Practical aspects related to application of chitin and its derivatives in wound management

Karolina SKOŁUCKA-SZARY*, Piotr RIESKE, Sylwester PIASKOWSKI – Department of Research and Development, Celther Polska Sp. z o.o., Zakroczym, Poland

Please cite as: CHEMIK 2016, **70**, 2, 89–98

Introduction

Chitin (from the Greek word *chiton* – covering) is the second most widespread natural polysaccharide after cellulose. It was first isolated from fungi in 1811 by H. Braconnot [1], and its chemical structure was described for the first time in the doctoral dissertation of a Swiss researcher A. Hofmann in 1930 [2].

Chitin is a linear polysaccharide consists of 2-(acetylamino)-2-deoxy-D-glucose monomers linked with β-glycosidic bonds at 1 and 4 positions. Chemical structure of chitin differs from that of cellulose due to presence of an acetylamino group $–NHCOCH_3$ (at 2 position of N-acetylglucosamine unit) instead of one hydroxyl group [3]. The annual worldwide biosynthesis of chitin is estimated at 10^{10} to 10^{12} tons [4]. Chitin is a component of the cell walls of fungi [5], exoskeletons of arthropods (crustaceans, insects and arachnids) [6–8]; it can be also found in sponges [6] and anthozoans [9]. Chitin used in laboratory research and for industrial purposes is obtained primarily from marine invertebrates, such as crabs, shrimps, lobsters and krill. The process of chitin extraction is not complex but it is time consuming. It consists of grinding of crustacean exoskeletons, removal of $CaCO_3$ (usually with concentrated HCl) and protein (with $NaOH_{aq}$.), and finally decolorization [10–12]. Specific conditions for chitin extraction are adjusted for its biological source.

In recent years, it is observed a growing scientific attention to chitin. The search in the PubMed database, which contains medical and biological articles published in English, produced more than 19 thousand records related to chitin [13]. The first research paper about chitin, authored by S. Morgulis, was published in *Science* as early as in 1916 [14].

Many previous studies showed that chitin does not exert a cytotoxic effect *in vitro*. It is physiologically inert and biodegradable. It has antibacterial properties and shows affinity to proteins [15]. Due to its specific physicochemical properties, processing of chitin is difficult, and therefore this biopolymer is rarely used for industrial purposes. Usually, chitin is processed into forms of gels, membranes, fibers, polymer films [15], or as a component of polymer blends [16]. Chitin is used in chromatography, food industry (immobilization of enzymes), manufacturing of biosensors and cosmetics, as well as for processing of industrial pollutants (water treatment) [15]. However, in recent years the most attention was focused on its biomedical applications. It is used especially for wound dressing materials (active dressings) [17], active compounds delivery systems (medications and growth factors), in tissue engineering (cellular scaffolds, primarily in orthopedics) [18] and in regenerative medicine (differentiation of stem cells) [19].

Many previous experiments and clinical trials showed that chitin and its chemical modifications are promising biomaterials that may constitute a breakthrough in wound product industry. It was proved that chitin is able to accelerate wound healing due to the beneficial effects it exerts on various processes, such as angiogenesis, granulation, epithelization and scar formation [20]. All these processes play a key role in physiological wound healing [21]. Biodegradation of chitin within the wound environment results in a release of its oligomers and monomers [22]. Chitin activates macrophages, stimulates fibroblasts proliferation and influences processes of vascularization within the wound [23]. Those properties distinguish chitin from an array of available natural and synthetic polymers used in wound dressing materials.

The problem of poorly healing wounds affects millions of patients worldwide and can be potentially solved by the application of dressings containing chitin and its derivatives. According to literature, chronic wounds occur in 1–2% of population in developed countries [24, 25] and represent not only a serious therapeutic challenge (variable etiology, chronic inflammation, dynamic character of the process which is modulated by both systemic and local factors, the long-term and multidirectional treatment), but also a huge economic burden. The management of chronic wounds is estimated to contribute to ca. 2% of global healthcare costs in Europe [24].

Limitations of chitin processing and its chemical modifications

Chitin has a distinct crystalline structure; depending on its source, three amorphous forms of chitin, α-, β- and γ-chitin (rare derivative of α-chitin) can be found [26, 27]. α-chitin is the most commonly found natural chitin, present in fungi, exoskeletons of crustaceans, krill and insects [15]. Less prevalent β-chitin is primarily extracted from squids [28].

