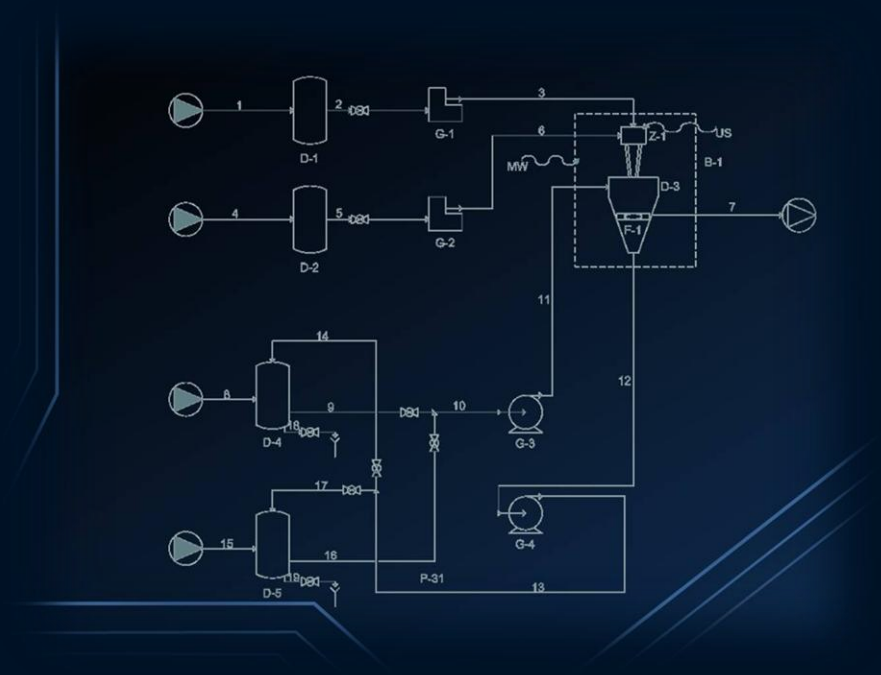
Novel technologies and process intensification in the production of micro-systems with pharmacological/nutraceutical activity



Annalisa Dalmoro

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Unione Europea

UNIVERSITÀ DEGLI
STUDI DI SALERNO

FONDO SOCIALE EUROPEO

Programma Operativo Nazionale 2007/2013
"Ricerca Scientifica, Sviluppo Tecnologico, Alta Formazione"
Regioni dell'Obiettivo 1 – Misura III.4
"Formazione superiore ed universitaria"

Department of Industrial Engineering

Corso di dottorato in Scienza e tecnologie per l'industria chimica, farmaceutica e alimentare - curriculum Ingegneria Chimica
(XI ciclo)

Novel technologies and process intensification in the production of micro-systems with pharmacological/nutraceutical activity

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Una ricerca comincia sempre con la Fortuna del Principiante.
E finisce sempre con la Prova del Conquistatore.

Paulo Coelho, L'alchimista, 1988

Publications

(*Inherent the Ph.D. project*)

- **Dalmoro A.**; Barba A.A.; d'Amore M.; Lamberti G.; (2012), "Microparticles production by a single-pot semi-continuous bench scale apparatus", submitted to AIChE Journal;

- Barba A.A.; **Dalmoro A.**; d'Amore M.; Lamberti G.; "Controlled release of drugs from microparticles produced by ultrasonic assisted atomization based on biocompatible polymers", Chem. Biochem. Eng. Q., 26(4) 345-354 (2012);

- Barba A.A.; **Dalmoro A.**; d'Amore M.; (2012) "An engineering approach to biomedical sciences: advanced strategies in drug delivery systems production", Translational Medicine @ UniSa, 4 (1) 5-11 (2012);

- **Dalmoro A.**; Barba A.A.; Lamberti G.; Grassi M.; d'Amore M.; "Pharmaceutical applications of biocompatible polymer blends containing sodium alginate", Advances in Polymer Technology, 31(3) 219-230 (2012);

- **Dalmoro A.**; Barba A.A.; Lamberti G.; d'Amore M.; "Intensifying the microencapsulation process: Ultrasonic atomization as an innovative approach", European Journal of Pharmaceutics and Biopharmaceutics, 80 471–477 (2012);

- **Dalmoro A.**; Barba A.A.; d'Amore M.; Lamberti G.; "Micro-Systems Production: A Promising New Technique with Low Energy Consumption", Scientia Pharmaceutica, 78 (3) 670-670 (2010);

