Pharmaceutical and polymer technological developments based on computer control

Theses of Ph.D. Dissertation

Submitted by
Csontos István
Ms.C.

Supervisor
Dr. Marosi György
Assoc. professor

Budapesti Universiti of Technology and Economics
Department of Organic Chemical Technology
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1. Introduction, aims

The automatic reactors are commonly used in the industry, because the safety of the production process and the consistent quality of the products can be most effectively guaranteed by automated systems. According to the literature, the capabilities of the highly automated batch and semi-batch reactors are not adequately exploited, because the development is mainly done by traditional laboratory techniques and equipment, even in the cases of new technologies. The more economical production is limited by the lack of controlled model equipment and specialized knowledge. The use of this equipment can be essential in developing environmental-friendly technologies, which is becoming a key question in chemical industry due to the increasing environmental pollution. Especially important are the technologies, which allow avoiding toxic or not regenerable chemicals, solvents or decreasing the amount of emitted toxic materials.

The surface modification techniques are also considered as environmental-friendly, material-saving methods, as the surface modification or establishing surface coating results in brand-new properties by using small amounts of added material. The surface and interface modification, and the synthesis of the materials needed for this purpose should also be carried out under controlled conditions.

The aim of the dissertation was at first to develop an experimental equipment combining the advantageous properties of reaction calorimeters and industrial process controlled systems. Further aim was to make the system suitable for practical education of organic chemical technologies, development of pharmaceutical intermediates, polymer additives and interface modification components. The demonstration of the advantages of process control utilizing recent lab-scale modeling methods and development of industrial scale process controlled technologies belonged also to the set of aims. Last but not least an important aim was to use the synthesized additives for the modification of polymer systems, especially for the improvement of the characteristics of the interfacial layer.

During the synthesis of the pharmaceutical intermediates and polymer additives in reactor calorimeter our aims were to

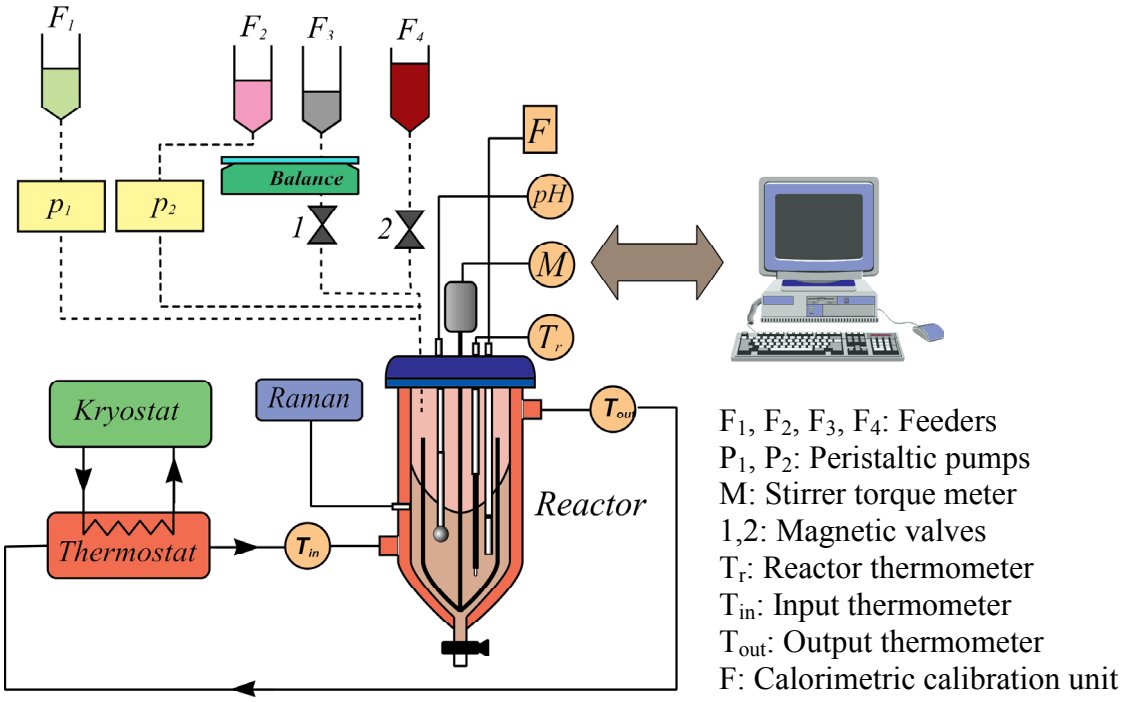
- achieve ***environmental advantages*** by elimination of the toxic and non-regenerable solvents, by developing solvent-free technologies and by decreasing the amount of side-products (to be dissipated), reactants (to be regenerated) and toxic gases (from the decomposition of the reagent),