Polymeric chains in amorphous α- and β-chitin forms are organized in many layers linked with numerous hydrogen bonds between C-O···NH groups. α-chitin is additionally strengthened by intermolecular hydrogen bonds that link layers of its crystalline structure [15, 29]. Different crystalline structure of those two amorphous forms directly determines the possibilities of their further processing. α-chitin is soluble in only few solvents, such as aqueous solution of thiourea, aqueous alkaline solution of urea [31], 5%LiCl/DMAC system [32–33], some ionic liquids, hexafluoroacetone, hexafluoro-2-propanol [34], methanesulfonic acid [35] and other aggressive organic solvents. On the other hand, β-chitin swells in water (forming slurry) and it is soluble in formic acid [36]. Due to its organized crystalline structure, chitin is poorly soluble in commonly used organic solvents which limits its medical application.

Moreover, the unique biological properties and constantly renewable resources of chitin inspire the scientists for new research on its chemical modifications. The start of extensive research on chitin dates back to 1970s (mostly in Poland, Italy and Japan) and continues to present days. Pioneers of research on chitin and its derivatives were S. Tokura, L. Szosland and R. A. A. Muzzarelli. The aim of current studies is to obtain novel biocompatible derivatives of chitin being eligible for further processing, and to form their more complex spatial arrangements [37–38]. Practical application of chitin (due to economic constrains, primarily α-chitin) is limited mainly to its esters and amino derivatives.

Corresponding author:
Karolina SKOŁUCKA-SZARY – M.Sc., e-mail: karolina.skolucka@celther.com

The majority of methods used for chemical modifications of chitin are based on reactivity of its three functional groups: two hydroxyl groups (at 6 and 3 position) and N-acetylamino group (at 2 position). Partial deacetylation of chitin (hydrolysis of amide groups to strongly alkaline amino groups) results in formation of the best known and most extensively studied derivative, chitosan (being a subject of more than 16 thousand PubMed-recorded studies) [39]. Chitosan is a biocompatible, biodegradable, hydrophilic polymer which is fully soluble in diluted organic acids' aqueous solutions [15]. The quality of chitosan is directly linked to its biological source and conditions of deacetylation, which is reflected by its degree of deacetylation, molecular weight, susceptibility to biodegradation and physicochemical properties. Present research focuses on its chemical (alkylation, hydroxyalkylation, acylation, phosphorylation, sulfonation and etc.) [40] and physicochemical modifications (synthesis of microcrystalline chitosan) [41].

Another way for chemical modification of chitin is esterification of its hydroxyl groups with short-chain fatty acids [42]. This modification resulted in formation of dibutyryl chitin (DBC), the best known hydrophobic diester of chitin, soluble in common organic solvents, such as acetone, ethanol, methanol, DMF, DMSO (and contrary to chitosan, insoluble in aqueous systems) [38]. Esterification of chitin with butyric anhydride in the presence of an acidic catalyst results in formation of DBC with a desirable molecular weight, which directly determines possibilities of its further processing [38, 43] (especially, electrospinning [44] and leaching, Photo 1). DBC has film- and fiber-forming properties [45]. The desire to improve mechanical and biological properties of DBC leaded to the development of two new biocompatible chitin diesters: chitin dipentanoate and chitin dihexanoate (Department of Research and Development Celther Polska Sp. z o. o.) [37–38]. Chemical structures of chitin and its major derivatives are presented on Figure 1.

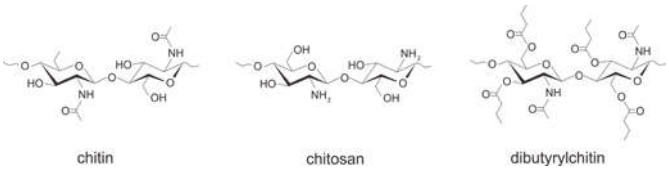

Fig. 1. Chemical structures of chitin and its derivatives

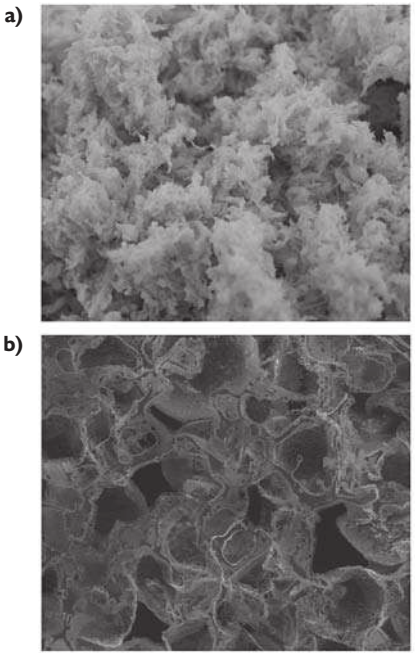

Photo 1. a) DBC fibers b) SEM image of a porous DBC scaffold (Celther Polska Sp. z o.o.)

