PEG Hydrogel Encapsulation of Eosin Functionalized Hydrophobic Aerogels via Supercritical Fluid Routes

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Abstract: A novel method for the sequential formation of silica aerogel and hydrogel composite is described. The composite was synthesized by encapsulation of hydrophobic aerogels with PEG hydrogel via photoinitiated polymerization. Disks of aerogels were synthesized by the two step sol-gel method using tetraethylortosilicate (TEOS) as the silica precursor. HCl and NH_4OH were used as hydrolysis and condensation catalysts respectively. After the gels were aged in ethanol, the alcogels were then contacted with a solution of eosin-Y, a photoinitiator, dissolved in ethanol. The adsorption of eosin-Y on the surface of alcogel led to a reddish transparent composite of silica aerogel with eosin-Y. The alcogels with eosin-Y were subsequently dried by supercritical CO_2 at 313 K and 10.3 MPa. The surface of eosin functionalized silica aerogels was rendered hydrophobic using hexamethyldisilazane (HMDS) as the surface modification agent, and $scCO_2$ as solvent at 20.68 MPa and 333.2 K. The effects of HMDS concentration in the fluid phase and the reaction time were investigated and the contact angles were found to be 130° at different conditions. The hydrophobic aerogels were dipped into a PEG diacrylate prepolymer solution, and photopolymerization was carried out using visible light (514 nm). The hydrogel coating around the hydrophobic aerogel was only restricted to the external surface of the monolithic disks, since the water based prepolymer solution did not penetrate into the hydrophobic aerogel structure. BET surface area and pore size distribution measurements were done for both non-coated and coated aerogel. The data show data that both hydrogel encapsulation and eosin-Y loading did not affect the pore structure of the aerogel. The novel composite would especially be attractive for drug delivery, biomaterials or other situations where unique properties of both aerogels and hydrogels would be used.

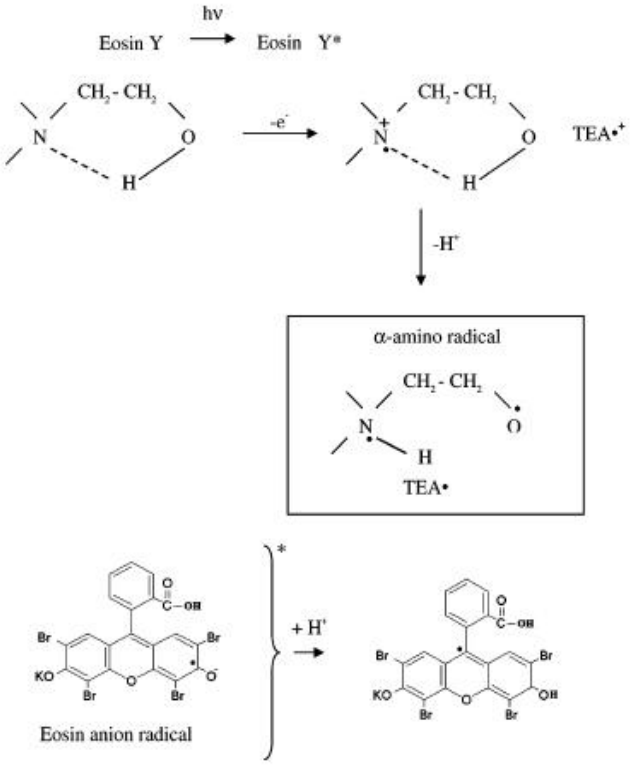
Keywords: PEG hydrogel, aerogel, photopolymerization, encapsulation, Supercritical CO_2

INTRODUCTION

Silica aerogels are sol-gel derived materials with high surface areas, high pore volumes and low densities [1]. They are produced by supercritical drying of the gels obtained via hydrolysis and condensation reactions of a silicon alkoxide precursor such as tetraethylorthosilicate (TEOS) in a solvent. The properties of silica aerogels can be tailored by manipulation of reaction conditions and reactant concentrations during their synthesis and they can be produced as monoliths in any shape [2]. As a result of such favorable properties, silica aerogels have been under investigation for use in many applications such as thermal insulation, dust collectors, glazing windows and particle detectors since their discovery in the 1930s [3,4]. Recent research efforts are being directed towards the development of composites of silica aerogels with a variety of organic and inorganic guest materials such as PEG [5], TiO_2 [6], and Pt [7]. Such composite materials are generally prepared either by addition of the guest material into the reaction mixture before [5,6] or after the gelation step. The latter is preferred in cases where the guest material can interfere with the polymerization chemistry resulting in undesirable structures or can convert into undesirable products. In addition to these methods, dry silica aerogels can also be impregnated with molecular precursors of the guest materials from the supercritical phase [7].

