University of Szeged

Faculty of Pharmacy

Department of Pharmaceutical Technology

Summary of PhD Thesis

Dynamic Force Measurements in Preformulation of Solid Dosage Forms

By

András Kelemen

Supervisor:

Prof. Dr. Habil Klára Pintye-Hódi DSc

Szeged

2012

1. Introduction

Solid dosage forms, currently the most common dosage forms in pharmacy, contain not only the active pharmaceutical ingredient (API), but also various ingredients such as fillers, sweeteners, etc. During the manufacturing of tablets, application of the appropriate pressure is very important, as it influences the quality of the comprimates. Knowledge of the elasticity of polymer films used in the coating process and the deformability of granules and pellets is very important during tablet manufacturing. In the case of conventional tablets, the swelling behaviour influences the rate of disintegration, which determines the rate of dissolution of the API from the tablet. Knowledge of the swelling behaviour of swellable matrices is also important, for this plays a role in prediction of the dissolution profile.

Determination of the above mentioned physical parameters of solid dosage forms is based on the measurement of dynamic forces. In consequence of the nature of the task, computer–aided measurement and evaluation technology is required.

2. Aims

The overall aim of the work reported in this dissertation was the development of measurement and analysis systems with which to study the effects of forces during drug powder compaction, and also the deformation process and swelling behaviour of solid dosage forms, through use of a digital computer. The specific aims were:

- to develop a software system relating to the use of an instrumented tablet machine to measure punch forces and displacement during compression;
- to develop algorithms with which to evaluate compaction data profiles;
- to develop a software system to be used in conjuction with a swelling force tester in order to study the swelling behaviour of comprimates and tablets;
- to develop a software system with which to study the deformation behaviour of solid dosage forms during loading.

3. Hardware and software

3.1. Hardware

A computer–based data acquisition (DAQ) denotes the process in which physical signals (mechanical force, displacement, etc.) are transformed into digital electrical signals for processing by a digital computer. Figure.1. outlines the scheme of computer–based DAQ system.

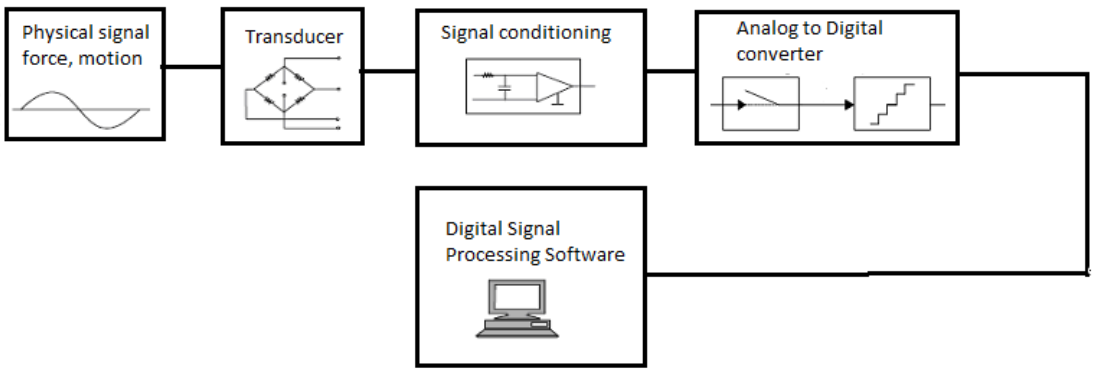

Figure 1. Outline of the DAQ system

A *transducer* converts a physical signal into an electrical signal. A *signal conditioning* converts the electrical signals of transducers into an acceptable format for an analog to digital converter (ADC). This means amplification, linearization, and low pass filtering. The *ADC* unit converts band-limited electrical signals into a digital sequence. The conversion involves sampling and quantization processes. A *digital signal processing* unit stores and displays the digital sequence and applies signal-processing algorithms, which calculate the desired parameters from the digital sequence through different methods.

A DAQ box (device and embedded software) was developed for digitalization of the force and displacement signals of instrumented tablet machine and the hardness tester. For swelling force tester an embedded DAQ unit was developed for acquisition of the swelling force signals. All DAQ units are based on microcontroller.