Clinical data on chitin derivatives

Many years of scientific and clinical research showed that the deacetylated form of chitin may constitute a breakthrough, not only in the production of active wound dressing materials, but also in emergency medicine (hemostatic dressings). The unique features of chitosan include its ability to activate macrophages, stimulate of fibroblast proliferation, cytokines and type IV collagen synthesis, uptake of growth factors, promote of angiogenesis, antibacterial and hemostatic properties [23]. Chitosan was shown to promote wound granulation and epithelization, as well as limitation of scar formation [46]. Similar to chitin, chitosan is susceptible to enzymatic biodegradation, which results in formation of biologically active oligosaccharides [23]. Another unique feature of chitosan is its cationic character [47]. Positively-charged molecules of chitosan interact with negatively-charged erythrocytes and thrombocytes activating extrinsic clotting cascade and providing effective bleeding control [48]. Moreover, chitosan may serve as a carrier for some therapeutic agents (DNA plasmids [49], siRNA [50], nanosilver particles [51]), which further enhances its beneficial effects on the healing process.

The first Polish chitosan-based wound dressing is TROMBOGUARD (Tricomed SA), awarded with a gold medal during the Poznan International Fair in 2011. This is an innovative three-layer hemostatic dressing, with active layer containing chitosan, sodium/calcium alginate and silver salt [52]. It is designated for dressing of trauma, surgical and gunshot wounds, as well as a component of home first-aid kits. The dressing has antibacterial properties and provides effective bleeding control within ca. 3 minutes post-application. It may stay on the wound for up to 24 hours, and previous research confirmed its 100% effectiveness in achieving rapid hemostasis [52]. Originally it was designed for military purposes and now it is available for the general public.

The most recent chitosan-based dressing available in the European market is KytoCel® (2014). This is a hemostatic, antibacterial fibrous wound dressing containing acylated form of chitosan. It can be used both as a hemostatic dressing and as an absorbent dressing eliminating excessive exudate from the wound (due to its gelling properties). Furthermore, it plays a protective role and prevents maceration of the wound edges [53]. Its efficacy and safety were confirmed in the clinical trial including a group of patients with epidermolysis bullosa [54].

Another therapeutically promising derivative of chitin is DBC. Many previous studies, conducted both in Poland and abroad, showed that DBC is a modern biodegradable biomaterial that exerts beneficial effects on wound healing [38, 55–58]. *In vivo* studies demonstrated that DBC-based dressings exert beneficial effects on granulation (as shown by increased level of glycosaminoglycans within the wound), promote collagen crosslinking (formation of more durable tissue) [57] and protect the wound against excessive loss of moisture (providing optimally humid environment) [59]. DBC-based fibrous dressings are biodegradable [59] and do not need to be changed. However, DBC-based dressings are still not available in the market.

Commercially available wound dressings containing chitin and its derivatives

Wound dressings containing chitin and its derivatives show complete biocompatibility (lack of cytotoxic, irritating and allergenic effects). The wound dressings can be completely made of chitin and its derivatives or used as active compounds. Those dressings are available in various forms: as powder, non-woven, sponge or gel, and play variable functions (active wound dressing, hemostatic agent) [60]. The first chitin-based wound dressing was released in Japan (Beschitin®, 1982 [61]). Nowadays, a small part of wound dressings listed in Table 1 are also available in Europe, including Poland.

Table 1

Examples of wound dressings containing chitin and its derivatives, available commercially worldwide [16, 23, 52–53, 60–63]

Component	Form and mechanism of action	Trade name and manufacturer
Chitin	- non-woven (microfibers), - bleeding control, - CE-certified and FDA-approved.	Syvek-Patch® (Marine Polymer Technologies)
Chitin	- non-woven, - promotes granulation, - prevents scar formation.	Beschitin® (Unitika)
Chitin	- sponge, - promotes granulation, - prevents scar formation, - management of trauma wounds with massive loss of tissue.	ChitiPack S® (Eisai Co.)
Chitosan acetate	- fibrous form, - promotes skin regeneration.	Chitopack C® (Eisai Co.)
Modified chitosan	- foam, - bleeding control, - CE-certified.	Excel Arrest® (Hemostasis LLC Co.)
Lyophilized chitosan acetate	- bleeding control, - FDA-approved.	Hemcon Bandage® (Hemcon)
Soluble chitosan salt	- bleeding control.	Chito-Seal® Topical Hemostasis Pad (Abbott Vascular Devices)
Chitosan	- rapidly polymerizing gel, - bleeding control.	ChitoSeal™ (Luna Innovations Inc.)
Chitosan-coated silica fibers with PE	- bleeding control, - highly absorptive, - CE-certified and FDA-approved.	Traumastat® (Ore-Medix)
Chitosan with sodium/calcium alginate and Ag (active layer)	- bleeding control, - prevents secondary infection of the wound, - CE-certified.	Tromboguard® (Tricomed)
Microcrystalline chitosan and placental tissue	- biological dressing, - sponge, - inhibition of pathogen growth, - absorptive.	Choriochit (Regional Blood Donation and Blood Treatment Center)
Acylated form of chitosan	- fibrous form, - good absorptive properties, - bleeding control.	KytoCel® (Aspen Medical)
Composition of collagen and chitosan	- absorptive foam, - provides moisture environment within the wound, - CE-certified.	Vulnosorb® (Tesla-Pharma)
Chitosan powder with iodine	- secondary dressing, -disinfecting and cleaning properties, - CE-certified.	Chitodine® (IMS)
Soluble chitosan salt	- fibrous form, - bleeding control (vascular surgeries), - antibacterial, - CE-certified and FDA-approved.	Clo-Sur™ P.A.D, Clo-Sur™ PLUS P.A.D (Scion Cardio-Vascular)