Proceedings

- **A. Dalmoro**, A.A. Barba, G. Lamberti, M. d'Amore (2012), Sistemi particellari shell-core prodotti via atomizzazione assistita da ultrasuoni, *Convegno GRICU 2012* Montesilvano (PE) ITALY, 16-19 settembre 2012
- S. Cascone, **A. Dalmoro**, G. Lamberti, A.A. Barba (2012), Metodi innovativi di preparazione e testing per sistemi farmaceutici, *Convegno GRICU 2012* Montesilvano (PE) ITALY, 16-19 settembre 2012
- **A. Dalmoro,** M. d'Amore, A.A. Barba, Shell-core particles production by coaxial double channel device, presented to *8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, 19th-22nd March 2012, Istanbul (Turkey)
- I. Galdi, **A. Dalmoro**, G. Lamberti, G. Titomanlio, A.A. Barba, M. d'Amore, Modeling of the controlled drug release from solid matrices based on swellable/erodible polymeric hydrogels, presented to *19th International Congress of Chemical and Process Engineering CHISA 2010 and the 7th European Congress of Chemical Engineering ECCE-7*, 28th August – 1st September 2010, Prague (Czech Republic)
- **A. Dalmoro**, I. Galdi, G. Lamberti, G. Titomanlio, A.A. Barba, M. d'Amore, Targeted oral drug delivery by pH-sensitive microparticles, presented to *19th International Congress of Chemical and Process Engineering CHISA 2010 and the 7th European Congress of Chemical Engineering ECCE-7*, 28th August – 1st September 2010, Prague (Czech Republic)
- I. Galdi, **A. Dalmoro**, G. Lamberti, G. Titomanlio, A.A. Barba, M. d'Amore, Swelling, erosion and drug release in hydrogel based solid matrices, presented to *7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, 8th-11th March 2010, Valletta (Malta).
- Dalmoro, I. Galdi, G. Lamberti, G. Titomanlio, A.A. Barba, M. d'Amore. "PH-sensitive microparticles for enteric drug delivery by solvent evaporation from double emulsion", presented to *7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, 8th-11th March 2010, Valletta (Malta).

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Abstract

Purpose of the PhD thesis was to develop a novel microencapsulation process, designing and building a single-pot semi-continuous bench scale apparatus. The novel process is based on the coupling of two emerging techniques, involving ultrasound and microwave, used in atomization and heating operations, respectively. The process has been designed to respond to the needs for process intensification, i.e. improvement of process efficiency and cutting down of energy consumption. With this aim, a review of the main processes used for microencapsulation was first performed: conventional processes showed a number of drawbacks, such as high energy consumption, batch configuration, use of solvents and long times of production. On the basis of the state of the art, the idea of an intensified apparatus for particles production, exploiting alternative resources, such as ultrasound and microwave, was formulated. The apparatus was composed of three main sections: feeding, atomization, separation/stabilization. The feeding and atomization sections were built connecting a double channel ultrasonic atomizer to a system for feeding solutions in a purposely designed separation/stabilization section, thus realizing a semi-continuous apparatus. Separation section consisted of a wet-collector, i.e. a sort of hydrocyclone, which allowed a uniform distribution of the hardening solution and the consequent contact with the atomized drops, a filtering device, and a microwave oven. The wet-collector was placed into the microwave oven to obtain an "on-line" drying. Recirculation of the hardening solution, to renew contact surface between droplets and cross-linker, was guaranteed by a system of centrifugal pumps. In this configuration, when atomization occurred, drops were harvested in the wet-collector. After atomization, the obtained suspension was collected in the cross-linker tank, then the filtering device was inserted in the lower part of the wet-collector, so that hardening solution was recovered and particles

settled on the filter, when the suspension was brought again to the wet-collector and after its complete emptying. An eventual following washing step can be done in a similar way to the previous hardening step. Finally, particles were stabilized by microwave drying, and then recovered.

The steps for building the microencapsulation apparatus were accurately shown. Then, criteria used for components selection, in order to obtain the best performances from the plant, were highlighted. After building the plant, the process parameters were defined. First, the research for the best combination of feeding parameters, such as type of materials, composition, concentration and feed rate, that assure the encapsulation of the core material in the shell, was carried out. Then, the parameters of the ultrasonic atomizer (atomization section), essentially power, were tuned. Finally, for stabilization/separation section, fundamental was the relevant stabilization step, where microwave power was set to avoid too high temperatures that could degrade molecules.