3.2. PC side softwares

3.2.1. Tablet machine

The software has a wide range of possibilities to show and evaluate the force and displacement signals, e.g. display force–time, displacement–time and force–displacement curves (Figs 2 and 3.), and it calculates the compression parameters in a manner dependent on the display profiles.

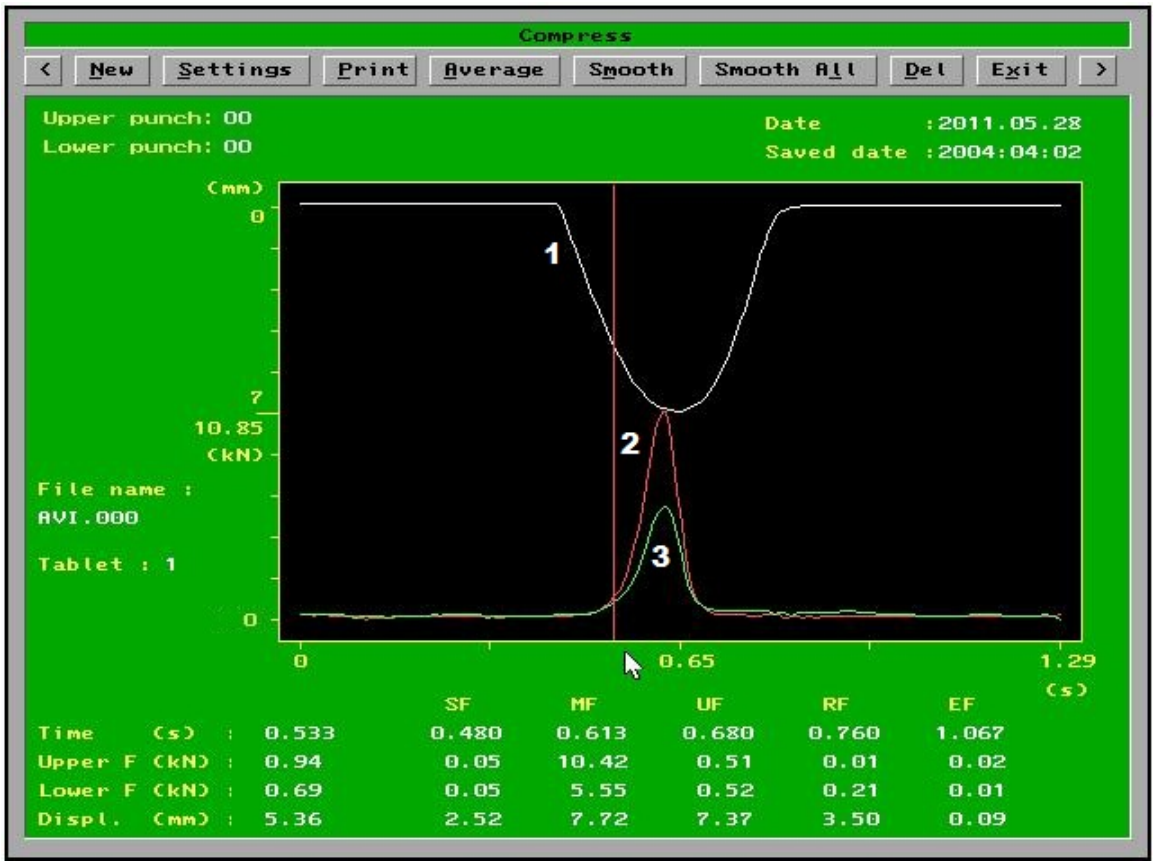

Figure 2. Screen shot of force–time, displacement-time curve analysis (AVICEL PH-101);
1. displacement-time, 2. upper punch force–time, 3. lower punch force–time diagrams.
SF: the time in seconds when the upper punch impacts into the die, **MF**: the maximum upper punch force, **UF**: the time in seconds when the upper punch leaves the die. R**F**: the residual force, **EF**: the ejection force.

It is often seen that the compression force reaches its maximum value before the upper punch reaches its maximum distance, as shown in Figure 2. This effect occurs in consequence of the stress relaxation of the powder. This is a characteristic feature of solids that exhibit plastic deformation behaviour during compression.