Registration requirements for medical devices based on chitin and its derivatives

European medical device market develops extensively and it is opened for innovative products. Nevertheless, practical applications of chitin and its derivatives in medical products is still limited. This is a consequence of the restrictive legislation (The Act of 20th May 2010 on Medical Devices [64] with its amendment- Act of 11th September 2015 [65], Council Directive 93/42/EEC of 14th June 1993 concerning medical devices, a number of harmonized standards) that oblige manufacturers to conduct complex, long-term (lasting years) and costly trials. Wound dressings containing chitin and its derivatives are considered as products of animal origin and classified as class III medical devices (Council Directive 93/42/EEC, rule no. 17) [66]. Due to the highest medical device's classification, chitin-based products require ISO 13485 certification and the following standards: PN-EN ISO 10993:2010 (Biological evaluation of medical devices, in particular parts no. 1, 3, 5, 9 , 10 and 12–18), PN-EN ISO 22442:2008 (Medical devices utilizing animal tissues and their derivatives) and subjected to clinical trials. High investment in certification and standardization, as well as a likelihood of failure in clinical trials, may explain why chitin and its derivatives are still relatively less popular in Europe, even owing their established clinical effectiveness.

Conclusions

Many previous studies confirmed that chitin exerts beneficial effects on wound healing. However, due to constraints in its industrial processing, practical application of chitin is limited primarily to its deacetylated form. Nevertheless, a large body of evidence from studies conducted in Celther Polska Sp. z o.o. suggests that not only dibutyryl chitin, but also other innovative chitin diesters (chitin dipentanoate and chitin dihexanoate) have a chance to be commercially available in medical devices or used in the regenerative medicine.

Chitin and its derivatives are used primarily as active wound-dressing materials and modern bleeding control products. Although wound dressing materials based on chitin and its derivatives are more innovative than an array of competitive products, they are still relatively less popular in the European market.

Analysis of available resources implies that aside from restrictive regulatory legislation, application of these biopolymers in medical devices may be also limited by other critical factors, such as chemical (e.g. potential traces of proteins) and microbiological purity, and repeatable quality (degree of deacetylation, range of molecular weights, etc.) of raw materials used for each batch.

Poland is one of the leaders in research on chitin. There is a number of studies and R&D projects (including some being in their commercialization phase) in progress, which is reflected by many Polish patent applications, scientific publications and first commercialized medical products based on chitin and its derivatives.

Literature

1. Khoushab F., Yamabhai M.: Chitin Research Revised. Marine Drugs 2010, **8**, 7, 1988–2012.
2. Thakur V. K., Thakur M. K.: Eco- friendly Polymer Nanocomposites: Chemistry and Applications. Springer 2015, 51.
3. M. H. Struszczyk: Chitin and Chitosan Part I: Properties and Production. Polimery 2002, **47**, 5, 316–325.
4. Percot A., Viton C., Domard A.: Optimization of chitin extraction from shrimp shells. Biomacromolecules 2003, **4**, 1, 12–8.
5. Lenardon M. D., Munro C. A., Gow N. A.: Chitin synthesis and fungal pathogenesis. Current Opinion in Microbiology 2010, **13**, 4, 416–423.
6. Ehrlich H.: Chitin and Collagen as Universal and Alternative Templates in Biomineralization. International Geology Review 2010, **52**, 7–8, 661–699.
7. Merzendorfer H., Zimoch L.: Chitin metabolism in insects: structure, function and regulation of chitin synthases and chitinases. The Journal of Experimental Biology 2003, **206**, 24, 4393–4412.
8. Kaya M., Seyyar O., Baran T., Erdoğan S, Kar M.: A Physicochemical Characterization of the Fully Acetylated Chitin Structure Isolated from Two Spider Species. International Journal of Biological Macromolecules 2014, **65**, 553–558.
9. Juárez-de la Rosa B. A., Quintana P., Ardisson P. L., Yáñez-Limón J. M., Alvarado-Gil J. J.: Effects of thermal treatments on the structure of two black coral species chitinous exoskeleton. Journal of Material Science 2012, **47**, 2, 990–998.
10. Hayes M., Carney B., Slater J., Brück W: Mining marine shellfish wastes for bioactive molecules: chitin and chitosan- Part A: extraction methods. Biotechnology Journal 2008, **3**, 7, 871–877.
11. Younes I., Rinaudo M.: Chitin and Chitosan Preparation from Marine Sources. Structure, Properties and Applications. Marine Drugs 2015, **13**, 1133–1174.