The ability of the novel plant to obtain micronized systems, that exhibit a behavior interesting for the pharmaceutical or nutraceutical markets, was tested. Micro-particles characterization showed that it is possible to obtain a shell-core configuration encapsulating two functional molecules, vitamin B12 and α-tocopherol. Some important results were: 1) high loading and enteric (gastro-resistant) behavior of micro-particles; 2) delayed release for shell-core micro-systems compared to matrix ones; shell-core configuration in macro-scale (beads) able to prevent degradation of α-tocopherol, instead observed in matrix beads. Moreover, microwave treatment (not harsher for the short irradiation times) caused, especially for shell-core configuration, a little delay in molecule release. Resuming, better release properties for systems produced in the novel apparatus were achieved by the coupling of ultrasonic atomization and microwave drying. Furthermore, the basic transport phenomena occurring in the ultrasonic assisted atomization were investigated, emphasizing the role of operative parameters, and literature correlations, based on forces balance, were also applied for droplets size prediction. All these results endorses the usefulness of the novel plant, based on the combination of two powerful tools of process intensification, ultrasonic atomization and microwave drying, to obtain micro-systems, particularly interesting for specific drug delivery

applications. Moreover, working at room conditions and in absence of solvents, improving the energy transfer rate (faster process times), reducing process chambers volume (low particles inertia in ultrasonic atomization, single-pot process realization), enhancing the product quality (micro-particles with tailored features), makes the apparatus more attractive in terms of improved inherent safety and reduced costs.

References

[1] P. Venkatesan, R. Manavalan, K. Valliappan, Microencapsulation: A vital technique in novel drug delivery system, Journal of Pharmaceutical Sciences, 1 (2009) 26-35.
[2] J. Silva, Effect of drug properties on the release from CAP microspheres prepared by a solvent evaporation method, Journal of microencapsulation, 16 (1999) 95-103.
[3] P. Colombo, P. Catellani, A. Gazzaniga, E. Menegatti, E. Vidale, Principi di tecnologie farmaceutiche, Casa Editrice Ambrosiana, Milano, (2004).
[4] M. Ré, B. Biscans, Preparation of microspheres of ketoprofen with acrylic polymers by a quasi-emulsion solvent diffusion method, Powder Technology, 101 (1999) 120-133.
[5] N. Barakat, A. Ahmad, Diclofenac sodium loaded-cellulose acetate butyrate: Effect of processing variables on microparticles properties, drug release kinetics and ulcerogenic activity, Journal of microencapsulation, 25 (2008) 31-45.
[6] S. Benita, Microencapsulation: methods and industrial applications, Informa HealthCare, 2006.
[7] S. Freitas, H. Merkle, B. Gander, Microencapsulation by solvent extraction/evaporation: reviewing the state of the art of microsphere preparation process technology, Journal of controlled Release, 102 (2005) 313-332.
[8] S. Lyons, S. Wright, Apparatus and method for preparing microparticles, in, 2003.
[9] J. Herrmann, R. Bodmeier, Biodegradable, somatostatin acetate containing microspheres prepared by various aqueous and non-aqueous solvent evaporation methods, European Journal of Pharmaceutics and Biopharmaceutics, 45 (1998) 75-82.
[10] J. Beyger, J. Nairn, Some factors affecting the microencapsulation of pharmaceuticals with cellulose acetate phthalate, Journal of Pharmaceutical Sciences, 75 (1986) 573-578.
[11] F. Gabor, Ketoprofen-poly (D, L-lactic-co-glycolic acid) microspheres: influence of manufacturing parameters and type of

polymer on the release characteristics, Journal of microencapsulation, 16 (1999) 1-12.
[12] Y. Yang, T. Chung, N. Ping Ng, Morphology, drug distribution, and in vitro release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method, Biomaterials, 22 (2001) 231-241.
[13] W. Obeidat, J. Price, Preparation and evaluation of Eudragit S 100 microspheres as pH-sensitive release preparations for piroxicam and theophylline using the emulsion-solvent evaporation method, Journal of microencapsulation, 23 (2006) 195-202.
[14] H. Chen, J. Wu, H. Chen, Preparation of ethylcellulose microcapsules containing theophylline by using emulsion non-solvent addition method, Journal of microencapsulation, 12 (1995) 137-147.
[15] V.S. Mastiholimath, P.M. Dandagi, S.S. Jain, A.P. Gadad, A.R. Kulkarni, Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma, International Journal of Pharmaceutics, 328 (2007) 49-56.
[16] I. Péter Sipos, Influence of preparation conditions on the properties of Eudragit microspheres produced by a double emulsion method, Drug Development Research, 64 (2005) 41-54.
[17] M. Lai, R. Tsiang, Microencapsulation of acetaminophen into poly (L-lactide) by three different emulsion solvent-evaporation methods, Journal of microencapsulation, 22 (2005) 261-274.
[18] P. Sansdrap, A. Mo s, Influence of manufacturing parameters on the size characteristics and the release profiles of nifedipine from poly (DL-lactide-co-glycolide) microspheres, International Journal of Pharmaceutics, 98 (1993) 157-164.
[19] Y. Maa, C. Hsu, Microencapsulation reactor scale-up by dimensional analysis, Journal of microencapsulation, 13 (1996) 53-66.
[20] Y. Maa, C. Hsu, Liquid-liquid emulsification by static mixers for use in microencapsulation, Journal of microencapsulation, 13 (1996) 419-433.
[21] B. Amsden, The production of uniformly sized polymer microspheres, Pharmaceutical research, 16 (1999) 1140-1143.
[22] H. Liu, Science and engineering of droplets: fundamentals and applications, William Andrew, 2000.
[23] M. Rawat, S. Saraf, Influence of selected formulation variables on the preparation of enzyme-entrapped eudragit S100 microspheres, AAPS PharmSciTech, 8 (2007) 289-297.
[24] M. Kitajima, T. Yamaguchi, A. Kondo, N. Muroya, Encapsulation method, in, 1972.