- improve the ***economical efficiency*** of the technologies, e.g. by developing technologies suitable for up-scaling and by determining the optimal reaction conditions, thermal and kinetic characteristics,
- provide ***safe execution*** of the reactions by determining the parameters affecting the accumulation of the reagents and the enthalpy changes of the exothermic portions of the processes, as well as by thermal simulation calculations of the industrial equipment.

During the technological developments of the synthesis of pharmaceutical intermediates in many cases there was a need for experiments in industrial-sized reactors. The synthesis of polymer additives was in connection with specific polymer technological aims. By the surface modification of filler, reinforcing and flame retardant materials with the synthesized products our aim was to influence efficiently the mechanical properties and the transport processes.

2. Experimental

The flexible laboratory system, developed by us, got the name reactor calorimeter in order to distinguish it from the equipment described in the literature. This meets the requirements of the reaction calorimeters, but does not have their limitations. It can be adapted to reactors of different capacity and operated in batch, semi-batch and continuous mode. The supervisory program allows full control on the data acquisition and the advanced process control strategies. The user-interface is detailed and can be configured by the user. It supports the transfer of the technologies from the laboratory to the industrial level. The system has an accurate temperature controller, the variation of which is less then ±0.1 °C in isotherm mode. The computer controlled laboratory reactor calorimeter, developed for accurate and reproducible synthesis of new additives and co-additives and examination of organic chemical reactions (alkylation, chloromethylation, diazotization and polymerization), can be seen in the following figure:



Scheme of the reaction calorimeter system

3. New scientific results

1. ***Reactor calorimeter***, a new laboratory process controlled equipment, was developed in order to perform research and educational tasks. This automatic, computer-controlled system is suitable for development of batch and semi-batch chemical technologies.

   - After performing a lot of experiments in the ***reactor calorimeter*** we found that operation concept of the process control suggested in the literature should be improved. We elaborated a ***basic process level*** program part above the basic operation level for generalization the process control program. At this level the general operation routines belonging to unit processes of chemistry can be developed and stored. This level includes the characteristic parameters of the unit process. Development of a new technology requires only these key parameters. The creation of process control recipes is highly reduced in this way. (There is no need to set up the instrument specific parameters repeatedly.) Recipe modules at basic process level have been elaborated in this work for aromatic alkylation, chloromethylation and diazotization reaction types.
   - The ***reactor calorimeter*** integrates the advantages of the reaction calorimeters and the industrial process controlled systems, supports the

determination of thermodynamic parameters between the practical conditions of the technology, and the progress of the reaction can be monitored on-line. The control algorithm of ***the elaborated technology can be transferred easily to industrial size***.

- New educational concept was created: organic chemists are needed being able to integrate the advantages of the process control into the developed technology during the labor scale optimization. On the basis of the described experimental research a ***laboratory practice of computerized process control*** of batch and semi-batch type reactions was ***firstly established in the education of organic chemical technologies***.

2. The economical efficiency of production, the improvement of safety and the consideration of ***green chemistry*** were achieved in the technological development of pharmaceutical intermediates:

- Replacement of environmental pollutant and toxic solvents were carried out. The optimal conditions of the reaction were determined with the new solvent.
  - The synthesis of 7-isopropoxy-isoflavone was achieved in different regenerable solvents that appropriate for industrial use instead of dimethyl formamide. Economic decision is required to choose the optimal solvent considering the benefits of the developed technology and the less yield.
  - The benzene in the synthesis of 3,4-diethoxy benzyl chloride was replaced with cyclohexane, which is much less toxic solvent. The conversion rate of the reaction is higher in the new solvent. The computer control of this process permits the minimization of the concentration of the by-products. The patent plan of the developed algorithm was given to the industrial partner.