12. Arbia W., Arbia L., Adour L., Amrane A.: Chitin Extraction from Crustacean Shells Using Biological Methods- A Review. Food Technology and Biotechnology 2013, **51**, 1, 12–25.
13. "http://www.ncbi.nlm.nih.gov/pubmed/?term=chitin" 30.01.2016.
14. "http://www.ncbi.nlm.nih.gov/pubmed/17743391" 30.01.2016.
15. Rinaudo M.: Chitin and chitosan: Properties and applications. Progress in Polymer Science 2006, **31**, 7, 603–632.
16. Yu L.: Biodegradable Polymer Blends and Composites from Renewable Resources. John Wiley & Sons 2009, 136.
17. Jayakumar R., Prabaharan M., Sudheesh Kumar P. T., Nair S. V., Tamura H.: Biomaterials based on chitin and chitosan in wound dressing applications. Biotechnology Advances 2011, **29**, 3, 322–337.
18. Anitha A., Sowmya S., Sudheesh Kumar P. T., Deepthi S., Chennazhi K. P., Ehrlich H.: Chitin and chitosan in selected biomedical applications. Progress in Polymer Science 2014, **39**, 9, 1644–1667.
19. Wan A. C. A., Tai B. C. U.: CHITIN- A promising biomaterial for tissue engineering and stem cell technologies. Biotechnology Advances 2013, **31**, 1776–1785.
20. Azuma K., Izumi R., Osaki T., Ifuku S., Morimoto M., Saimoto H., Minami S., Okamoto Y.: Chitin, Chitosan, and Its Derivatives for Wound Healing: Old and New Materials. Journal of Functional Biomaterials 2015, **6**,1, 104–142.
21. Skórkowska-Telichowska K., Bugajska- Prusak A., Pluciński P., Rybak Z., Szopa J.: Fizjologia i patologia przewlekle niegojących się owrzodzeń oraz sposoby ich miejscowego leczenia w świetle współczesnej wiedzy medycznej. Dermatologia Praktyczna 2009, **5**, 15–29.
22. Muzzarelli R. A. A.: Human enzymatic activities related to the therapeutic administration of chitin derivatives. CMLS Cellular and Molecular Life Sciences 1997, **53**, 131–140.
23. Muzzarelli R. A. A.: Chitins and chitosan for the repair of wound skin, nerve, cartilage and bone. Carbohydrate Polymers 2009, **76**, 2, 167–182.
24. Menke N. B., Ward K. R., Witten T. M., Bonchev D. G., Diegelmann R. F.: Impaired wound healing. Clinics in Dermatology 2007, **25**, 1, 19–25.
25. Gottrup F.: A specialized wound- healing center concept: importance of multidisciplinary department structure and surgical treatment facilities in the treatment of chronic wounds. The American Journal of Surgery 2004, **187**, 38S-43S.
26. Rudall K. M., Kenchington W.: The chitin system. Biological Reviews 1973, **48**, 4, 597–633.
27. Rudall K. M.: Chitin and its association with other molecules. Journal of Polymer Science Part C: Polymer Symposia 1969, **28**, 1, 83–102.
28. Lavall R. L., Assis O. B., Campana-Filho S. P.: Beta-chitin from the pens of Loligo sp.: extraction and characterization. Bioresource Technology 2007, **98**, 13, 2465- 2472.
29. Draczyński Z.: Kopoliester Butyrylo-Acetylowy Chityny jako nowy aktywny składnik nanokompozytów polimerowo-włóknistych, Zeszyty naukowe Politechnika Łódzka 2013, Nr. 1159.
30. Hu X., Du Y., Tang Y., Wang Q., Feng T., Yang J. et al.: Solubility and property of chitin in NaOH/ urea aqueous solution. Carbohydrate Polymers 2007, **70**, 4, 451–458.
31. Chen B., Sun K., Zhang K.: Rheological properties of chitin/ lithium chloride, N,N-dimethyl acetamide solutions. Carbohydrate Polymers 2004, **58**, 1, 65–69.
32. Terbojevich M., Carraro C., Cosani A.: Solution studies of the chitin-lithium chloride-N,N-dimethylacetamide system. Carbohydrate Research 1988, **180**, 1, 73–86.
33. Rutherford F. A., Austin P. R.: Muzzarelli R. A. A., Pariser E. R., edit.: Proceedings of the First International Conference on Chitin/Chitosan. MIT Sea Grant Report MITSG 1978, **78–8**, 182–191.
34. Pillai C. K. S., Paul W., Sharma C. P.: Chitin and chitosan polymers: Chemistry, solubility and fiber formation. Progress in Polymer Science 2009, **34**, 7, 641–678.
35. Kaifu K., Nishi N., Komai T., Tokura S., Somorin O.: Studies on chitin. V. formylation, propionylation and butyrylation of chitin. Polymer Journal 1981, **13**, 241–245.
36. Kurita K.: Controlled functionalization of the polysaccharide chitin, Progress in Polymer Science 2001, **26**, 9, 1921–1971.
37. Skołucka-Szary K., Ramięga A., Piaskowska W., Janicki B., Grala M., Rieske P., Stoczyńska-Fidelus E., Piaskowski S.: Chitin dipentanoate as the new technologically usable biomaterial. Materials Science and Engineering: C Materials for Biological Applications 2015, **55**, 50- 60.
38. Skołucka-Szary K., Ramięga A., Piaskowska W., Janicki B., Grala M., Rieske P., Bartczak Z., Piaskowski S.: Synthesis and physicochemical characterization of chitin dihexanoate- A new biocompatible chitin derivative- In comparison to chitin dibutyrate. Materials Science and Engineering: C Materials for Biological Applications 2016, **60**, 489- 502.
39. "http://www.ncbi.nlm.nih.gov/pubmed/?term=chitosan" 30.01.2016.