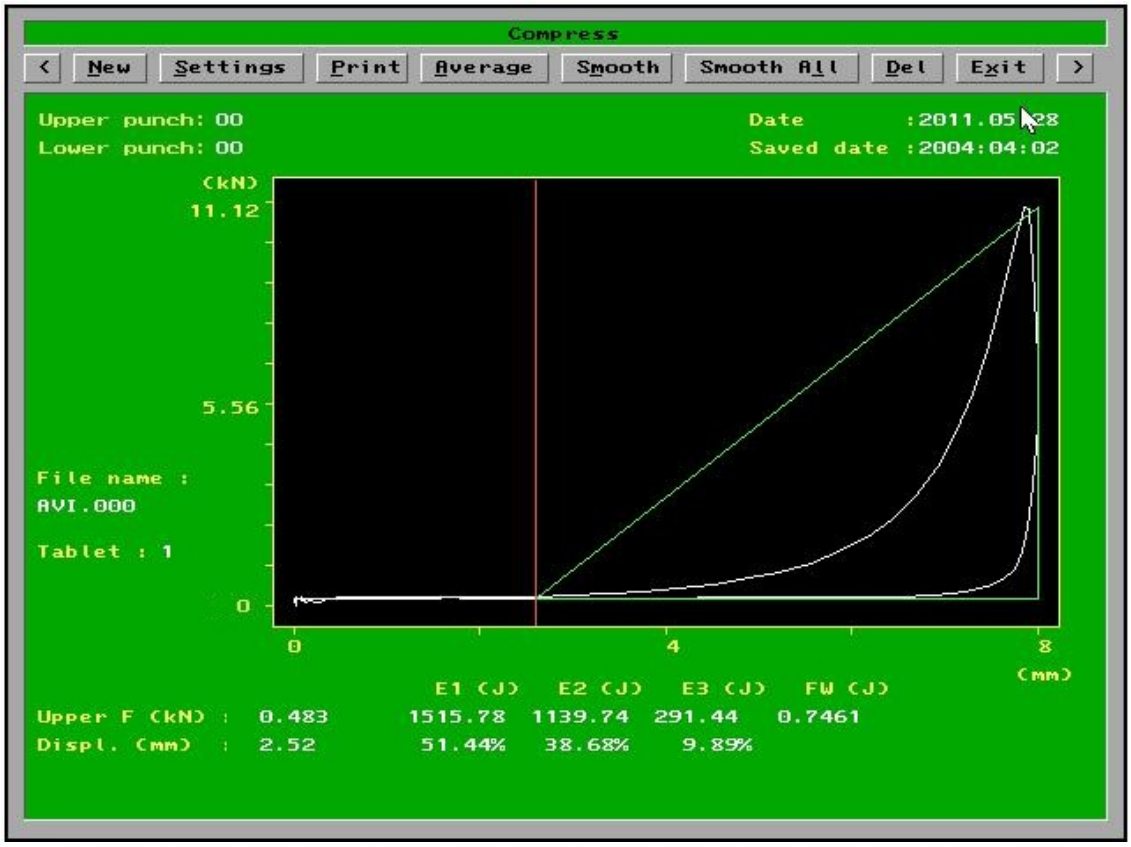

Figure 3. Screen shot of force–displacement curve analysis (AVICEL PH-101). **E1**: Energy lost by rearrangement of the particles during compression; **E2**: Energy of compaction; **E3**: Energy recovered during decompression; **FW**:friction work.

The developed equipment in conjunction with the software is suitable for determination of all the critical compressional parameters which play important roles in production and in the quality of tablets.

3.2.2. Swelling force tester

Conventional tablets always contain disintegrants which promote rapid disintegration of the tablets. The swelling kinetics of these disintegrants can most commonly be described with the RRSBW (Rosin-Rammler-Sperling-Bennett-Weibull) distribution

$$F(t) = F_{\infty}(1 - e^{-\frac{(t-T)^{\beta}}{a}})$$

where $F(t)$ is the swelling force (F_s) as a function of time t, F_{∞} is the maximum value of the swelling force, T is the lag time, a is a scale parameter that describes the time dependence, and β describes the shape of the curve.

