

# Pharmaceutical and Macromolecular Technologies in the Spirit of Industry 4.0

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## Abstract

Well designed (multilayer, adaptive, reactive) interphases, being a key element of multicomponent structures, could be tailored to different requirements through controlled technologies. This is the link connecting various green, safe, healthy materials and innovative pharmaceuticals. Upgraded recycling could be performed by interfacial consolidation of self-reinforced composites, the flame retardancy of which is feasible with surprisingly low amount of flame retardant. Examples are shown how the reinforced and foamed forms of thermosetting and thermoplastic biopolymers can play a significant role (after flame retardant modification) in the development of airplanes and electric cars. Biopolymer nanofibres, such as polycaprolactone and polyhydroxybutyrate, could be formed with increased productivity for various medical uses. Raman-based control of the units of integrated continuous technologies has been elaborated including controlled formation of crystals with polymer interlayer for direct tableting.

## Keywords

interface modification, recycling, biocomposites, pharmaceutical crystallization, Raman control

## 1 Introduction

Roots of the current research work to be described in this paper originate from activities on multicomponent polymer systems and composites, (fire) safety, recycling, oriented fibres, and formulation of pharmaceutical systems, as well as solid-state analysis and process control methods developed in the recent decades. The accumulated knowledge has been integrated by now to a coherent mind-set within the FirePharma group in a synergistic way. This proved to be a good basis for serving new technologies consisting of integrated interactive flow-type units. After highlighting some parts of this basis a short overview of the outcome is shown in this paper through selected examples.

Polymerization of lactames and acrylates, investigated by Bertalan and Anna [1, 2], reinforced the macromolecular chemistry knowledge in the first macromolecule school of Hungary founded by Zoltan Csűrös.

More important stage of development was a basic (internationally patented) finding of multicomponent polymer systems utilized industrially by the largest Hungarian

polymer producer company. The essence of this finding was a multilayer interphase that accomplished a smooth (mechanical and chemical) transition between different phases of composites (converting the well-known Buzagh-principle to solid phase) [3]. Dielectric spectroscopy identified the Maxwell-Wagner-Sillars (MWS) interfacial polarization occurring in such composites [4]. Synthesis of reactive surfactants and the first proposal for their introduction into interphases of reinforced polymer systems further improved the stiffness-toughness balance of composites [5].

Reliable and reproducible synthesis of these additives required the development of a computer-controlled batch reactor system applying sequential controller program. It was used not only for preparing interfacial additives but also azo-pigments and polymer nanocomposites [6-9]. Completing the controlled reactor with a fibre-optic Raman probe and converting the complex Raman spectra to control signal, the first Raman-controlled processes could be developed and published [10, 11].

Adaptive interfaces, that can be stimulated thermally, were also developed and applied around nanoparticles serving the fire safety of polymeric and composite structures. The developed non-halogenated flame retardancy principle utilized P-N-B-Si synergism and introduced also CNT and/or clay nanoparticles into the polymer matrices [12-15]. The internationally patented, finding could be utilized by a large German additive producing company [16]. Mathematical model of the mechanism of action described the performance of the fire retarded polymer system quite well supporting the scaled-up application [17].

Another patent referred to the recycling of cross-linked PE with thermally reversible urethane crosslink points [18]. Recycling proved to be especially advantageous and economic, when combined with flame retardancy. For this purpose PUR-waste, as active component of FR additive system, was introduced in polyolefin waste, furthermore, residue of glycolised PUR waste was found to have FR activity too [19-21].

Modified interphase initiated enhanced orientation and crystallinity in multicomponent fibres governed by local stress release mechanism. This phenomenon could be utilized both in technical and flame retarded polypropylene fibres [22, 23]. Nanofibres, prepared by electrospinning, became important in nanofiltration technology [24].

Pharmaceutical utilization of the knowledge, acquired through working with processing technologies of polymer fibres and nanocomposites, led the authors to apply Raman analysis, twin screw extrusion and nanofibre formation for drug delivery systems as well as to develop humidity-resistant nanostructured tablet coating [25-28].

These pioneering activities allowed learning important elements of green technology including the use of renewable materials with well-designed interphases, energy saving light-weight structures, green chemistry with organo- and biocatalysis, advanced monitoring, control and optimization and eco efficient flow technology with integrated, interactive units. Recent advancement in these fields, performed in FirePharma laboratories, is introduced through selected examples in the next sections.