[25] M. Li, O. Rouaud, D. Poncelet, Microencapsulation by solvent evaporation: State of the art for process engineering approaches, International Journal of Pharmaceutics, 363 (2008) 26-39.
[26] J. Ramstack, Apparatus and method for preparing microparticles using liquid-liquid extraction, in, 2002.
[27] M. Rickey, J. Ramstack, D. Lewis, Preparation of biodegradable, biocompatible microparticles containing a biologically active agent, in, 2003.
[28] S. Gouin, Microencapsulation: industrial appraisal of existing technologies and trends, Trends in Food Science & Technology, 15 (2004) 330-347.
[29] C. Wischke, S. Schwendeman, Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles, International Journal of Pharmaceutics, 364 (2008) 298-327.
[30] J. Coulson, J. Richardson, Chemical Engineering, Volume 2: Particle Technology and Separation Processes, Pergamon, (1991).
[31] A. Stankiewicz, J. Moulijn, Re-engineering the chemical processing plant: process intensification, M. Dekker, New York, 2004.
[32] G. Cravotto, A. Barge, L. Boffa, E. Calcio Gaudino, W. Bonrath, Ultrasound-microwave coupling: an efficient tool for chemical-process intensification, in, GPE-EPIC, 2nd International Congress on Green Process Engineering, 2nd European Process Intensification Conference, 2009.
[33] B. Redding Jr, Apparatus and method for making microcapsules, in, 1993.
[34] G. Alisch, E. Brauneis, B. Pirstadt, N. Iffland, E. Brandau, Process and plant for the production of spherical alginate pellets, in, 1995.
[35] B. Amsden, R. Liggins, Methods for microsphere production, in, 2001.
[36] D. Bomberger, P. Catz, M. Smedley, P. Stearns, System and method for producing drug-loaded microparticles, in, 2002.
[37] J. Gibson, R. Holl, A. Tipton, Emulsion-based processes for making microparticles, in, 2002.
[38] P. Herbert, M. Healy, Production scale method of forming microparticles, in, 2004.
[39] M. Tyo, Y. Hsu, M. Hedley, Continuous-flow method for preparing microparticles, in, 2004.
[40] J. Piechocki, D. Kyle, Continuous spray-capture production system, in, 2009.