A high purity requirement for the end product in pharmaceutical industries is the driver behind efforts to develop supercritical CO_2 based processes. In recent years, use of supercritical CO_2 as a solvent or an anti-solvent in pharmaceutical processes has been receiving increased attention. Furthermore, supercritical fluid based processes are used to micronize drugs, to extract the drug components from a wide variety of substances and to encapsulate drugs in polymeric matrices. A relatively recent field which utilizes supercritical fluid in the pharmaceutics is development of aerogels for drug delivery. The tunable surface and pore properties of porous silica aerogels make them promising candidates for the development of novel drug delivery devices [8,9]. In such an approach, the drug components are dissolved in the supercritical fluid and are loaded into the porous aerogels. The method enables control of drug release rates. For example, a drug adsorbed on a hydrophilic silica aerogel can be released much faster than from its crystalline form [8]. The loading of the drug in the aerogel matrix can be controlled by the hydrophobicity of the aerogel surface which governs the adsorption isotherms.

Another important class of materials in pharmaceutics, biotechnology and medicine is hydrogels [10]. They have been prepared for use as drug carriers for the release of drugs, peptides and proteins due to their three dimensional, hydrophilic networks [11]. For example, polyethylene glycol (PEG) can be chemically crosslinked into hydrogels and used as reservoir devices for the controlled delivery of smaller molecular weight drugs. PEG hydrogel has received significant attention, especially because of its non-toxic, non-immunogenic and hydrophilic character. Previous studies investigated the kinetics of PEG hydrogel formation, and diffusion of various drugs and/or proteins from these PEG hydrogels [12,13,14]. Hydrogels can also be designed to be responsive to various properties such as pH, temperature, concentration of a metabolite or electric field which may be utilized for different applications.



In this work, a novel composite material was synthesized by encapsulation of hydrophobic aerogels within PEG hydrogel via surface initiated photopolymerization [15]. Immobilized initiator on the surface of the aerogel started the formation of PEG diacrylate hydrogels on the surface. Eosin was used as the photoinitiator because of its spectral properties that perfectly suit its use as an initiating system for an argon ion laser [16]. In the presence of an electron donor such as triethanolamine (TEA), which acts as a co-initiator, eosin initiates acrylate polymerization when irradiated [17,18]. It is generally accepted that polymerization occurs as a result of the formation of free radicals originating from triethanolamine. The photoinitiation mechanism, as described in figure 1, involves irradiation with green light (514 nm), as a result of which, eosin is excited

Figure 1: Schematic Representation of the Photoinitiation Process

to the triplet state. Subsequently, electron transfer from triethanolamine to the excited triplet state of the eosin dye produces an eosin anion radical and a triethanolamine cation radical. This is followed by rapid proton loss from the triethanolamine radical cation ($TEA^{\bullet+}$), resulting in a neutral α-amino radical ($TEA^{\bullet}$), which is generally assumed to initiate free-radical polymerization [16-19]. Simultaneously, the proton released from the triethanolamine cation radical is transferred to the eosin anion radical, yielding a neutral eosin radical.

MATERIALS AND METHODS

Materials. For the synthesis of silica aerogels, TEOS (98.0 %) and NH_4OH (2.0M in ethanol) were purchased from Aldrich, HCl was purchased from Riedel-de Haen (37%). Ethanol was obtained from Merck (99.9%). For the modification, HMDS were obtained from Alfa Aesar (98%). Carbon dioxide (99.998 %) was purchased from Messer Aligaz. For the hydrogel formation, Eosin Y (98%), 1-vinyl 2-pyrrolidinone (99+%), poly(ethylene glycol) diacrylate (PEG-DA) (MW ¼ 575 Da) were obtained from Aldrich. Triethanolamine (>99.5%) was obtained from Fluka. All chemicals were used as-received.