## 2 Experimental

### 2.1 Materials

Drugs: carvedilol (Sigma-Aldrich, Hungary) with purity:  $\geq 98\%$ , melting point:  $117\text{ }^{\circ}\text{C}$ , spirinolactone (Gedeon Richter Plc., Hungary) melting point:  $205\text{--}220\text{ }^{\circ}\text{C}$ , water solubility at  $25\text{ }^{\circ}\text{C}$   $28\text{ mg/l}$ , tolperisone hydrochloride (Sigma-Aldrich, Hungary) purity:  $\geq 98\%$  (HPLC)

melting point:  $171\text{--}174\text{ }^{\circ}\text{C}$ . In self-reinforced composites highly oriented isotactic polypropylene (iPP) homopolymer multifilament (Stradom S.A., Poland) was used as reinforcement and propylene-ethylene copolymer (rPP) based thermoplastic elastomer (Versify 4200, Dow Chemical Company, USA) was selected as matrix material. Biopolymers, were purchased from the producers: polylactic acid (PLA) of Ingeo™ Biopolymer 3052D type (NatureWorks LLC USA), polycaprolactone (PCL, Perstorp, Capa™ 6800, Mw = 80,000), polyhydroxybutyrate (PHB, Mw = 973,000) was obtained from the producer (Biomer, Germany). Intumescent flame retardant was Exolit AP462, (Clariant GmbH, Frankfurt am Main, Germany), a melamine formaldehyde resin micro-encapsulated ammonium polyphosphate (APP) based additive. Fibrous additives were multi-walled carbon nanotube (CNT) Baytubes C 150 HP (Bayer, Germany), and Ultrafine cellulose fibre (Arbocel UFC100 J. Rettenmaier & Sohne GmbH, Rosenberg, Germany) with average fibre length of  $8\text{ }\mu\text{m}$ .

### 2.2 Methods

Raman image analyses were performed using a Horiba Jobin-Yvon LabRAM system coupled with an external 785 nm diode laser source and an Olympus BX-40 optical microscope. Small area maps were collected with  $50\times$  objective (laser spot size:  $\sim 2.0\text{ }\mu\text{m}$ ) and  $6\text{ }\mu\text{m}$  and  $12\text{ }\mu\text{m}$  step size in the X (perpendicular to the fibre orientation) and in the Y direction (parallel to the fibre orientation), respectively. In each experiment the acquisition time of a single spectrum was 30 s and 3 such spectra were averaged at each pixel. The analysed area was  $36 \times 12$  pixels, i.e.  $210 \times 132\text{ }\mu\text{m}^2$ . Kaiser RamanRxn2® Hybrid in situ analyser (Kaiser Optical Systems, USA) with a 400 mW, 785 nm diode laser (Invictus) and PhAT (Pharmaceutical Area Testing) probe was used for process-Raman measurements. Spectra were acquired with 15 s illumination time in the spectral range of  $200\text{--}1890\text{ cm}^{-1}$  with a resolution of  $4\text{ cm}^{-1}$ .

Laser Pyrolysis-Fourier Transformed Infrared Spectroscopy (LP-FTIR) method is a coupled system consisting of a carbon-dioxide laser ( $10.6\text{ }\mu\text{m}$ , SYNRAD 48-1), applicable for laser induced pyrolysis, connected with a special gas cell of FTIR spectrometer (Bruker Tensor 37 type, resolution:  $4\text{ cm}^{-1}$ , detector: DTGS). In situ FTIR allows their identification and quantification of components with 3D software of OPUS 5.5 without loss of any component.

Mass loss type cone calorimeter (made by FTT Inc) measurements were performed according to the ISO 13927

standard method. Specimens (100 mm × 100 mm) were exposed to a constant heat flux of 25 kW/m<sup>2</sup> and ignited.

Scanning electron microscopic (SEM) images were taken with a JEOL JSM-5500 LV type apparatus (JEOL Ltd., Akishima, Tokyo, Japan) applying accelerating voltages of 10-15 keV. All the samples were coated with gold-palladium alloy before examination.

