An Interactive Software Tool for the Design of Pharmaceutical Products and Processes

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ABSTRACT

A software tool will be developed to integrate and simulate the unit operations as well as the complete process. This is intended to facilitate the teaching and learning of the design of pharmaceutical processes. Part of the software was developed using Microsoft Visual Basic over a period of two years subsequent to our previous work. The objective of this summary paper is to illustrate the power of this software code, ProWare®, which simulates 'powder processing' in pharmaceutical process. It enables students to simulate the packaging process of API into various forms: tablets, powders, capsules and granules. Students can obtain various results, like particle-size distribution and equipment sizing calculated by built-in empirical equations and mathematical models. To extend the software, more features will be added. These are the unit operations of reaction, recovery and purification, and final dosage form.

Keywords

ProWare®, pharmaceutical process, process integration and simulation, powder processing, pharmaceutical dosage form

INTRODUCTION

Over 90% of commercial drugs are in solid form; they may be powders, granules, tablets or capsules. Pharmaceutical process engineering, especially bulk solids processing, is a very important topic in the current Chemical Engineering curriculum. Students a required to learn how to design and develop such high-value-added products and processes. A generic pharmaceutical process is shown in Figure 1. It consists of four main steps: (1) reaction of active pharmaceutical ingredients (API), (2) recovery and purification of the API, (3) powder processing, and (4) final dosage form. Design and development of the full-chain process requires extensive and tedious calculations, which tend to stifle the creative thinking of students. Consequently, a teaching tool with the proper GUI and engineering contents is needed.
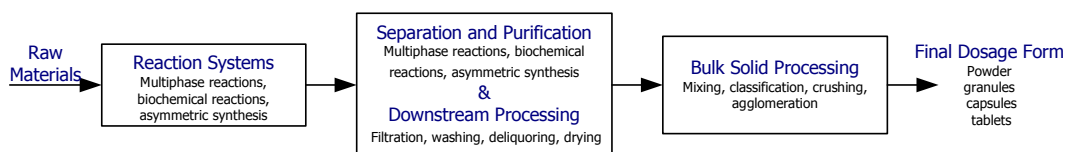
Figure 1. A generic pharmaceutical process

The ultimate goal of this project is to develop a software tool to integrate and simulate the design of unit operations and the complete process, especially the dosage form that cannot be handled by the existing commercial software. Co-author K.Y. Fung and four UG students developed a software tool, called ProWare, over a period of two years using Visual Basic [1]. ProWare gives a preliminary image of the ultimate software, which simulates the unit operations of 'powder processing' in a pharmaceutical process. This paper summarizes the current development of ProWare and how it will help in teaching and learning the development of pharmaceutical process engineering. To develop the software further, we will begin from ProWare and then add in other unit operations of reactions, separations and purifications.

CURRENT DEVELOPMENTS

Unlike commodity chemical processes, purified API solids should serve in final dosage forms such as powders, granules, tablets and capsules. Bulk solids processing is important to ensure that APIs possess optimum particle size distribution (PSD) and are in precise quantity in the tablets or capsules. ProWare can currently simulate bulk solids processing involving mixing with excipients, classification, crushing, agglomeration (see Figure 1). Built-in heuristics or models in the software guide the users on decision-making at each major step. It can generate different processes under different project specifications for in-class demonstrations. ProWare can also give recommendations to students on how to change the flowsheet or other equipment specifications in order to obtain the desired PSD without spending too much time on complicated and tedious calculations.

ProWare – Input Interface

The simulation starts from the selection of excipients, components that are added to a pharmaceutical dosage form to provide auxiliary functions. Figure 2 shows the interface for the excipient selection. Users may first specify the major ingredients and other parameters such as the mass per dosage and mean particle size as well as their physical properties, etc. The next step is to select excipients from the software database or to define other excipients provided that their physical parameters, such as density, are available.

