Using an Interactive CD-ROM to Teach Pharmacy Students Unit Operations

by Cristián Tapia, Carlos Basualto, Jaime Sapag-Hagar, Fernando Valenzuela Lozano, Mauricio Muller, and GianFranco Zunino

Introduction

One of the main challenges for pharmacists working in the pharmaceutical industry in Chile is the ability to develop a validation program. Development of such a program requires an understanding of the details and basis for each process step, and the ultimate expectations. If the process and product are known, it allows the pharmacist to establish the design of a validation program using reasonable and appropriate requirements or criteria, process limits, and critical instruments. With this objective in mind, an educational CD-ROM was developed as a complement to the traditional practical-theoretical teaching of unit operations to pharmacy students. The CD-ROM aims to contribute to a satisfactory understanding by the pharmacy students of the equipment and the procedures normally used in the pharmaceutical industry.

Background

This CD-ROM contains five main subjects:
1. Solids
2. Liquids
3. Semisolids

Note: English translations of figures are shown in yellow.
Oral solid dosage forms are one of the most important pharmaceutical dosage forms normally produced with the most common being tablets, capsules, and powders. The traditional method for producing tablets normally involves two size enlargement processes in sequence, i.e., a granulation of the fine particulate drug, often milled with a filler, followed by the compaction of the granulated powder. Capsules are frequently chosen as the dosage form for clinical trials, not only because of their safety and reliability, but because their use accelerates the entire process. Since capsules have less need for excipients, less time is required for the formulation and validation of additional raw materials.

Powders are the oldest of the solid dosage forms; their use has diminished as oral powders, but they are still used as topical powders.

**Student Audience**

The Unit Operations course, which is unique to pharmaceutical engineering given by the faculty of Chemical and Pharmaceutical Sciences at the University of Chile, is offered to pharmacy students during their third year of study, following the basic formation, and commences their professional module. The course is considered particularly important in building the connection between the physicochemical principles studied during the basic formation and pharmaceutical technology, which is taught following the Unit Operations course.

Historically, the Unit Operations course has been offered to large classes of more than 100 students through a traditional lecture format, seminar sessions devoted to problem solving, and laboratory experience. Such a classical approach has a number of inherent problems, including, passive learning, difficulty in applying the concepts learned to real life problems, and little or no responsibility with the students for self-learning.

**Software Used**

The CD-ROM was created using Version 8.0 of Macromedia® Director which, at the time of development, was one of the most commonly used software tools for creating interactive multimedia. Photographs were processed with Version 5.5 of Adobe® Photoshop®, and the videos were edited using Version 5.0 of Adobe® Premiere®. The exercises for the self-evaluation section were developed using Microsoft® Excel 2000.

**Design of Navigation**

The navigation of the CD-ROM was designed to emphasize the relationship between the type of pharmaceutical product or service, the process flowsheet, and the unit operations involved in the process. The solid dosage forms were represented on the CD-ROM by tablets, capsules, and powders – *Figure 1*.

**Tablets**

For tablet manufacturing, a flowsheet of the process was designed. This considered both the basic equipment and the principal equipment used for manufacturing tablets by wet granulation in Chile. The flowsheet illustrated the sequential stages involved in the process, beginning with materials weighing for each lot through to tablets packaging. By clicking each illustration, information about the main aspects of each step is displayed, including the equipment used and the key parameters involved in each operation.

The dry mixing and wet massing of the powders can be performed using basic equipment such as planetary mixers, or more modern equipment, such as high-speed mixer/granulators and the one pot system. The more basic procedures in tablet manufacturing use oscillating granulators for the wet and dry granulated screening process.

On the drying step of the process, both the equipment normally used (tray dryers, fluid bed dryers, and one pot...
system) and the key parameters involved in their operation are explained. The one pot system is shown by means of a video, in which a production manager explains its operation. The mixing of granulate with lubricant is achieved using tumbler mixers, such as a double cone mixer, twin-shell blender, or a handling system used in the one pot system. The procedure for determination of the optimal mixing time using a 'Mixing Index' is explained. The powder mixture is tableted by a rotary tablet press with a variety of levels of automation. The newest rotary tablet presses have an automatic self-adjust, rejecting tablets that are out of specification and maintaining equipment control. Records of each lot, which supports the validation process, are generated.