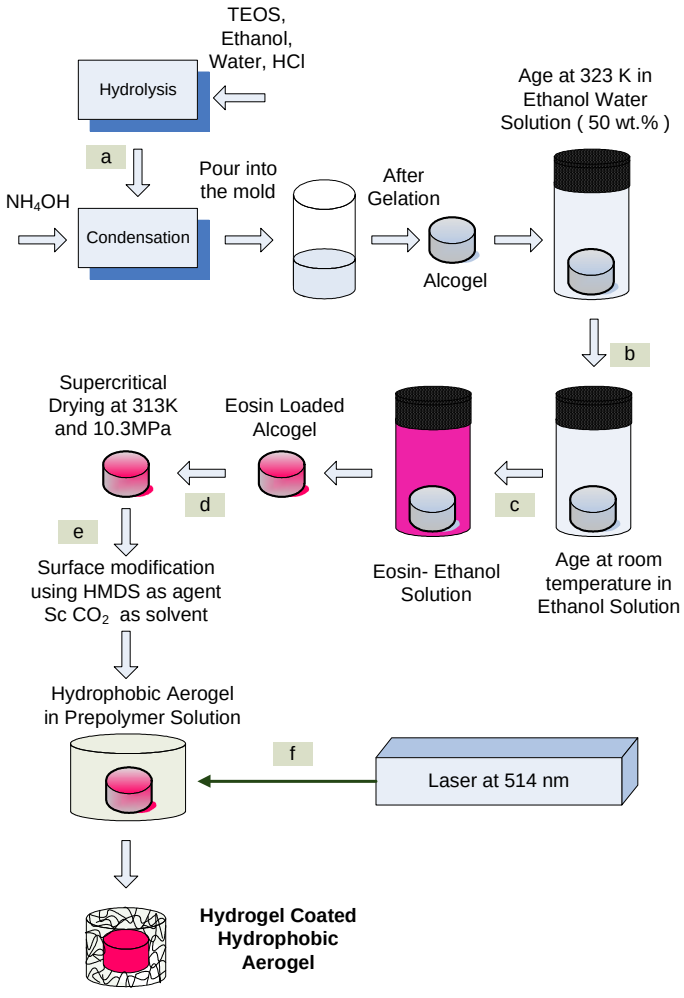


Figure 2: Schematic representation of the overall synthesis

Procedure of synthesis of silica aerogel and modifications. Disks of aerogels with a diameter of 13.7 mm and a height of 3.3 mm were synthesized by the two step sol-gel method using TEOS as the silica precursor [20]. HCl and NH_4OH were used as hydrolysis and condensation catalysts respectively (Fig. 2-a). The overall molar ratio of TEOS: Water: HCl: NH_4OH were kept constant at 1: 4: $2.44x10^{-3}$: $2x10^{-2}$ respectively. The alcogels were aged in ethanol-water (50 wt. %) solution at 323 K for 1 day and in ethanol solution at room temperature for 3 days (Fig. 2-b). The aim of the aging step was to improve the mechanical strength of the alcogels. After aging step, they were contacted with 2mM eosin-Y, a photoinitiator, in ethanol solution. The adsorption of eosin-Y on the surface of alcogel led to a reddish transparent composite of silica alcogel with eosin-Y (Fig. 2-c). The alcogels with eosin-Y were subsequently dried by supercritical CO_2 ($scCO_2$) at 313 K and 10.3 MPa (Fig. 2-d).

The hydrophilic and eosin functionalized aerogel formed in steps a through e, was rendered hydrophobic using supercritical fluid deposition technique. Hexamethyldisilazane (HMDS) was used as the surface modification agent, and $scCO_2$ as solvent at 20.68 MPa and 333.2 K (Fig. 2-e). By replacing the hydrogen atoms in the surface silanol groups by a hydrolytically

stable organofunctional group (e.g. Si-$(CH_3)_3$, hydrophobic aerogels were obtained. Finally, eosin loaded hydrophobic aerogels were immersed in PEG-diacrylate prepolymer solution and photopolymerization was carried out using visible light (514 nm) for 3 min for each surface of the aerogels (Fig. 2-f). The hydrogel precursor was prepared with concentrations of 225 mM triethanolamine, 25% (w/w) PEG diacrylate (MW = 575 Da), and 37mM 1-vinyl-2-pyrrolidinone (NVP). The solution was adjusted to pH 8 using HCl. Precursor solutions were filter sterilized using a 0.2 μm syringe Teflon filter. This step resulted in the formation of a crosslinked thin PEG hydrogel coating through surface-initiated polymerization around the hydrophobic aerogels.