[41] T. Brandau, Preparation of monodisperse controlled release microcapsules, International Journal of Pharmaceutics, 242 (2002) 179-184.
[42] R. Pareta, M. Edirisinghe, A novel method for the preparation of biodegradable microspheres for protein drug delivery, Journal of The Royal Society Interface, 3 (2006) 573.
[43] M. Chang, E. Stride, M. Edirisinghe, Controlling the thickness of hollow polymeric microspheres prepared by electrohydrodynamic atomization, Journal of The Royal Society Interface, 7 (2010) S451.
[44] Y. Lee, F. Mei, M. Bai, S. Zhao, D. Chen, Release profile characteristics of biodegradable-polymer-coated drug particles fabricated by dual-capillary electrospray, Journal of controlled Release, (2010).
[45] A. Dalmoro, A.A. Barba, G. Lamberti, M. d'Amore, Intensifying the microencapsulation process: Ultrasonic atomization as an innovative approach, European Journal of Pharmaceutics and Biopharmaceutics, (2012).
[46] A. Patist, D. Bates, Ultrasonic innovations in the food industry: From the laboratory to commercial production, Innovative food science & emerging technologies, 9 (2008) 147-154.
[47] D. Ensminger, F. Stulen, Ultrasonics: data, equations, and their practical uses, CRC Press, 2009.
[48] B. Avvaru, M. Patil, P. Gogate, A. Pandit, Ultrasonic atomization: effect of liquid phase properties, Ultrasonics, 44 (2006) 146-158.
[49] R. Rajan, A. Pandit, Correlations to predict droplet size in ultrasonic atomisation, Ultrasonics, 39 (2001) 235-255.
[50] K. Park, Y. Yeo, Microencapsulation using ultrasonic atomizers, in, 2003.
[51] L. Rodriguez, N. Passerini, C. Cavallari, M. Cini, P. Sancin, A. Fini, Description and preliminary evaluation of a new ultrasonic atomizer for spray-congealing processes, International Journal of Pharmaceutics, 183 (1999) 133-143.
[52] N. Ashgriz, Handbook of Atomization and Sprays: Theory and Applications, Springer, 2011.
[53] B. Bittner, T. Kissel, Ultrasonic atomization for spray drying: a versatile technique for the preparation of protein loaded biodegradable microspheres, Journal of microencapsulation, 16 (1999) 325-341.
[54] S. Freitas, H. Merkle, B. Gander, Ultrasonic atomisation into reduced pressure atmosphere--envisaging aseptic spray-drying for microencapsulation, Journal of controlled Release, 95 (2004) 185-195.

[55] P. Luz, A. Pires, O. Serra, A low-cost ultrasonic spray dryer to produce spherical microparticles from polymeric matrices, Química Nova, 30 (2007) 1744-1746.
[56] P. Burke, L. Klumb, J. Herberger, X. Nguyen, R. Harrell, M. Zordich, Poly (lactide-co-glycolide) microsphere formulations of darbepoetin alfa: spray drying is an alternative to encapsulation by spray-freeze drying, Pharmaceutical research, 21 (2004) 500-506.
[57] C. Berkland, E. Pollauf, D. Pack, K. Kim, Uniform double-walled polymer microspheres of controllable shell thickness, Journal of controlled Release, 96 (2004) 101-111.
[58] Y. Yeo, K. Park, A new microencapsulation method using an ultrasonic atomizer based on interfacial solvent exchange, Journal of controlled Release, 100 (2004) 379-388.
[59] R. Graves, D. Poole, R. Moiseyev, L. Bostanian, T. Mandal, Encapsulation of Indomethacin Using Coaxial Ultrasonic Atomization Followed by Solvent Evaporation, Drug development and industrial pharmacy, 34 (2008) 419-426.
[60] J. Legako, N. Dunford, Effect of Spray Nozzle Design on Fish Oil–Whey Protein Microcapsule Properties, Journal of Food Science, 75 (2010) E394-E400.
[61] L. Pilon, H. Berberoglu, Method and apparatus for liquid microencapsulation with polymers using ultrasonic atomization, in, 2005.
[62] H. Liu, Science and Engineering of Droplets:: Fundamentals and Applications, William Andrew, 1999.
[63] R.J. Lang, Ultrasonic atomization of liquids, The journal of the acoustical society of America, 34 (1962) 6-8.
[64] K.A. Ramisetty, A.B. Pandit, P.R. Gogate, Investigations into ultrasound induced atomization, Ultrasonics Sonochemistry, (2012).
[65] A.A. Barba, M. d'Amore, S. Cascone, G. Lamberti, G. Titomanlio, Intensification of biopolymeric microparticles production by ultrasonic assisted atomization, Chemical Engineering and Processing: Process Intensification, 48 (2009) 1477-1483.
[66] www.sono-tek.com, in.
[67] www.verderflex.com, in.
[68] www.watson-marlow.com, in.
[69] R.A. Arterburn, The sizing and selection of hydrocyclones, Design and Installation of Comminution Circuits, (1982) 592-607.
[70] W. Yu, H. Song, G. Zheng, X. Liu, Y. Zhang, X. Ma, Study on membrane characteristics of alginate-chitosan microcapsule with cell growth, Journal of Membrane Science, 377 (2011) 214-220.