The software offers a broad array of possibilities through which to illustrate and evaluate the F_s versus time curves with the important parameters (time, F_s, $t_{63.2\%}$, and dF/dt) exemplified in Figure 4.

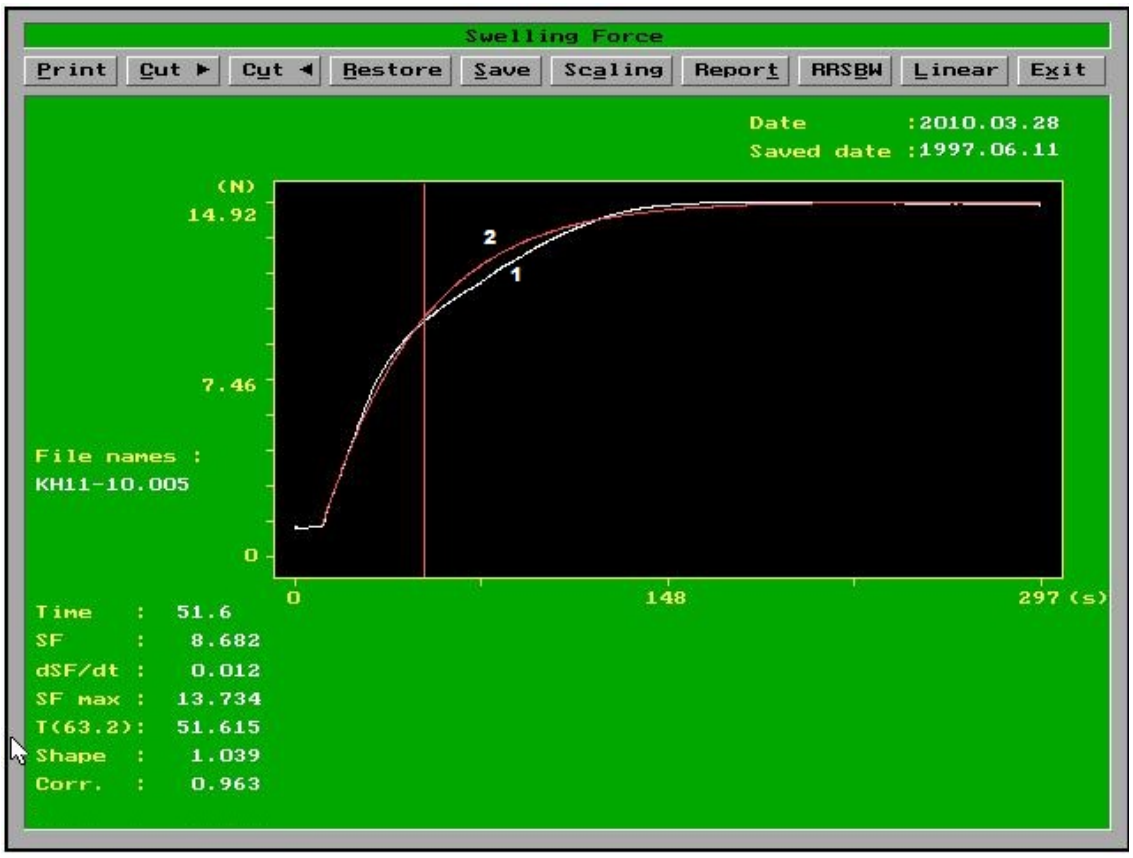

Figure 4. .Screenshot of F_s curve.
Curve 1 is the force–time curve, Curve 2 is the RRSBW curve fitted to the force–time curve. **SF**: F_s, **dSF/dt**: derivation of F_s at the position of the cursor. **SF max**: maximum value of F_s, **T(63.2)**: the characteristic swelling time, **Shape**: shape parameter (β), **Corr**: correlation coefficient

The characteristic swelling time ($t_{63.2\%}$) and shape parameter are calculated from RRSBW equation by linear fitting.

Another type of tablets, swelling matrix tablets, often exhibit swelling kinetics profiles that can not be described with the RRSBW distribution. The mathematical model used to fit this profile was the power law model

$$\frac{F(t)}{F_\infty} = kt^n$$

where $F(t)$ is the measured swelling force at time t, F_∞ is the maximum value of F_s, n is the shape parameter and k is the swelling rate constant.