40. Mourya V. K., Inamdar N.: Chitosan-modifications and applications: Opportunities galore. Reactive and Functional Polymers 2008, **68**, 1013- 1051.
41. Struszczyk H., Kivekäs O.: Microcrystalline Chitosan- Some Areas of Application. British Polymer Journal 1990, **23**, 261.
42. Yang B. Y., Ding Q., Montgomery R.: Preparation and physical properties of chitin fatty esters. Carbohydrate Research 2009, **344**, 3, 336–342.
43. Szosland L.: Synthesis of highly substituted butyryl chitin in the presence of perchloric acid. Journal of Bioactive and Compatible Polymers, Journal of Bioactive and Compatible Polymers 1996, **11**, 1, 61–71.
44. Błasińska A., Krucińska I., Chrzanowski M.: Dibutyrylchitin nonwoven biomaterials manufactured using electrospinning method. FIBRES & TEXTILES in Eastern Europe 2004, **4**, 48, 51–55.
45. Szosland L., Stęplewski W.: Rheological characteristic of dibutyrylchitin semi-concentrated solutions and wet spinning of dibutyrylchitin fiber. Advances in Chitin Science 1998, **II**, 531–536.
46. Dai T., Tanaka M., Huang Y. Y., Hamblin M. R.: Chitosan preparations for wounds and burns: antimicrobial and wound healing effects. Expert Review of Anti-infective Therapy 2011, **9**, 7, 857–879.
47. Yang T. L.: Chitin- based Materials in Tissue Engineering: Applications in Soft Tissue and Epithelial Organ. International Journal of Molecular Sciences 2011, **12**, 3, 1936- 1963.
48. Cheung R. C. F., Ng T. B., Wong J. H., Chan W. Y.: Chitosan: An Update on Potential Biomedical and Pharmaceutical Applications. Marine Drugs 2015, **13**, 8, 5156–5186.
49. Guo R., Xu S., Ma L., Huang A., Gao C.: Enhanced angiogenesis of gene-activated dermal equivalent for treatment of full thickness incisional wounds in a porcine model. Biomaterials 2010, **31**, 7308–7320.
50. Liu X., Ma L., Liang J., Zhang B., Teng J., Gao C.: RNAi functionalized collagen-chitosan/silicone membranę bilayer dermal equivalent for full thickness skin regeneration with inhibited scarring. Biomaterials 2013, **34**, 2038–2048.
51. Lu S., Gao W., Gu H.Y.: Construction, application and biosafety of silver nanocrystalline chitosan wound dressing. Burns 2008, **34**, 623–628.
52. Kucharska M., Struszczyk M. H., Niekraszewicz A., Ciechańska D., Witczak E., Tarkowska S., Fortuniak K., Gulbas-Diaz A., Rogaczewska A., Płoszaj I., Pluta A., Gąsiorowski T.: Tromboguard® – first aid wound dressing. Progress on Chemistry and Application of Chitin and Its Derivatives 2011, **XVI**, 121–130.
53. "http://woundcare-today.com/products-pyramid/protease-modulators/kytocelr-gelling-fibre-dressing" 30.01.2016.
54. "http://www.aspenmedicaleurope.com/wp-content/uploads/2013/10/Denyer-J.-Gibson-E.-KytoCel…-in-Severe-EB-Wounds-UK-2014–550L10.14.pdf" 30.01.2016.
55. Chilarski A., Szosland L., Krucińska I., Kiekens P., Błasińska A., Schoukens G., Cisło R., Szumielewicz J.: Novel Dressing Materials Accelerating Wound Healing from Dibutyrylchitin. FIBRES & TEXTILES in Eastern Europe 2007, **15**, 4, 63, 77–81.
56. Muzzarelli A. A. R., Guerrieri M., Goteri G., Muzzarelli C., Armeni T., Ghiselli R., Cornelissen M.: The biocompatibility of dibutyryl chitin in the context of wound dressings. Biomaterials 2005, **26**, 5844- 5854.
57. Blasinska A., Drobnik J.: Effects of Nonwovens Mats of Di-O-butyrylchitin and Related Polymers on the Process of Wound Healing. Biomacromolecules 2008, **9**, 776-782.
58. Krucińska I., Komisarczyk A., Paluch D., Szymonowicz M., Zywicka B., Pielka S.: The impact of the dibutyrylchitin molar mass on the bioactive dressings used to treat soft tissue wounds. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2012, **100**, 1, 11–22.
59. Kiekens P., Szosland L., Krucińska I., Schoukens G., Błasińska A., Chilarski A., Kornobis E.: Novel dibutyrylchitin dressing materials stimulating wound healing. AUTEX 2006- NC State University- Conference Proceedings 2006.
60. Mazurek P., Kuliński S., Gosk J.: Możliwości wykorzystania chityny i chitozanu w leczeniu ran. Polimery w Medycynie 2013, **43**, 4, 297–302.
61. Inamdar N., Mourya V.: Chitosan and Low Molecular Weight Chitosan: Biological and Biomedical Applications, Advanced Biomaterials and Biodevices (ed. Tiwari A., Nordin A.N.). John Wiley & Sons 2014, 182-242.
62. Niekraszewicz A.: Chitosan Medical Dressings. FIBRES & TEXTILES in Eastern Europe 2005, **13**, 6 (54), 16–18.
63. "http://lunainc.com/wp-content/uploads/2014/04/Hemostatic-Agents-August-2013.pdf" 30.01.2016.
64. "http://isap.sejm.gov.pl/DetailsServlet?id=WDU20101070679" 30.01.2016.
65. "http://dziennikustaw.gov.pl/DU/2015/1918" 30.01.2016.
66. Struszczyk M. H., Struszczyk J. K.: Medical applications of chitin and its derivatives. Polish Chitin Society Monograph 2007, **XII**,139–147.