Figure 2. Interface for excipient selection

Flowsheet Generation

After all required information is entered, a process flowsheet interface will then be generated. As shown in Figure 3, a solid processing flowsheet is composed of crushes, blenders, a granulator, screens, and compactors. Students may specify the arrangement of crushers and blenders as well as that of the granulator. In general, APIs and selected excipients are mixed, crushed and blended before entering the granulator. The granules will, if necessary, be re-crushed in the second crusher to ensure better mixing. Streams of lubricant and disintegrant enter and mix in the second crusher prior to tableting or capsulation. Students may simply click the icon on the interface for specific heuristics to assist their process design. When the crusher arrangement and granulation process selection are provided, the final process flowsheet may be synthesized as shown in Figure 4.
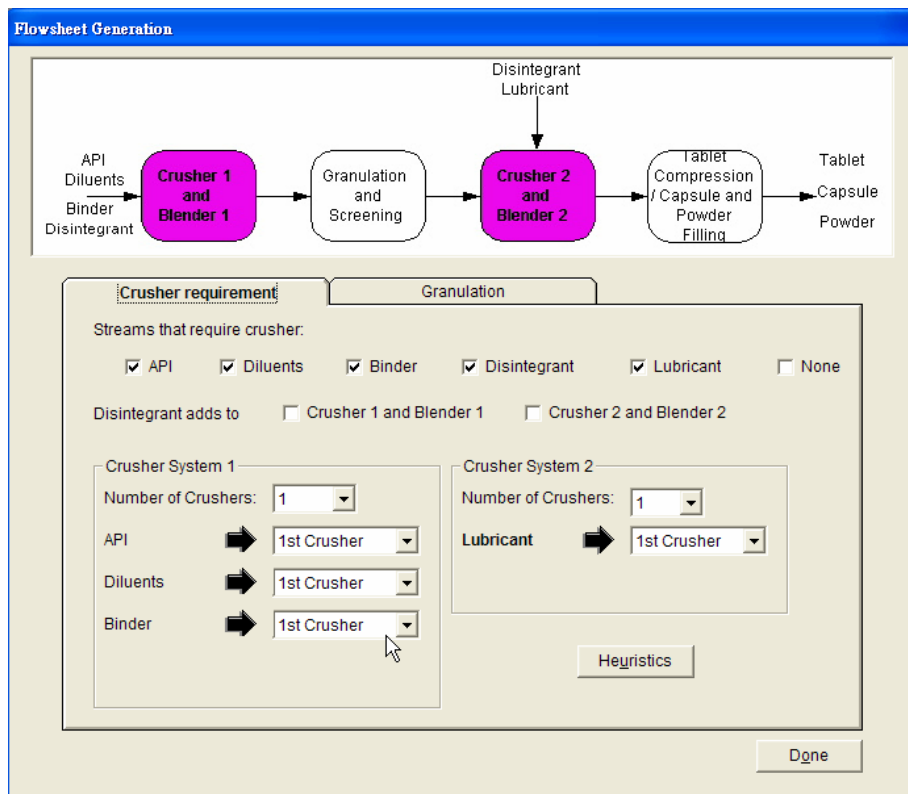
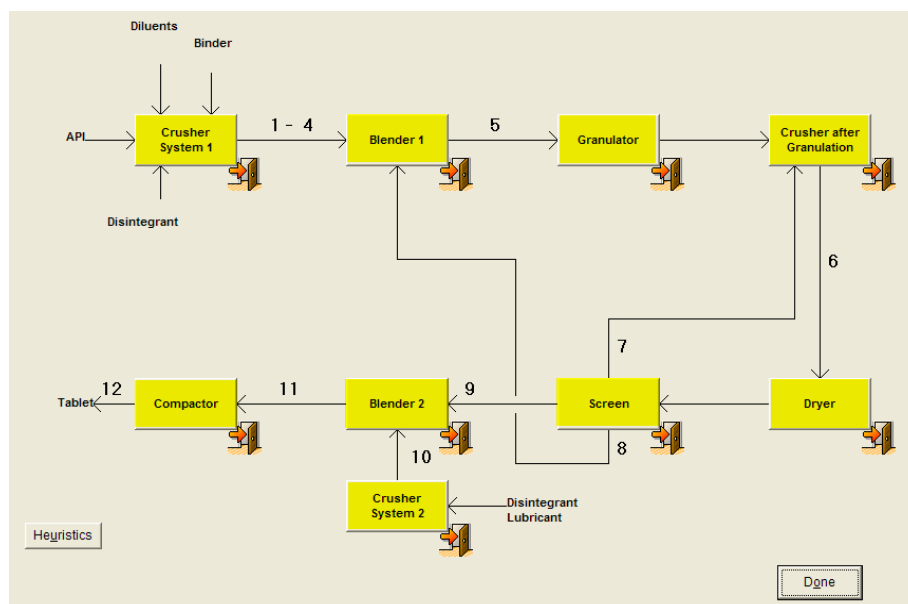Figure 3. Interface for flowsheet synthesis

Figure 4. The process flowsheet synthesized in the software

Equipment Selections and Specifications

The simulation then moves to another phase: equipment selections and specifications. Students may select the equipment and enter operating parameters by simply clicking the unit operation icons. The software will guide students in specifying key operating parameters for each piece of equipment.