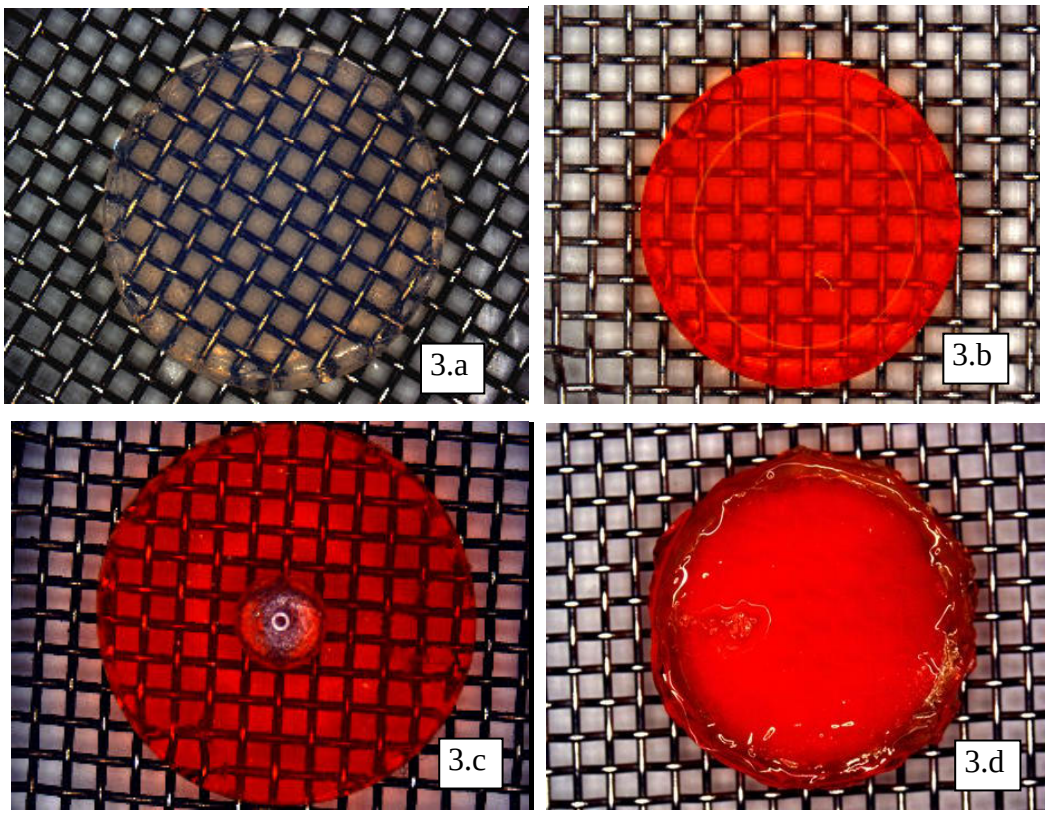
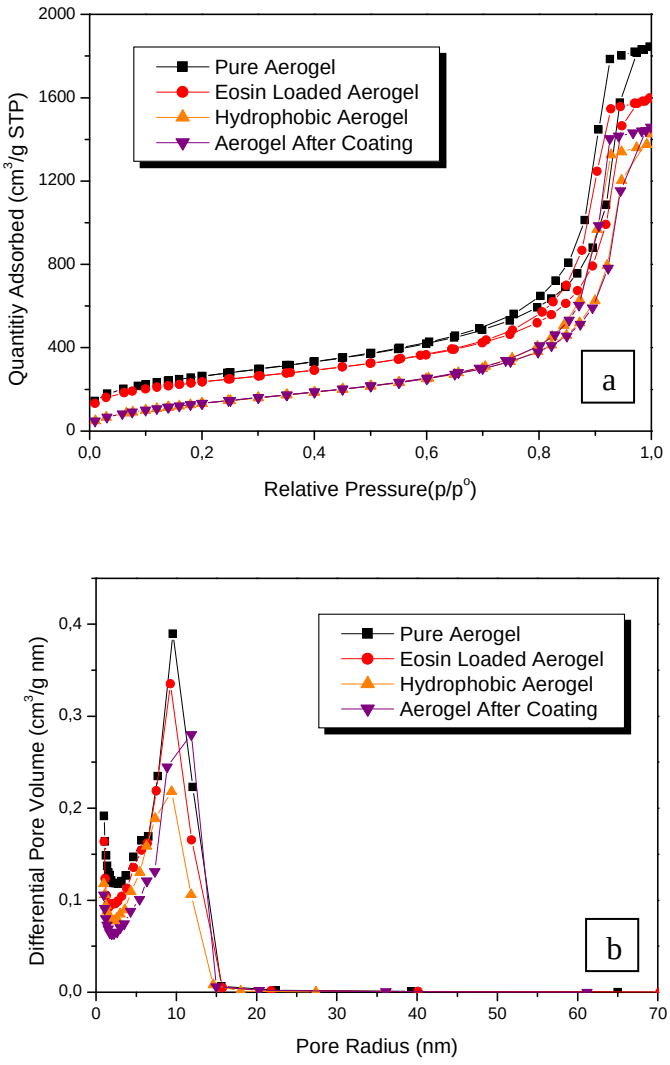