Acknowledgements

This paper was partially supported by Polish Agency for Enterprise Development, Grant No. POIG.01.04.00–10–020/10.

Professor Piotr RIESKE – Ph.D., D.Sc., graduated from Medical Analytics at the Medical University of Lodz, where he also received his Ph.D.. He took part in post-doctoral internship at the Thomas Jefferson University and Hahnemann University Hospital in Philadelphia, where he worked on differentiation of marrow stem cells and after moving to Temple University he was involved in differentiation of neural stem cells and reprogramming of fibroblasts toward pluripotent stem cells project. Since 2012, he has managed Department of Tumor Biology at Medical University of Lodz. In 2013, he was awarded full professorship. He was one of the founders of biotech company Celther Polska, where current, is CSO. Currently, he is engaged in cancer molecular biology research and in development of innovative anti-cancer therapies. During his long lasting experience, he participated in tens of biotechnological and medical product commercializations and he was Principal Investigator in several KBN, NCN, PARP grants and Polpharma Science Foundation grant. Prof. Rieske is an author of 58 scientific publications, 2 patents and several patent applications.

e-mail: piotr.rieske@celther.com, phone: +48 42 681 25 25

Sylwester PIASKOWSKI – Ph.D., graduated from Medical Diagnostics at the Medical University of Lodz, Poland, where he also received his Ph.D.. He was one of the founders of Celther Polska biotech company, where he is currently Director of Production. He works also in the Department of Tumor Biology, Medical University of Lodz. S. Piaskowski (Ph.D.) participated in tens of biotechnological and medical product commercializations and he was Principal Investigator in several KBN, NCN, PARP grants. S. Piaskowski (Ph.D.) is an author over 35 scientific publications, several patent applications and 2 patents.

e-mail: sylwester.piaskowski@celther.com, phone: +48 42 681 25 25

Karolina SKOŁUCKA-SZARY – M.Sc., graduated from Macrofaculty at the Faculty of Chemistry and Biomedical Engineering at the Faculty of Automatic Control, Electronics and Computer Science at the Silesian University of Technology. Since 2011, she has worked in Celther Polska as a chemist in the R&D project co-funded by the EU. Since 2014, she is a Ph.D. student in the Department of Tumor Biology at Medical University of Lodz. Her research interests include mainly the synthesis of modern polymeric biomaterials and design of innovative products applicable in the wound treatment. She is an author of 4 scientific publications and 2 patent applications.