### 3 Results and discussion

#### 3.1 Technologies of green, safe and healthy materials

Composites, consisting of various polymers and inorganic constituents, represent the most serious problem when the practical implementation of recycling is in place. The inorganic reinforcements confuse the density-based sorting, cause abrasion of the milling units, support fire spreading (like the candlewick) and limit the applicability of recirculates. Our answer to this challenge is the development of fully recyclable self-reinforced FR-composites, in which both the matrix and reinforcing fibres are made of the same polymer family (e.g. polypropylene) and consolidated through their interfacial layers. This approach led us to an unexpected new advancement in fire-safety. An unknown mechanism of fire control has been recognized, which is governed by shrinkage of reinforcing fibres and thus contribute to extinguishing of fire. This way the amount of (harmless) FR additive, needed to achieve self-extinguishing level, could be reduced to one third of the original value [29, 30]. Such composites are easily processable by simple thermoforming methods if the level of heat-induced relaxation of the reinforcing fibres can be controlled. In order to facilitate this precise processing of self-reinforced composites, novel Raman monitoring and control methods have been proposed by the authors [31]. Scheme of the principle and Raman images visualizing the relaxation is shown in Fig. 1.

Recycling can utilize the in-line spectroscopic control in several ways. Sorting, based on infrared identification of each waste item, is well known, however, it cannot be applied for black pieces. A new laser pyrolysis-assisted (LP-FTIR) method, developed by the authors [32], solved this problem allowing identification of black wastes through their volatile pyrolysis products. Additionally, LP-Raman combination allows in-line control of intumescent flame retardant content (through its charring efficiency) along the production of FR composites. These approaches are shown in Fig. 2 a and b. Upgraded innovative recycled products could be developed by combining polyolefin fraction of selected wastes with flame retardant additives [33].

Flame retarded biopolymers represent another category of green and safe materials. Biocomposites suitable for airspace or other high-tech applications are, however, not available on the market. Therefore new sugar-based bioepoxy types have been synthesized recently that proved to meet the severe requirements of an airplane construction (e.g. glass transition temperature above 160°C) [34]. Carbon fibre reinforced composites and natural fibre reinforced full-bio composites could be developed in fire-safe form and the latter one processed to airplane furniture as shown in Fig. 3.

Unique epoxy-composite was required for the protection of an airplane, made of polymer composite, against lighting attack. The requirement, beyond the mechanical chemical and thermal resistance, was electrical conductivity as well. For this purpose conductive nonwoven reinforcement made of carbon nanofibre, containing carbon nanotubes (shown in Fig. 4), were developed and prepared in a special continuous oven [35].

Thermoplastic all-bio composites in flame retarded form have been prepared at the first time by the authors [36, 37]. Such safe and light-weight composites are especially advantageous for producing electrical cars, in which

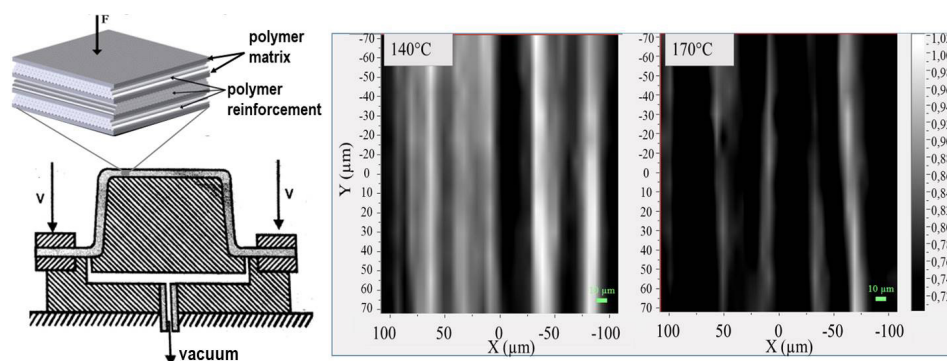


Fig. 1 Thermoforming of self-reinforced polypropylene composite and demonstration of the heat-induced relaxation of reinforcing fibres by Raman mapping (bright bands represent the oriented fibres, while the dark bands the relaxed ones)

