-IR)

Fourier transform infrared spectra of ethylcellulose microcapsules at different mole ratios were obtained using Perkin Elmer Spectrum BX FTIR (wave-numbers 400 – 4000 cm^{-1}) at room temperature. The KBr tablet method was applied.

Antifungal test

Antifungal tests were performed according to AATCC Test Method 30 Antifungal activity, assessment of textile materials: Mildew and rot resistance of textile materials. However, the test method was modified based on the study of Gregory et al. [15], where *Trichophyton rubrum* was used as the test culture and Malt extract peptone agar as the growth media of

T. rubrum. Antifungal properties of the fabrics were observed after 1, 5, 10, 15, 20 and 25 washing cycles.

Results and discussion

Characterisation of microcapsules

SEM photographs of morphologies of the microcapsules are shown in ***Figure 1***. As can be seen in the figure, the microcapsules have a spherical shape and diameters varying between 5 and 120 μm. Particles processed from higher viscosity yielded a more porous surface than lower viscosity polymers, which is in agreement with other studies [11, 13]. ***Figure 1*** also depicts optical microscope photographs of microcapsules. Microcapsules in which TER was used as the core material have smaller diameters than those of KET microcapsules.

Figure 2 shows the FTIR spectra of KET-ethylcellulose microcapsules. The OH stretching band of ethylcellulose appeared around 3480 cm^{-1} due to the intramolecular H-bridge between OH groups. This band is characteristic for all kinds of polysaccharides. Antisymmetric stretching of CH_2 groups of ethylcellulose appeared at 2974 cm^{-1} and symmetric stretching of CH_2 groups showed peaks at 2878 and 2877 cm^{-1}, with microcapsules made from ethocell premium 7 and 4, respectively. Another characteristic peak of cellulose based polymers appeared at 1457 cm^{-1} caused by symmetric ring stretching of CH_2 at pyrane. The band around 790 cm^{-1} can be assigned to pyrane ring stretching, and that band at 1374 cm^{-1} can be explained by CH deformation due to ethylcellulose. On the other hand, the characteristic band of ketoconazole, which is that of amide I bound, was clearly observed at around 1645 cm^{-1} due to C=O stretching vibration. C-Cl stretching vibrations at 585 - 590 cm^{-1} can also be observed. The existence of ethylcellulose and ketoconazole in the microcapsule slurry was confirmed by observation of specific absorption bands of both ketoconazole and ethylcellulose polymer.

In the case of terbinafine, FTIR spectra of microcapsules are depicted in ***Figure 3***. The characteristic bands of ethylcellulose appeared around 3481, 2974, 2873, 1457, 1376 and 792 cm^{-1}; due to OH stretching of the intramolecular H-bridge between OH groups, antisymmetric stretching of CH_2, symmetric stretching of CH_2 groups, symmetric ring stretching of CH_2 at pyrane and CH deformation and pyrane ring stretching, respectively. N-CH_3 stretching of terbinafine was observed around 2873 cm^{-1}. However, C≡C stretching bands between 2260 and 2100 cm^{-1} could be observed due to the overlap of the ethylcellulose polymer.

XRD patterns of KET - ethylcellulose microcapsules are shown in ***Figure 4***.

Figure 6. *SEM micrographs of microcapsule attachment on cotton.*

The intensity peaks of ketoconazole were observed around 10.5, 7.2, 15.9, 16.9, 19.2, 19.9 and 27.4 2θ due to its crystalline structure. However, in spite of the crystalline peaks of ketoconazole, the amorphous nature of ethylcellulose can also be observed, and it can be inferred that ketoconazole microencapsulation of ketoconazole was not molecularly homogeneous or that ketoconazole was partially microencapsulated. In the case of terbinafine (***Figure 4***), the crystalline nature of the core material was overlapped by the amorphous nature of the ethylcellulose polymer. It can be inferred that microencapsulation of terbinafine was molecularly homogeneous.

DSC thermographs of microcapsules are shown in ***Figure 5***. Those of ketoconazole indicate that endothermic peaks appeared at around 150 °C for both ethylcellulose types due to the melting

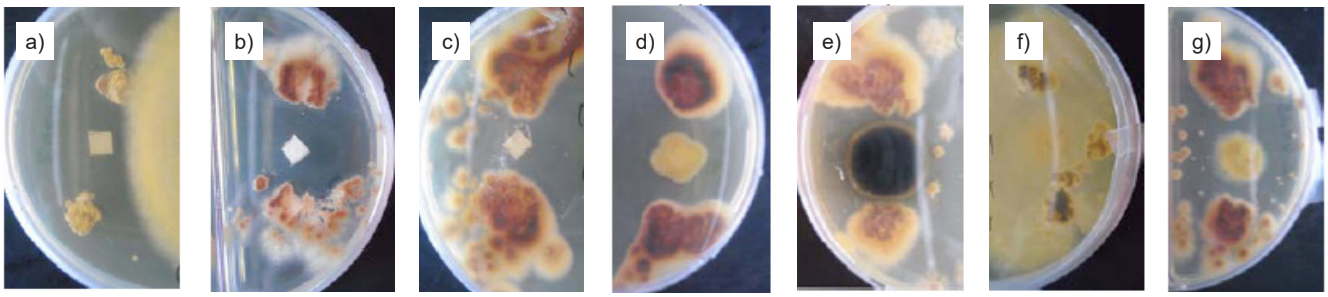

Figure 7. *Antifungal test results of KET microcapsules (ethocell premium 4): a) unwashed, b) 1 washing cycle, c) 5 washing cycles, d) 10 washing cycles, e) 15 washing cycles, f) 20 washing cycles, g) 25 washing cycles.*