3.2.3. Hardness tester

During the evaluation, the software displays the deformation curve, the calculated work curve, the differential curve, and the parameters of the breaking point of the material (Figs 5 and 6.). For pellets, the software calculates four characteristic points (Figure 5). The deformation of a pellet starts short period of elastic deformation. The first characteristic point is the maximum value of the elastic deformation. In the second stage, a short period of plastic deformation occurs. The second characteristic point is the end of the plastic deformation. The third stage involves plastoelastic or viscoelastic deformation depending on the material. The third characteristic point is the end of this stage, at which point the pellet begins to break. The last characteristic point is the point when the pellet breaks totally and the pressure jowl reaches the sample holder.

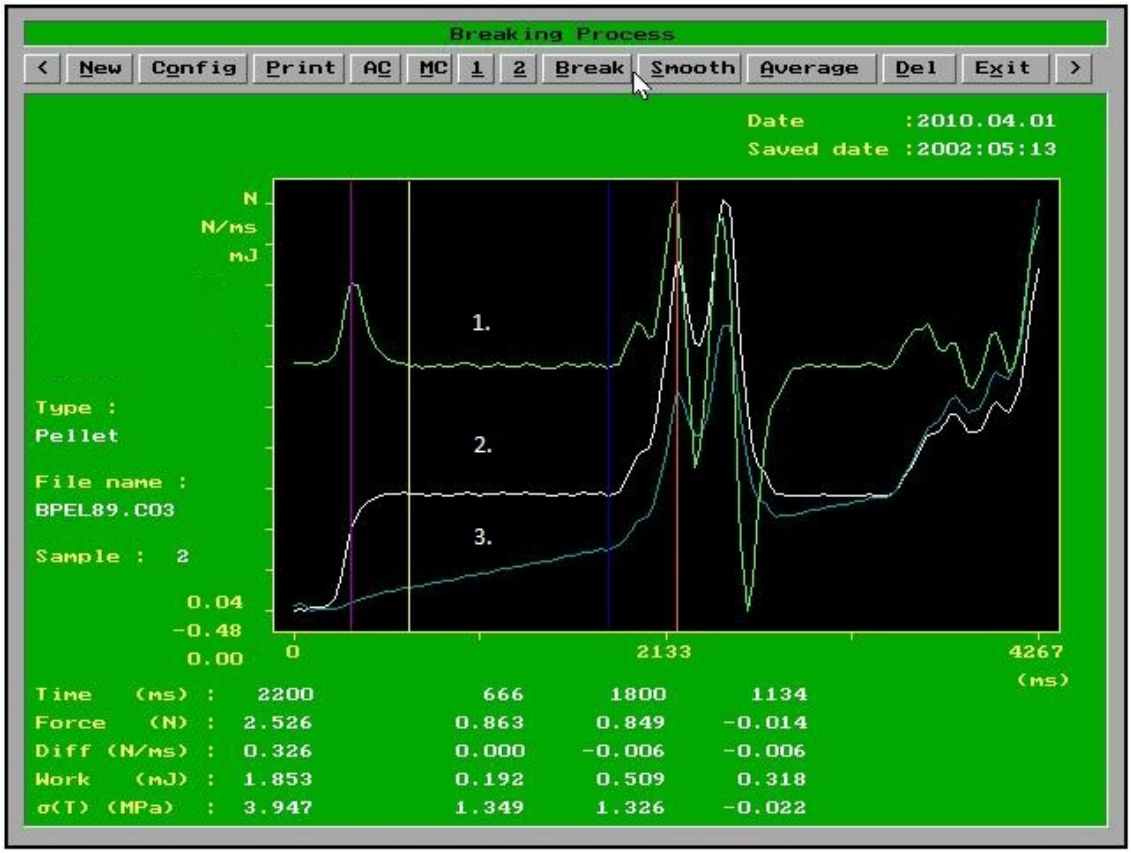

Figure 5. Deformation curve of a pellet
1: Differential curve, 2: deformation curve, 3: energy curve.