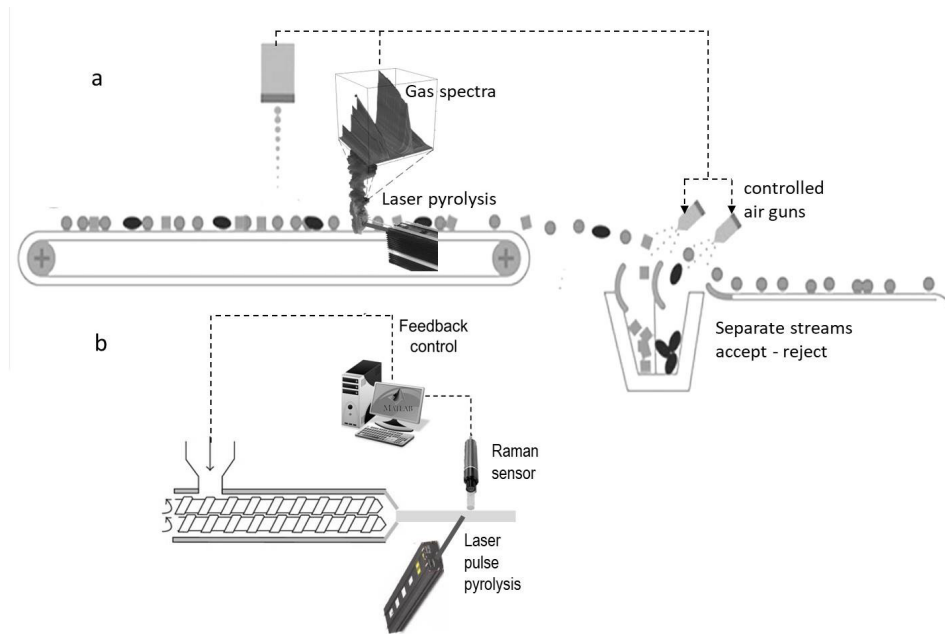


Fig. 2 Use of LP-FTIR for chemical identification of black pieces at waste sorting technology (a), control of intumescent flame retardant content through feedback from laser pyrolysis assisted Raman spectrometry (b)

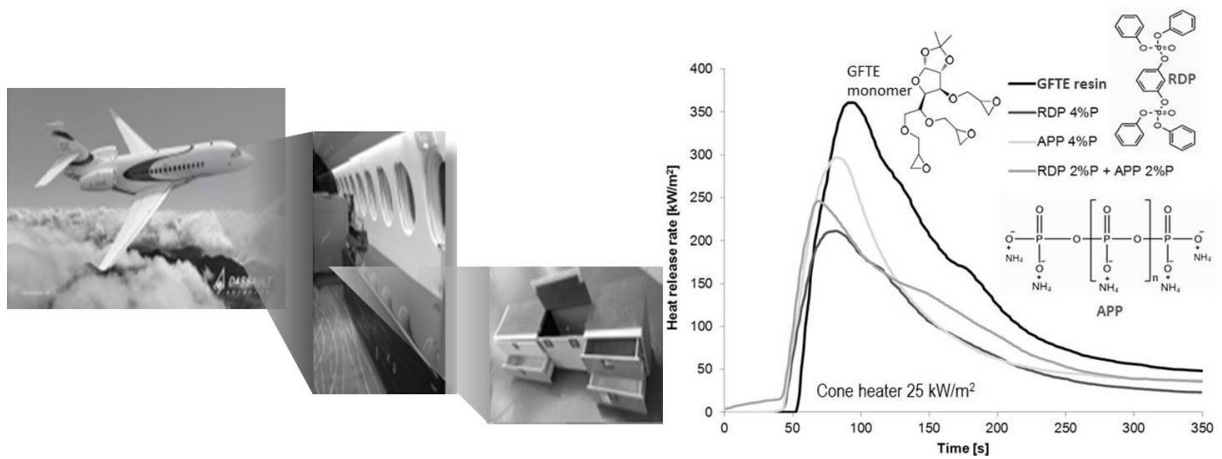


Fig. 3 Airplane-furniture made of bioepoxy composite and its heat release rate results