[71] M. George, T.E. Abraham, Polyionic hydrocolloids for the intestinal delivery of protein drugs: alginate and chitosan--a review, Journal of Controlled Release, 114 (2006) 1-14.
[72] H. Zhang, H. Wang, J. Wang, R. Guo, Q. Zhang, The effect of ionic strength on the viscosity of sodium alginate solution, Polymers for Advanced Technologies, 12 (2001) 740-745.
[73] W. Gombotz, S. Wee, Protein release from alginate matrices, Advanced Drug Delivery Reviews, 31 (1998) 267-285.
[74] C. DeRamos, A. Irwin, J. Nauss, B. Stout, 13C NMR and molecular modeling studies of alginic acid binding with alkaline earth and lanthanide metal ions, Inorganica chimica acta, 256 (1997) 69-75.
[75] H. Tønnesen, J. Karlsen, Alginate in drug delivery systems, Drug development and industrial pharmacy, 28 (2002) 621-630.
[76] G. Fundueanu, C. Nastruzzi, A. Carpov, J. Desbrieres, M. Rinaudo, Physico-chemical characterization of Ca-alginate microparticles produced with di! erent methods, Biomaterials, 20 (1999) 1435.
[77] M.S. Shoichet, R.H. Li, M.L. White, S.R. Winn, Stability of hydrogels used in cell encapsulation: An in vitro comparison of alginate and agarose, Biotechnology and bioengineering, 50 (1996) 374-381.
[78] A. Dalmoro, A.A. Barba, G. Lamberti, M. Grassi, M. d'Amore, Pharmaceutical applications of biocompatible polymer blends containing sodium alginate, Advances in Polymer Technology, (2012).
[79] E.S. Chan, B.B. Lee, P. Ravindra, D. Poncelet, Prediction models for shape and size of ca-alginate macrobeads produced through extrusion-dripping method, Journal of colloid and interface science, 338 (2009) 63-72.
[80] E. Pasut, R. Toffanin, D. Voinovich, C. Pedersini, E. Murano, M. Grassi, Mechanical and diffusive properties of homogeneous alginate gels in form of particles and cylinders, Journal of Biomedical Materials Research Part A, 87 (2008) 808-818.
[81] Sigma-Aldrich, in.
[82] S.P. Stabler, R.H. Allen, Vitamin B12 deficiency as a worldwide problem, Annu. Rev. Nutr., 24 (2004) 299-326.
[83] F. Aranda, A. Coutinho, M. Berberan-Santos, M. Prieto, J. G mez-Fern ndez, Fluorescence study of the location and dynamics of?-tocopherol in phospholipid vesicles, Biochimica et Biophysica Acta-Biomembranes, 985 (1989) 26-32.

[84] E.F. Bell, History of vitamin E in infant nutrition, The American Journal of Clinical Nutrition, 46 (1987) 183-186.
[85] M. Simonoska Crcarevska, M. Glavas Dodov, K. Goracinova, Chitosan coated Ca-alginate microparticles loaded with budesonide for delivery to the inflamed colonic mucosa, European Journal of Pharmaceutics and Biopharmaceutics, 68 (2008) 565-578.
[86] A.A. Barba, S. Chirico, A. Dalmoro, G. Lamberti, Simultaneous measurement of theophylline and cellulose acetate phthalate in phosphate buffer by uv analysis, Can J Anal Sci Spectros, 53 (2009) 249-253.
[87] T.W. Wong, L.W. Chan, S.B. Kho, P.W. Sia Heng, Design of controlled-release solid dosage forms of alginate and chitosan using microwave, Journal of controlled Release, 84 (2002) 99-114.
[88] R.E. Mardziah, T.W. Wong, Effects of microwave on drug-release responses of spray-dried alginate microspheres, Drug development and industrial pharmacy, 36 (2010) 1149-1167.
[89] A. Metaxas, R.J. Meredith, Industrial microwave heating, Inst of Engineering & Technology, 1983.
[90] R.E. Mudgett, Microwave properties and heating characteristics of foods, Food Technology, 40 (1986).
[91] C.M. Sabliov, C. Fronczek, C. Astete, M. Khachaturyan, L. Khachatryan, C. Leonardi, Effects of temperature and UV light on degradation of α-tocopherol in free and dissolved form, Journal of the American Oil Chemists' Society, 86 (2009) 895-902.
[92] T. Pongjanyakul, S. Puttipipatkhachorn, Xanthan–alginate composite gel beads: Molecular interaction and in vitro characterization, International Journal of Pharmaceutics, 331 (2007) 61-71.
[93] A.A. Barba, M. d'Amore, S. Cascone, G. Lamberti, G. Titomanlio, Intensification of biopolymeric microparticles production by ultrasonic assisted atomization, Chemical Engineering and Processing: Process Intensification, 48 (2009) 1477-1483.
[94] H.B. Li, F. Chen, Y. Jiang, Determination of vitamin B12 in multivitamin tablets and fermentation medium by high-performance liquid chromatography with fluorescence detection, Journal of Chromatography A, 891 (2000) 243-247.
[95] E.L. SMITH, K. FANTES, S. BALL, J. WALLER, W. EMERY, B12 Vitamins (Cobalamins), (1951).
[96] Y. Xu, C. Zhan, L. Fan, L. Wang, H. Zheng, Preparation of dual crosslinked alginate-chitosan blend gel beads and in vitro controlled

release in oral site-specific drug delivery system, International Journal of Pharmaceutics, 336 (2007) 329-337.
[97] J. Crank, The mathematics of diffusion, (1979).