For polymer films and conventional tablets (Figure 6), the software calculates the location of the breaking point from the maximum absolute value of the differential curve. For a film, it is possible that the film does not break away. In that case, the breaking is the value of the force when the pressure jowl reaches the sample holder.

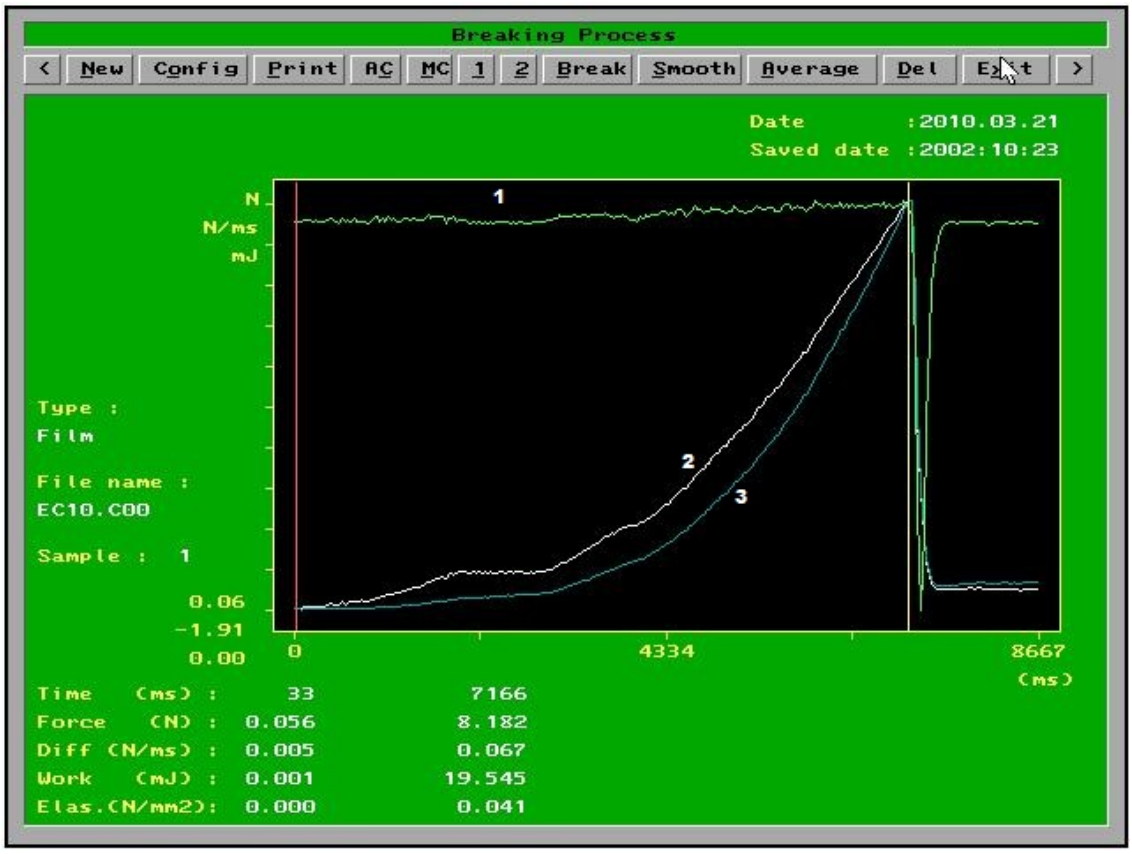

Figure 6. Screen shot of deformation curve of polymer film (the curve 1. the differential curve; curve 2 depicts the force; and the curve 3. the energy).

4. Results

The developed softwares used with successful in the solution of the different pharmaceutical technological problems:

1. For gums, which have a very elastic behaviour, the energy of elastic recovery (E_3) was found to vary linearly with the increasing compression force. Furthermore, the deformation tests showed that the increase of pressure force did not cause any significant changes in the deformability of the comprimates.

2. During the compressibility study of filmcoated crystals was established, that the filmcoating polymer decreased the plasticity, but the other parameters of tablettability (friction, filling space, flowability, etc.) were improved.

3. The software is suitable for study of the swelling force of a conventional tablet and a swellable matrix system. The swelling behaviour of conventional tablet can be described with the RRSBW distribution. But the process of swellable matrices can describe with the power law model.