Results of Particle Size Distribution

Finally, the particle size distribution (PSD) along the processing train could be calculated by the built-in population balancing equations. Figure 5 displays the PSD results along a specific process. PSD results for different streams of the flowsheet are displayed to help users visualize the change in particle size during the process. Usually, there is a specification for the PSD entering the compactor or capsule-filling machine. If the final PSD does not match the specification, users may go back to the input interface or equipment specification stage to change the process parameters. Results may also be exported to Microsoft Excel for comparison. Equipment sizing is also performed in the software. This helps students to understand the scale of processes.
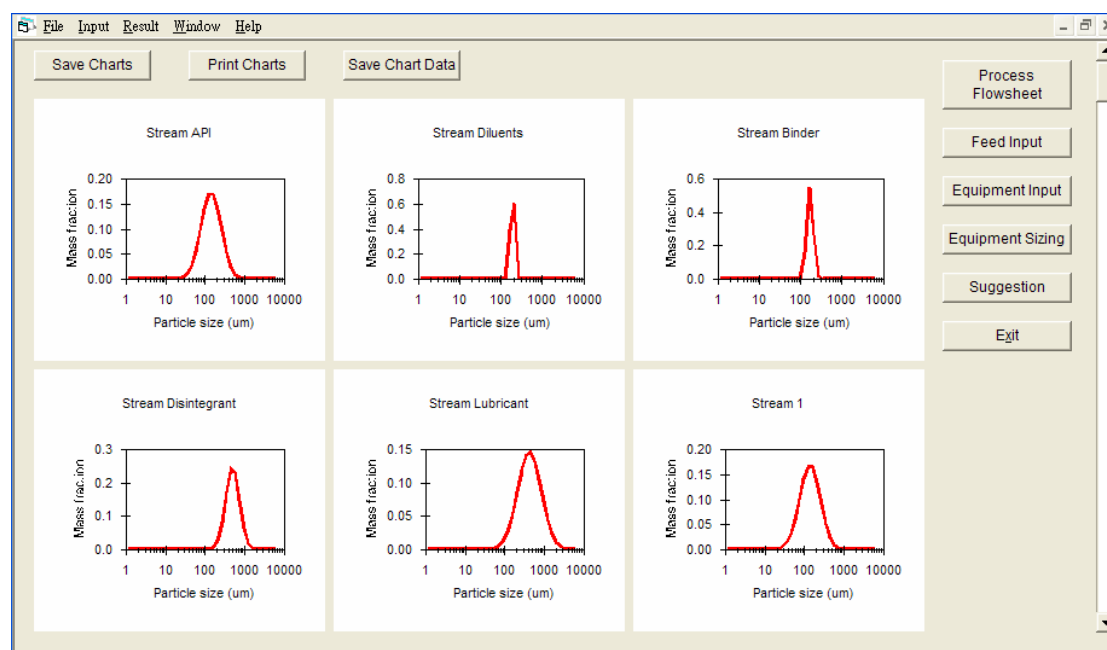

Figure 5. PSD results calculated in the software

FURTHER DEVELOPMENT

In order to simulate the whole pharmaceutical process, the existing ProWare® GUI will be modified by adding unit operations of reactions, and separations and purifications, as well as the final dosage forms. It will also include reactors, crystallizers, extractors, chromatographic columns, distillation columns, and tableting machines, etc. The design models of some of these unit operations are in the later stages of development and will be added to the software.

For the reactor module, reaction conditions, reactor selection and specification will be included in the software. The software generates results for reactor performance including its recovery and yield. To achieve this, a strong database of thermodynamics properties is needed.

The separation and purification module includes crystallizers, extractors, chromatographic columns, distillation columns, filters, washers and dryers. Crystallizers should be the final equipment in the separation process since powders need to be generated for the bulk solids processing and the final dosage form production. The size of the crystals is very important since it affects the whole bulk solids processing sequence and its size will be modeled by using population balance equations.

For bulk solids processing and pharmaceutical dosage form production, each unit operation can be extended to include a more detailed design of the equipment. Experimental results are required to obtain the empirical relations between the equipment operating parameters and the parameters required in calculating the particle size distribution. This work will be carried out in parallel with the programming tasks.

ACKNOWLEDGEMENTS

REFERENCE

[1]. Cheng, Y. C., Lee, H. K., Tsang, K. F. and Tsang, S. K. (2003). *Development and Marketing of a Software Tool for Powder Processing of Traditional Chinese Medicines*. Final Year Design Project of Department of Chemical Engineering.