Figure 3: a Image of the pure aerogel, b Image of the Eosin doped hydrophilic aerogel, c Image of water droplet on the Eosin doped hydrophobic aerogel, d Image of the hydrogel coated hydrophobic aerogel.

RESULTS

It is observed from Figures 3-a and 3-b that the colorless transparent aerogel obtained a red color due to the presence of eosin within the aerogel structure. The figure also shows that eosin molecules were homogeneously distributed throughout the aerogel. After surface modification step, hydrophobicity of the aerogel was verified by placing a water droplet and measuring the contact angle on the surface of the aerogel (Fig. 3-c). The contact angle for the eosin modified hydrophobic aerogel was found to be 130^o. Figure 3-d shows the image of a PEG hydrogel coated eosin functionalized hydrophobic aerogel. The thickness of the hydrogel coating was approximately 0.3 mm.

The effects of the eosin loading and the surface modification step on the pore structure of the aerogel were investigated with the nitrogen adsorption analysis by Micromeritics ASAP 2020 surface analyzer. As seen in Table 1, the presence of eosin on the aerogel surface caused the BET surface area to decrease slightly with no appreciable changes in the average pore diameter. Further modification of the eosin functionalized aerogel surface with HMDS



decreased the cumulative pore volume, surface area and also increased the average pore size slightly. This can perhaps be attributed to the presence of some bottleneck type pores which are blocked by Si-$(CH_3)_3$ groups. The adsorption isotherms and pore size distributions of modified aerogels are compared in Figures 4-a and 4-b. All samples exhibited similar pore size distribution and type H1 isotherm which indicates that the materials consist of compacts agglomerates of approximately uniform spheres of silica and such a network is not disrupted by eosin loading, surface modification, and PEG hydrogel coating.

BET surface area and pore size distribution measurements were carried out for both non-coated and coated aerogels. The data showed that the surface area of the hydrophobic aerogel did not change after encapsulation with PEG hydrogel. Also, the isotherms and pore distributions of the two samples were nearly identical which indicate that the hydrogel coating was only restricted to the external surface of the monolithic disks and the water based prepolymer solution did not diffuse into the hydrophobic aerogel structure.

Figure 4: a Effect of eosin loading and surface modification on nitrogen adsorption**,** b Effect of eosin loading and surface modification on pore size distribution

Table 1: Properties of Aerogel Composites After Each Step in Synthesis

	BET Surface Area	BJH Desorption Cumulative Pore Volume	BJH Desorption Average Pore Radius
Pure Aerogel	926 m^2/g	2.9 cm^3/g	5.9 nm
Eosin Loaded Aerogel	820 m^2/g	2.5 cm^3/g	6.0 nm
After Surface Modification	528 m^2/g	2.1 cm^3/g	6.4 nm
After Hydrogel Coating	529 m^2/g	2.2 cm^3/g	6.7 nm