CURRICULUM VITAE

Ing. Annalisa Dalmoro was born in 01/11/1984. She achieved the bachelor degree in Chemical Engineering, cum laude, in 2006, with a thesis entitled "Analysis of transport phenomena in matrices of swellable hydrogels". Then she gained the Master Degree in Chemical Engineering, cum laude, in 2009 with a thesis entitled "Enteric micro-particles coated with smart polymers for controlled drug delivery applications".

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Publications:

1. Barba A.A.; **Dalmoro A.**; d'Amore M.; (2012), "Microwave assisted drying of cellulose derivative (HPMC) granular solids", in press on Powder Technology;
2. Barba A.A.; **Dalmoro A.**; d'Amore M.; Lamberti G.; "Controlled release of drugs from microparticles produced by ultrasonic assisted atomization based on biocompatible polymers", Chem. Biochem. Eng. Q., 26(4) 345-354 (2012);
3. Barba A.A.; **Dalmoro A.**; d'Amore M.; Lamberti G.; "In vitro dissolution of pH sensitive micro-particles for colon-specific drug delivery", in press on Pharmaceutical Development and Technology;

4. Barba A.A.; **Dalmoro A.**; d'Amore M.; (2012) "An engineering approach to biomedical sciences: advanced strategies in drug delivery systems production", Translational Medicine @ UniSa, 4 (1) 5-11 (2012);
5. **Dalmoro A.**; Barba A.A.; Lamberti G.; Grassi M.; d'Amore M.; "Pharmaceutical applications of biocompatible polymer blends containing sodium alginate", Advances in Polymer Technology, 31(3) 219-230 (2012);
6. **Dalmoro A.**; Barba A.A.; Lamberti G.; d'Amore M.; "Intensifying the microencapsulation process: Ultrasonic atomization as an innovative approach", European Journal of Pharmaceutics and Biopharmaceutics, 80 471–477 (2012);
7. **Dalmoro A.**; Lamberti G.; Titomanlio G.; Barba A.A.; d'Amore M.; "Enteric Micro-Particles for Targeted Oral Drug Delivery", AAPS PharmSciTech, 11(4) 1500-1507 (2010);
8. **Dalmoro A.**; Barba A.A.; d'Amore M.; Lamberti G.; "Micro-Systems Production: A Promising New Technique with Low Energy Consumption", Scientia Pharmaceutica, 78 (3) 670-670 (2010);
9. **Dalmoro A.**; Villano O.; Barba A.A.; Lamberti G.; "Dosare dove serve", NCF-Notiziario Chimico E Farmaceutico, 49 (4) 112-114 (2010);
10. Barba, A.A.; **Dalmoro, A.**; De Santis, F.; Lamberti, G. "Synthesis and characterization of P(MMA-AA) copolymers for targeted oral drug delivery", *Polymer Bulletin*, 62(5) 679-688 (2009)
11. Barba, A.A.; Chirico, S.; **Dalmoro, A.**; Lamberti, G. "Simultaneous measurement of Theophylline and Cellulose Acetate Phthalate in Phosphate Buffer by UV analysis", Canadian Journal of Analytical Sciences & Spectroscopy, 53(6) 249-253 (2009)
12. Chirico S., **Dalmoro A.**, Lamberti G., Russo G., Titomanlio G., "Analysis and modeling of swelling and erosion behavior for pure HPMC tablet", Journal of Controlled Release, 122 (2) 181-188 (2007)

Proceedings:

Dalmoro A.; Barba A.A.; Lamberti G.; d'Amore M., Sistemi particellari shell-core prodotti via atomizzazione assistita da ultrasuoni, presented to Convegno *GRICU 2012-Ingegneria chimica: dalla nanoscala alla macroscala)*, 16th-19th September 2012, Montesilvano (PE) (Italy) - *SPEAKER*

Cascone S.; **Dalmoro A.**; Lamberti G.; Barba A.A., Metodi innovativi di preparazione e testing per sistemi farmaceutici, presented to Convegno *GRICU 2012-Ingegneria chimica: dalla nanoscala alla macroscala)*, 16th-19th September 2012, Montesilvano (PE) (Italy) - *SPEAKER*