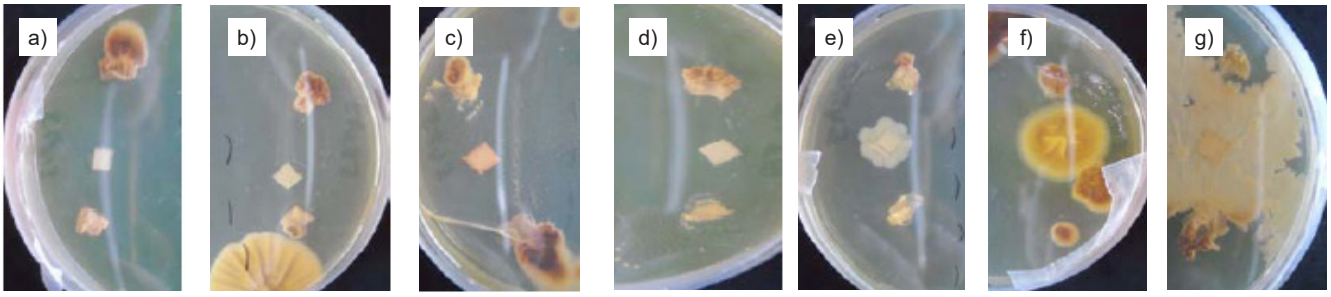

Figure 8. *Antifungal test results of TER microcapsules (ethocell premium 4): a) unwashed, b) 1 washing cycle, c) 5 washing cycles, d) 10 washing cycles, e) 15 washing cycles, f) 20 washing cycles, g) 25 washing cycles.*

point of ketoconazole, which is 146 °C. The endothermic peaks of ketoconazole microcapsules support the XRD patterns of ketoconazole microcapsules. Contrarily the melting or decomposition endothermic peak of terbinafine was not observed. Hence it can be stated that terbinafine was successfully microencapsulated using ethylcellulose with molecular homogeneity.

Attachment of ethylcellulose microcapsules onto cotton fabric

Badulescu et al. investigates grafting ethylcellulose microcapsules onto cotton fabrics using 1,2,3,4-butane tetracarboxylic acid with two catalysts, cyanamide and N,N'-dicyclohexylcarbodiimide [13]. They reported that esterification between 1,2,3,4-butane tetracarboxylic acid, ethylcellulose microcapsules and hydroxyl groups of cellulose can occur simultaneously. Cotton fabric was impregnated by dispersion which consisted of microcapsules and a crosslinking agent. The crosslinking agent - modified dihydroxy ethylene urea reacts with the cellulose backbone via OH groups of both cellulose and dihydroxy ethylene urea in the acid catalysis. During the condensation reaction between cellulose and dihydroxy ethylene urea, a polycondensation reaction can occur between two of the dihydroxy ethylene urea. Thus a network is placed between cellulose macromolecules which consists of a condensation product of dihydroxy ethylene urea.

Figure 6 shows the microcapsules attached onto fibres, which may indicate that the attachment of ethylcellulose microcapsules onto cotton occurred by crosslinking reaction because of the absence of an additional coating layer.

Antifungal assessment

Figures 7 and ***8*** show antifungal test results achieved by using *T. rubrum* culture. The inhibition zone gradually decreased with an increase in washing cycles; however, antifungal properties of the fabrics applied remained up to 5 washing cycles in the case of both ketoconazole and terbinafine microcapsules. Hong & Park suggest that microcapsules which have diameter below 10 μm have resistance to washing [16]. As mentioned before, the diameters of microcapsules varied between 5 and 120 μm, thus the antifungal properties of microcapsule applied fabrics disappeared after 5 washing cycles.

Conclusions

Terbinafine and ketoconazole were microencapsulated by solvent evaporation using two types of ethylcellulose. DSC and XRD results indicated that terbinafine was completely homogeneously microencapsulated by ethylcellulose in spite of ketoconazole. The presence of both a wall and core material were observed by FTIR analysis. Morphologies of the microcapsules were observed by SEM. The microcapsules had spherical shapes; however, the diameters varied between 5 and 120 μm.

Microcapsules were successfully applied to cotton fabric using a dihydroxyethyleneurea based crosslinking agent. Antifungal properties of the cotton fabrics still remained up to 5 washing cycles against *T. rubrum* for both two antifungal agents.

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