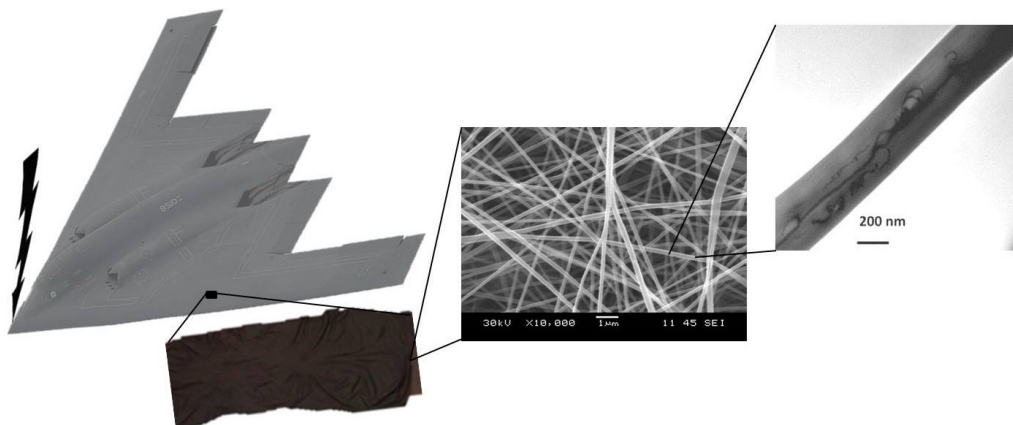


Fig. 4 Lightning protection of composite airplane using conductive nanofibrous epoxy layer



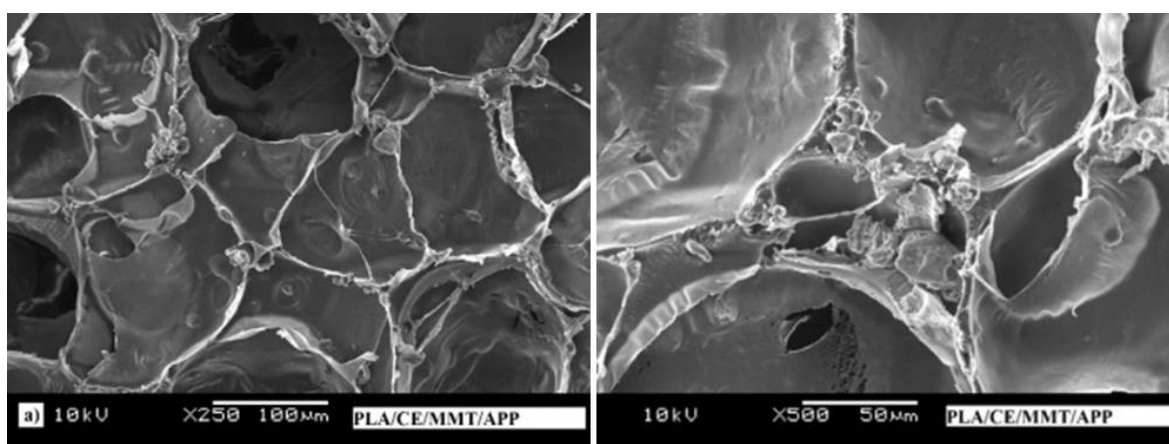


Fig. 5 SEM images of flame retarded PLA foams for light-weight fire-safe structures

the low consumption of energy and resistance against short circuit are of great importance. For this purpose biofoams have been developed in flame retarded form. Electron microscopic analyses revealed the flame retardant additives concentrated at the cell wall joints, as shown in Fig. 5, which proved to be of key importance regarding expandability and charring ability.

The biodegradable foams, when applied as cushion materials for packaging, have a significant environmental importance as well. In order to ensure the best foam structure for each application continuous non-destructive control of density is under development.

Green chemistry can advantageously use similar materials of high surface area for catalytic purposes. Utilizing the acquired skill in forming such materials, nanofibres have been prepared and used for organic and biocatalysis. The organo- and biocatalysts, prepared through bulk and surface modification of nanofibres (with active molecules and enzymes), preserved their activity even after several times of use [38, 39]. Other type of surface modification, achieved by plasma treatment, optimized the performance of electrospun biofibres made of various macromolecules, such as polycaprolactone and polyhydroxybutyrate, for using as scaffold in tissue engineering [40]. Online quantitative monitoring of the growth of cells can be performed using diffuse fibre-optic Raman spectroscopy [41].