Dalmoro A.; d'Amore M.; Barba A.A., Shell-core particles production by coaxial double channel device, presented to *8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, 19th-22nd March 2012, Istanbul (Turkey) - *SPEAKER*

Galdi I.; **Dalmoro A.**; Lamberti G.; Titomanlio G.; Barba A.A.; d'Amore M.. "Modeling of the controlled drug release from solid matrices based on swellable/erodible polymeric hydrogels", presented to *19th International Congress of Chemical and Process Engineering CHISA 2010 and the 7th European Congress of Chemical Engineering ECCE-7*, 28th August – 1st September 2010, Prague (Czech Republic) - *SPEAKER*

Dalmoro A.; Galdi I.; Lamberti G.; Titomanlio G.; Barba A.A.; d'Amore M.. "Targeted oral drug delivery by pH-sensitive microparticles", presented to *19th International Congress of Chemical and Process Engineering CHISA 2010 and the 7th European Congress of Chemical Engineering ECCE-7*, 28th August – 1st September 2010, Prague (Czech Republic) - *SPEAKER*

Galdi I.; **Dalmoro A.**; Lamberti G.; Titomanlio G.; Barba A.A.; d'Amore M. "Swelling, erosion and drug release in hydrogel based solid matrices", presented to *7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, 8th-11th March 2010, Valletta (Malta) - *SPEAKER*

Dalmoro A.; Galdi I.; Lamberti G.; Titomanlio G.; Barba A.A.; d'Amore M. "PH-sensitive microparticles for enteric drug delivery by solvent evaporation from double emulsion", presented to *7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, 8th-11th March 2010, Valletta (Malta) - *SPEAKER*

Barba A.A., Chirico S., **Dalmoro A.**, Galzerano B., Lamberti G., "Water and drug mass fraction profiles in HPMC/TP matrices", presented to *36th Meeting of Controlled Release Society*, 18th-22nd July 2009, Copenhagen (Denmark) - *SPEAKER*

Barba A.A., D'Amore M., **Dalmoro A.**, Lamberti G., Titomanlio G.,"Enteric coated micro-particles for targeted and controlled release", presented to *36th Meeting of Controlled Release Society*, 18th-22nd July 2009, Copenhagen (Denmark) - *SPEAKER*

Chirico S., **Dalmoro A.**, Lamberti G., Russo G., Titomanlio G., "Radial water up-take in pure HPMC tablet analysis and model prediction", proceedings of Pharmaceutical Sciences World Congress, 22th -25th April 2007, Amsterdam (Netherlands)

Acknowledgments

I would like to thank all the people who helped and supported me during these years of my Ph.D-experience.

A warm thanks to my supervisors for giving me the opportunity to carry out an interesting and pleasant work. In particular, much gratitude to prof. Matteo d'Amore for being a valuable reference point thanks to his knowledge, experience and humanity. A special "Thanks" to prof. Anna Angela Barba, who was not only a coach and a guide, but especially a friend and a confidant, the best I could hope!

Thanks also to prof. Gaetano Lamberti for having taught me love for research and for his continuous presence, only apparently offstage, but ever comforting.

I gratefully acknowledge prof. Giuseppe Titomanlio, especially for our sketch about my final Ph.D. presentation, the pharmacists and "the balance is not closed"!

I want to express my gratitude to my scientific referees, prof. Roland Bodmeier and prof. Nadia Passerini, for their availability to take part of my scientific committee and for their valuable suggestions.

A great thanks to my PhD-mate, Sara, for sharing the good and the bad situations, "the corner of mess-ups", the Gricu experience and the trips all over the Europe!

Thanks also to Valentina: we shared troubles and happiness since bachelor degree up to this important goal.

This Ph.D. has given me the opportunity to meet nice people for funny moments: the Gricu-mates…some of them became "my business partners".

Many thanks go to my two Sisters, Barbara & Monica: the lab T5a brought us together and it made us inseparable.

A kind thanks to the girls of lab. Impianti & Processi, who cheered up the work in the lab, and not only!!! Especially thanks to the "mad group" composed of Amanita, Clara, Enza, Giovanna, Margherita e Michela, headed by Giovanna: in her discovered an Authentic friend! I can't forget the two official "blighters" of the lab, Peppe and Marco, who made lighter work days with our coffees and lunches.

Here I come to the most important people of my life: my parents…thanks to them I have become what I am nowadays, and Gianni, who always supported me in everything, giving me serenity and love.

Finally I thank all the people with whom I have shared experiences, "mess-ups", a coffee, a pizza or a chat.

Simply thanks again to people who have believed and still believe in me…