CONCLUSION

In summary, we developed a technique to synthesize a novel composite of hydrophobic aerogel and hydrogel, which was formed as a result of encapsulation of hydrophobic aerogel within PEG hydrogel via surface initiated photopolymerization. The results showed that the hydrogel encapsulation did not alter the porous structure of the aerogel. We think that this new composite will have an important role in pharmaceutics due to its unique structure which may allow the loading of two different drugs and sequential drug release profiles. Due to the bilayer structure of the composite, the release sequence of the drugs can also be adjusted such that hydrophilic drug located in the outer layer will dissolve first, and hydrophobic drug loaded within the hydrophobic aerogel will release subsequently. It is also possible to design a degradable PEG hydrogel layer, such that the network structure can be broken down through biological processes such as enzymatic digestion or as a result of change in pH [21] which may enhance the release of the drug loaded within the aerogel. The novel composite would especially be attractive for drug delivery, biomaterials or other situations where combinations of unique properties of both aerogels and hydrogels would be beneficial

Acknowledgments This study was supported by grants from the College of Engineering at Koç University in Turkey, the Turkish Academy of Sciences-L'Oreal Young Women in Science 2009 Award to Seda Kızılel and TUBITAK grant no.107M326.

REFERENCES :

[1] STOLARSKI, M., WALENDZIEWSKI, J., PIANK, M.S.B., Applied Cat. A., Vol. 177, **1999**, p. 139
[2] DORCHEH, A.S., ABBASI, M.H., J. Materials Processing Tech., Vol. 199, **2008,** p. 10
[3] HRUBESH, L.W., J. Non-Cryst. Sol., Vol. 225, **1998**, p. 335
[4] SCHMIDT, M., SCHWERTFEGER, F., J. Non-Cryst. Sol., Vol. 225, **1998**, p. 364
[5] MARTIN, J., HOSTICKA, B., LATTIMER, C., NORRIS, P.M., J. Non-Cryst. Sol., Vol. 285, **2001**, p. 222
[6] AMLOUK, A., EL MIR, L., KRAIEM, S., Alaya, S., J. Phys. Chem. Solids, Vol. 67, **2006**, p. 1464
[7] ERKEY, C., J. Supercrit. Fluids, Vol. 47, **2009**, p. 517
[8] SIMIRNOVA, I., MAMIC, J., ARLT, W., Langmuir, Vol. 19, **2003**, p. 8521
[9] GORLE, B.S.K., SMIRNOVA, I., MCHUGH, M.A., J. Supercrit. Fluids, Vol. 48, **2009**, p. 85
[10] PARK, H., PARK, K., In: OTTENBRITE RM, HUANG SJ, PARK K (ed) Hydrogels and Biodegradable Polymers for Bioapplications. ACS Symposium Series 627, American Chemical Society, Washington DC, **1996**
[11] PEPPAS, N.A., BURESA, P., LEOBANDUNGA, W., ICHIKAWAB, H., European Journal of Pharmaceutics and Biopharmaceutics, Vol. 50, **2000**, p. 27
[12] BROMBERG, L.J., Apply. Polym. Sci., Vol. 59, **1996**, p. 459
[13] LOWMAN, A.M., PEPPAS, N.A., Macromolecules, Vol. 30, **1997**, p. 4959
[14] KIZILEL, S., PEREZ-LUNA, V.H., TEYMOUR, F., Macromol. Theory Simul., Vol. 15, **2006**, p. 686
[15] KIZILEL, S., Langmuir, Vol. 20, **2004**, p. 8652
[16] VALDES-AGUILERA, O., PATHAK, C. P., SHI, J., WATSON, D., NECKERS, D. C., Macromolecules, Vol. 25, **1992**, p. 541
[17] ZAKRZEWSKI, A., NECKERS, D. C., Tetrahedron, Vol. 43, **1987**, p. 4507
[18] NECKERS, D. C., RAGHUVEER, K. S., VALDES-AGUILERA, O., Polym.Mater. Sci. Eng. Vol. 60, **1989**, p. 15
[19] NECKERS, D. C., HASSOON, S., KLIMTCHUK, E. J., Photochem.Photobiol., Vol. 95, **1996**, p. 33
[20] BRINKER, C.J., KEEFER, K.D., SCHAEFER, D.W., ACHLEY, C.S., J. Non-Cryst. Solids, Vol. 48, **1982**, p. 47
[21] RATNER, B.D., Biomaterials Science: An introduction to Materials in Medicine. Elsevier Academic pres, Amsterdam, **2004**