4 The software was also very well in the following of deformation process of pellets. It was established that their behaviour are different than the deformation process of polymer films or tablets.

The developed equipment is now in everyday use in the scientific research work and in the educational work in pre- and postgraduate courses at our department.

Process Analytical Technology (PAT) is currently playing an important role in the quality assurance of dosage forms in the pharmaceutical industry. It permits the monitoring and control of every step in the development cycle. The application of new equipment and algorithms makes possible the more precise determination of the preformulation parameters for the pharmaceutical industry.

5. Publications related to the thesis:

1. **Kelemen**, **A.**, Szöllösi, A., Zsótér, A., Pintye-Hódi, K., Török, C., and Erős, I. (2002): Measurement of the swelling force of some sodium strach glycolate products with new software. Hung. J. Ind. Chem. Vol. 30 pp. 73-76
   IF: 0,084
2. Muskó, ZS., Bajdik, J., Pintye-Hódi, K.,Szabó-Révész, P., **Kelemen**, **A.** and Erős, I. (2002).: Preparation of pellets containing theophylline. Pharm. Ind. 64. Nr.11. 1194-1198.
   IF:0,279
3. Bajdik, J., Pintye-Hódi, K., Novák, Cs., **Kelemen**, **A.**., Regdon Jr, G. and Erős, I. (2002): Indirect methods for determination of the protective effects of coating films on the surface of crystals. J. Therm. Anal. Calorim., Vol 68 613-627.
   IF:0,598
4. Kása Jr, P., Jójárt, I**., Kelemen .A**. and Pintye-Hódi, K. (2011): Formulation study of directly compressible chewable polymers containing ascorbic acid. Pharm. Dev. Tech. (DOI: 10.3109/10837450.2011.646426)
   IF: 1,107

Other publications

5. **Kelemen András**, Pintye-Hódi Klára, Erős István (2004): Mérés-adatgyűjtő és jelfeldolgozó szoftverek fejlesztése a szilárd gyógyszerformák preformulációs vizsgálataiban. Acta Pharm. Hung. 74. 177-186.
6. Szalay, A., **Kelemen, A.,** Kása Jr, P., Erős, I. and Pintye-Hódi, K. (2005): Effect of the particle size and shape parameters on the flow properties of sorbit. Eur. J. Pharm . Sci. 25; Suppl. 1. , S192 - S194.
7. Bajdik, J., Bölcskei, É., **Kelemen**, **A.** and Pintye-Hódi, K. (2007): Rapid method to study the sedimentation of a pigment suspension prepared for coating fluids. J. Pharm. Biomed. Anal. 44. 1159-1162.
   IF:2,76

8. Bajdik, J., Baki, G., **Kelemen**,**A.** and Pintye-Hódi, K.: (2007): Formulation of longacting solid intravaginal matrix systems containing laxtic acid. Eur. J. Pharm. Sci. 32, Issue 1, Suppl. 1, 35.
9. Bajdik, J., Baki, G., **Kelemen**,**A.** and Pintye-Hódi, K.:(2008): The effect of wetting of powder mixture on the preparation of hydrophillic matrix granules with high-shear granulator. Chem. Eng. Res. Des. 86 1-7.
   IF:0,989
10. Baki, G., Bajdik, J. **Kelemen**, **A.** and Pintye-Hódi, K. (2009): Formulation of a solid intravaginal matrix system to prolong the pH-decreasing effect of lactic acid. J. Drug. Del. Sci. Tech. 19 (2) 133-137.
    IF:0,508

Presentations

1. J. Bajdik, É. Bölcskei, **A. Kelemen**, P. Szabó-Révész, K. Pintye-Hódi: Technological opportunities to improve the stability of a pigment suspension prepared for coating fluids. 5th World Meeting on Pharmaceutics Biopharmaceutics and Pharmaceutical Technology, Geneva, 27-30 March, 2006 PO 53 (March 30)
2. J. Bajdik, G. Baki**, A. Kelemen**, K. Pintye-Hódi: Formulation of longacting solid intravaginal matrix systems containing lactic acid. 2_{nd} BBBB Conference on Pharmaceutical Sciences, Tallin-Tartu, Estonia, 2007.