### 3.2 Technologies of innovative pharmaceuticals

Raman micro-spectrometry combined with chemometry provides important support to the field of pharmaceutical technology. Qualitative, quantitative and structural analysis of pharmaceuticals, performed by Raman microscope, allows reverse engineering of solid dosage forms and identification of counterfeit products. Failures in

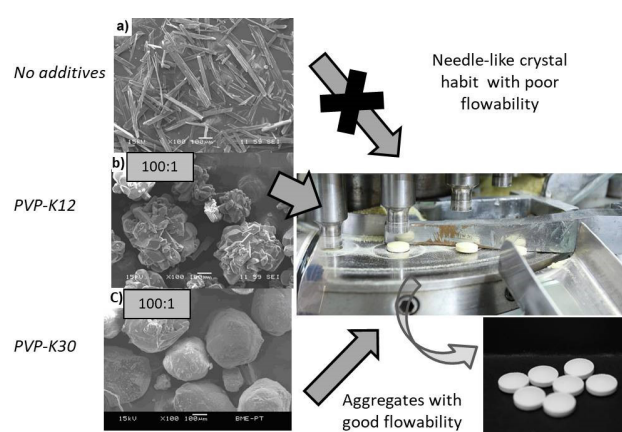


Fig. 6 Needle-like carvedilol crystals and spherical aggregates optimal for direct compression.

published compositions and their correction can be realized this way as it was performed in the case of isoptine [42]. Dual control, using fibre-optic Raman spectrometry combined with UV detection allowed us to add new abilities to reactors, in which drug syntheses or crystallization is performed. Polymer-assisted crystallization made possible, for example, to convert the hard-to-tablet needle-like carvedilol crystals to spheres suitable for direct compression as shown in Fig. 6. Interfacial polymer layer around the crystal particles made it feasible at very low (<1%) polyvinylpyrrolidone concentration.

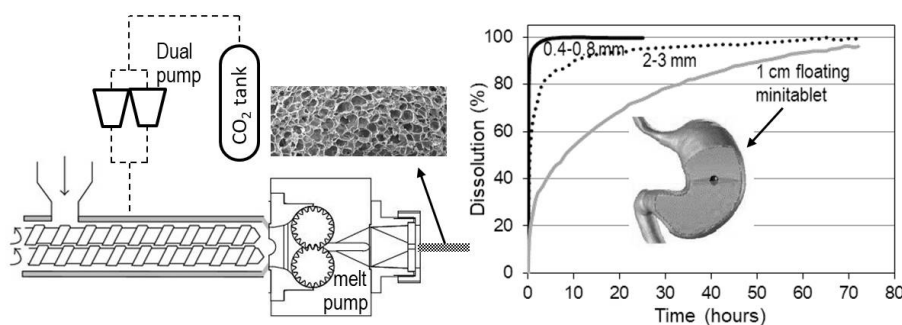
After applying similar control algorithms for bioprocesses [43] a particularly challenging new task occurred, requiring the elaboration of the first Raman-based monitoring, for fermentation of monoclonal antibodies (mAbs). Comparing the performance of Raman and NIR in-line spectroscopic analyses in the upstream process of this bi-drug, clear advantage for the former one appeared in the detection of glucose concentration (which is essential for

optimizing the fermentation circumstances). Encouraged by the achieved results [44] elaboration of continuous mAb-fermentation, assisted by Raman-based control, has been started.

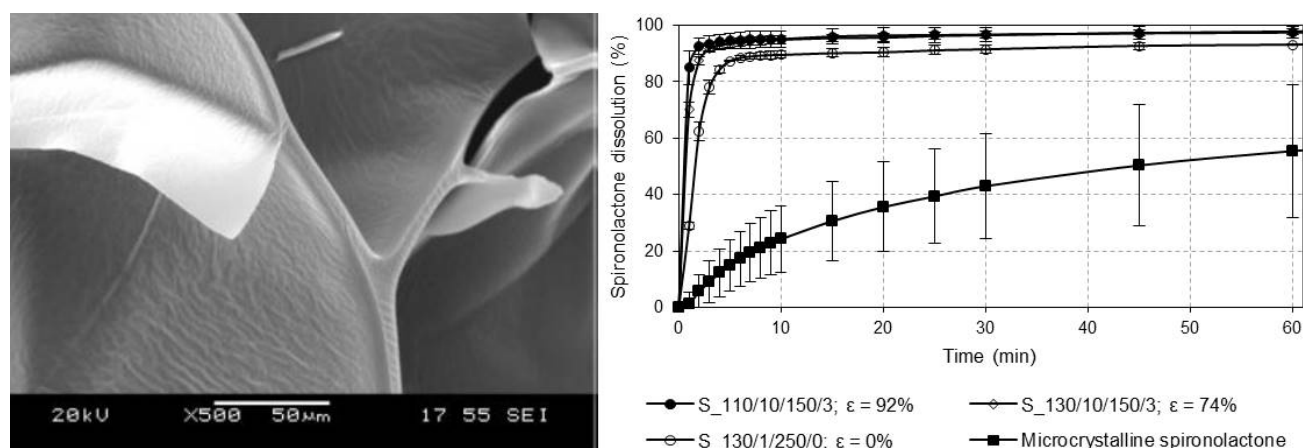
Continuous (bio)pharmaceutical technology became the main subject of our research work in this field. Melt and wet extrusion of a several model drugs [45, 46] helped to develop a unique infrastructure suitable for forming drug-containing fine foamed structures. Supercritical pharmaceutical extrusion technology [47] proved to be feasible both for forming floating tablet of sustained release and fast-release milled foams, containing tolperisone and spironolactone respectively, according to Figs. 7 and 8. Gear pump became an essential element of the controlled foaming technology, since a twin-screw extruder is not a pressure-generating device.