e-mail: karolina.skolucka@celther.com, phone: +48 42 681 25 25

Aktualności z firm

News from the Companies

Dokończenie ze strony 93

INWESTYCJE

Grupa Azoty ZAK SA oddaje do użytku kolejne inwestycje za 45 mln zł

45 mln zł wynosi łączna wartość kolejnych ważnych inwestycji zrealizowanych w Grupie Azoty ZAK SA w obszarze produkcji nawozów i OXO.

Wśród zakończonych projektów znalazły się m. in.: część modernizacji ciągu amoniakalnego, zwiększenie zdolności produkcji roztworów mocznika oraz wytwarzanie pary dla instalacji OXO z odpadowych strumieni gazowych. 10 lutego br. Zarząd kędzierzyńskiej Spółki podsumował realizacje tych zadań inwestycyjnych, które pozwolą Spółce zwiększyć zdolności produkcyjne, obniżyć koszty wytwarzania oraz zmniejszyć wpływ na środowisko naturalne. Podsumowano także rok 2015 z rekordowym poziomem nakładów inwestycyjnych w wysokości ok. 260 mln zł.

– Inwestycje to fundament, na którym każda firma działająca w oparciu o myśl innowacyjną powinna budować swoją przyszłość. Stąd cieszą nas kolejne oddane zadania inwestycyjne, stanowiące dobry przykład takiego podejścia – w 2015 r. zrealizowaliśmy 93% środków zaplanowanych na inwestycje, co stanowi rekordowy wynik dla ZAK-u. W 2015 r. przeznaczyliśmy 263 mln zł na inwestycje, w bieżącym roku zaplanowana kwota jest jeszcze wyższa: 380 mln zł. Nasza spółka jest bardzo wspierana przez Zarząd Grupy Azoty i realizuje w ten sposób także Strategię całej Grupy do roku 2020 – mówi Adam Leszkiewicz, Prezes Zarządu Grupy Azoty ZAK SA.

Jedna z najważniejszych inwestycji w 2015 roku o budżecie przekraczającym 30 mln zł, to modernizacja ciągu amoniakalnego, w ramach której zrealizowano m.in wymianę wnętrza reaktora syntezy amoniaku, zainstalowano i uruchomiono nowy efektywniejszy układ skraplania na stokażu bezciśnieniowym oraz wybudowano instalację rozdziału purge gazu. Cały projekt przyczynia się do obniżenia kosztów produkcji oraz zwiększenia zdolności produkcyjnych amoniaku w procesie wytwarzania nawozów azotowych. Zapewnia to Spółce oszczędności prawie 2 mln zł rocznie. Zrealizowany projekt intensyfikacji produkcji roztworów mocznika obejmuje rozbudowę węzła magazynowania i załadunku roztworów mocznika. Zdolności produkcyjne NOXy® zwiększą się z 50 do 100 tys. t/r, a zdolności załadowcze wzrosną o 100%, co pozwoli pozyskać nowe grupy odbiorców i umocnić pozycję Grupy Azoty na rynku produktów PULNOx® oraz NOXy®. Wartość jednostkowa inwestycji to prawie 7 mln zł. Jest to też kolejna modelowa inwestycja w zakresie ochrony środowiska – instalacja jest zupełnie bezodpadowa i nieemisyjna.

Projekt wytwarzania pary dla instalacji OXO z wykorzystaniem odpadowych strumieni gazowych, kosztował Spółkę niemal 8 mln zł. W ramach zadania wybudowano układ dwóch wysokiej mocy generatorów parowych wraz z infrastrukturą towarzyszącą. Nowa kotłownia parowa z jednej strony optymalizuje koszty wytwarzania produktów OXO, z drugiej – obniża oddziaływanie na środowisko poprzez ograniczenie ilości spalanego węgla i emisji pyłów.

Działając na podstawie Strategii Grupy Azoty 2013–2020 i jej Operacjonalizacji, a także dokumentu „Strategia rozwoju Grupy Azoty Zakłady Azotowe Kędzierzyn SA 2015–2020 oraz w perspektywie do 2025", Spółka konsekwentnie realizuje kompleksowy program rozwojowo–inwestycyjny. W 2015 r. poszerzyła swoje portfolio o pierwszy polski plastyfikator nieftalanowy Oxoviflex® oraz płynne nawozy saletrzano–mocznikowe (RSM), oddając do użytku dwie nowe instalacje. *(abc)*

(http://grupaazoty.com/pl 10.02.2016)

Dokończenie na stronie 122