- The ***efficiency of production*** was successfully increased in the case of the following reactions:
  - In the synthesis of 7-isopropoxy-isoflavone the suitable temperature and dosing profile enable the higher reaction temperature that means higher reaction rate. In this way the overboiling of the alkylation agent can be avoided and the loss of the reagent can be decreased. Good quality, filterable, reproducible product was achieved and 10-15 % alkylation agent was saved.

- In the case of the chloromethylation of the 1,2-diethoxy benzene in cyclohexane we reach the same yield during the production as in the original, benzene solvent. The affecting conditions of ratio of the unreacted 1,2-diethoxy benzene and the by-products were determined.

3. The results in the area of synthesis of ***polymer additives*** are the follows:

- For increasing the ***safety of the production*** of dangerous, ***peroxide*** type polymer ***initiators*** the thermal characteristics of the conventionally developed syntheses were determined. The correlation of the thermal runaway and stirring conditions were determined. We defined the conditions that enabling to avoid the risk.

- The syntheses of new type ***reactive surfactant*** additives were ***monitored by a novel Raman method.*** The progress of the Diels-Alder addition was followed directly in the reactor through optical cable equipped with special optics by the Raman spectra. The intensity decrease and the shift of the strips assigned to the double bounds proved the reaction. The most characteristic change was the decrease of the intensity of the unsaturated fatty acid at 1658 cm^{-1}.

- In the synthesis of new phosphatide and boroxosiloxane type flame retardant additives the elaborated control is based on the heat release and the changes of torque of the stirrer.

- ***New procedure was elaborated for preparing nanocomposite*** where the clay reacts with latex created by emulsion polymerization. The advantage of this water based, environmental-friendly method is that there is no need for organic solvent. The formation of nanocomposite was verified by WAXS method. The product was characterized by DSC and TG measurements. The structure of the nanocomposite was studied by AFM and SEM methods.

- New, ***efficient and environmental-friendly technology was developed*** for the synthesis of 1-phenilazo-2-naftol type pigments. Well-suited simulation of the diazotization process was used. The sequence of the control mode changes was combined with temperature and dosing profiles. The reaction time decreased by 11% in the new technology. The concentration of the nitrogen-oxides gases in the reactor decreased by 89% compared to another moderate automatic (dosing controlled) technology. The emission of the nitrogen oxides decreased by 97,8% compared to the manually controlled procedure. Applying the new

technology, the ***reproducibility*** of the pigment produced by azo-coupling significantly increased.

4. ***Applying the polymer additives*** synthesized in the reactor calorimeter the following results were achieved:

   - The effect of ***reactive surfactants*** on adhesion and homogeneity were observed (interfacial agent that combines the effect both dispersing and coupling agent). The chemical coupling between the reactive surfactant and the polymer matrix was proved by XPS method.

   - The effects of the reactive surfactants on the mechanical properties of polymer composites were investigated.
     - The strength and the modulus increased 20-127%, the elongation at break increased 258-392% comparing to the original value of polypropylene composite filled with $CaCO_3$ and reinforced with glass fibre after introduction of 1% reactive surfactant.
     - Reactive surfactant-elastomer multilayer structure was formed on the surface of the filler particles. In this way the tensile strength of oriented polypropylene fibres was increased by 25% even at higher degrees of orientation.
     - The effective intumescent flame retarded polymer system requires relatively high additive content. However the mechanical properties affected disadvantageously. The surface treatment with synergetic reactive surfactant improved not only the fire retardancy but also the tensile strength by 50%.

   - The cumulative effect of stabilizers (e.g. flame retardant) and surface modifier additives on the control of the transport processes and the stability was investigated. These have a great effect on the production, the processability, usability of the composites.
     - It was established that the hydrolytic stability of ammonium polyphosphate — pentaerythrite —melamine intumescent flame retarded additive system can be improved significantly by surface treatment with reactive surfactant. The water sensibility was determined by conductivity measurements of the aqueous solution after extraction of the flame retarded polymer samples. After the modification practically no dissolution occurs. Consequently the flame retardant components are hindered from migrating to the surface during utilization.

- It was established that application of polyboroxosiloxane elastomers improves the properties of the flame retarded systems. During the forced burning test of polypropylene containing intumescent flame retarded system and 1.5% polyboronoxosiloxane, a continuous, coherent layer was formed on the surface of the sample. This layer hinders the mass and heat transport, so the burning is inhibited actively. The flame retardancy effect was verified by TG measurements.

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