Nano-fibrous form of amorphous solid drug dispersions, prepared by various electrospinning (ES) techniques of increased productivity, using melt (MES)

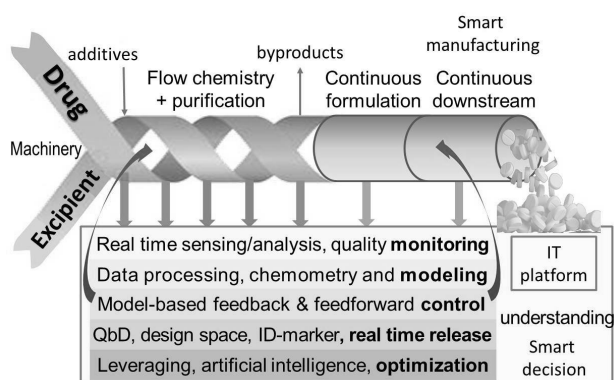
high speed (HSES), alternating current (ACES) circumstances, facilitate the bioavailability of drugs having poor water solubility [48-51]. Completely homogeneous distribution of drugs in polymer matrix was achieved this way according to Raman chemical mapping [52]. Ultrafast drug release of cardiovascular drug (carvedilol) was achieved from the prepared fibrous formulations (inserted into straws) suggesting that such a drug delivery system is suitable for storing the formulation in a stable solid dosage form and turning it rapidly into liquid form before administration [53]. The next steps towards realization of real-time release (i.e. evaluating and ensuring quality based on process data) in pharmaceutical technology were the development of controlled downstream processing (e.g. drying, milling) [54, 55]. These results, combined with flow drug chemistry, contribute towards the development of end to end pharmaceutical technology [56] with fully integrated interactive process units, the model of which is shown in Fig. 9.



**Fig. 7** Supercritical (Sc) extrusion for forming foamed floating minitablet of tolperisone and release profiles depending on the (grinding rate) particle size (polymer system: polyvinyl acetate+polyvinylpyrrolidone+polyethyleneglycol)



**Fig. 8** Rapid release of spironolactone from well grinded foam (polymer: Eudragit E), Sample names were composed from extrusion parameters in the order of prefix, temperature (°C), melt throughput (g/min), die pressure (bar), and CO<sub>2</sub> (%), separated by slashes. Porosity (%) is indicated by ε.



**Fig. 9** Model of an integrated end to end pharmaceutical process assisted with information technology (IT) including real-time monitoring and control, quality by design (QbD), predictions and optimizations based on artificial intelligence

#### 4 Conclusion

Environmentally motivated material and technology developments, shown through selected examples, can reinforce each other even if belonging to different domains of the industry. The presented ongoing research areas of the FirePharma group may express the commitment to innovative, controlled technologies, providing reliable production of various products. The real-time monitoring of the key

material characteristics and the relevant control of process units, which are communicating with each other, extend a multi-level supervision to the whole technology (similarly to the bioregulation of human beings). This complex activity serves, after all, the aims of industry/pharma 4.0, which result in improved quality, safety and decrease of ecological footprint. Common features in the development of "industry of the future" can be presented at the university education through the realized material and technology innovations, the examples of which are shown here.

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