The most common coating process consists basically of applying a coating solution over the tablets bed under hot air for improving solvent evaporation - Figure 2. Thus, a film coating on the tablet surface is formed. The coating process is controlled by the equipment used, such as a coating pan, a perforated coating pan (the most common equipment used for film coating), or a fluid bed coater, and by the key process parameters which, for the perforated coating pan, are:

a. pan variables (pan design, speed, pan load)

b. process air (air quality, temperature, flow rate)

c. spray variables (spray rate, degree of atomization, spray pattern, nozzle distance to bed)\textsuperscript{8a}

Capsules

Capsules are solid dosage forms in which the drug is enclosed within either a hard or soft soluble container or “shell.” Shells are usually formed from gelatin.\textsuperscript{9} The type of gelatin used is explained as well as the process for obtaining the gelatin from dry bone, calf, and pork skin.\textsuperscript{8b} For hard gelatin capsules, which are the most common, both parts, called the cap and the body, and the usual sizes of 000 to 5 are considered.

The process developed in the industry is explained and comprises the following steps - Figure 3.

1. Preparation of a powder formulation, which is simpler than a tablet formulation - the powder contains the drug, diluents, and excipients, which improve the flow properties of the powder mixture. The flow property is particularly important during the filling of capsules. The powder mixture is prepared with tumbler mixers to assure the homogeneity of the mixture.

2. Capsule filling - the fundamental operation of capsule filling machines includes:
   a. separation of the cap and body of the capsule
   b. filling the body with the mixture
   c. rejoining cap and body

3. Dusting and/or polishing

4. Packaging

Figure 3. Basic operations involved in capsules production.

Powders

The main unit operations involved in the manufacture of powder products are size reduction, sieving, and mixing. The mills normally used are either ball mills or hammer/cutter mills. The principles of operation of these types of mills are explained, as well as the advantages obtained when the solid raw materials and drugs are milled. Since sieving is the most widely used method for measuring particle size distribution, the most common standardized sieves and the key factors involved in the sieving procedures are explained. Powder mixing uses the identical tumbler mixers as tablets production, so the user of the CD-ROM is referred to the tablet section.

Self-Evaluation

One important part of the regular course in Unit Operations is to develop seminars where students solve problems guided by an academic tutor. Unfortunately, due to the increasing number of students, “discussing and solving difficulties” on an individual basis has become more and more difficult.

Figure 4. Example of a multiple-choice question.
Students are less motivated to attempt problems, and tutorials degenerate into a problems lecture where the tutor solves the problems with little student interaction. Since the Computer-Aided Learning (CAL) approach has been proved particularly to help weaker students, a self-evaluation section on the CD-ROM was developed that includes multiple choice/response questions, a puzzle, and exercises. It is hoped that this will assist students with self-learning.

Multiple Choice/Response Questions
Ten multiple-choice questions were developed on the following topics:

- Size reduction (energy requirements in comminution, key factors in the ball mill operation, solid properties that influence the size reduction operation)
- Mixing of powders (selection of mixers for specific applications, ‘Mixing Index’)
- Humidification operations (estimation of air humidity from water vapor pressure, using a psychometric diagram)
- Drying of solids (selection of drying equipment, use of drying curves)

Puzzle
The puzzle was designed to emphasize tablet manufacture by wet granulation, which is one of the most common manufacturing procedures for this solid dosage form. The puzzle is of a drag and drop type, which requires the student to correctly order the unit operations involved in the manufacturing process. When the puzzle is completed, an animation of the process with illustrations of each unit operation is displayed - Figure 5.

Exercises
The exercises were developed using Microsoft® Excel 2000. Excel sheets and movies, developed in Macromedia® Director®, were connected using Microsoft® ActiveX controls. The exercises were based on the tablet manufacture by wet granulation. They were divided in three sheets called:

- Mass Balance
- Drying
- Optimal Mixing Time

Mass Balance
In this section, the user can define the components of the formulation, their percentages on the formulation, the weight of the tablet, and the size of batch production. The mass balance of the granulation step is displayed and the user must define the concentration of the binding solution or the water used in the batch production. The questions are about the drying granulation step of the process. The user is asked to answer about the mass of water evaporated and the mass of dry granulate obtained for a certain percentage of residual humidity demanded for the dry granulate, which is also defined by the user between the range 1% - 4% humid basis - Figure 6.

Drying of Granulate
This section demonstrates the drying process for granulates developed in a fluid bed dryer, where the air used is heated with saturated steam. The user must define:

- the drying conditions: room temperature (°C)
• input air conditions as humidity (kg of water/kg of dry air) and temperature (°C)

• output air conditions like humidity (kg of water/kg of dry air) and temperature (°C)

• specifications of the boiler used for the production of saturated steam: vapor pressure (kgf/cm²), heat of vaporization (kcal/kg), boiler capacity (kg/h), boiler power (kW), and energy cost ($)

The questions are related with the following aspects:

a. Kg of dry air used

b. m³ of air under input conditions

c. kcal required for air heating

d. Kg of saturated steam required

e. cost of steam for each batch

**Optimal Mixing Time**

This section is related to the process step in which the dry granulate is mixed with the lubricant in a twin-shell blender. One of the most important operations in tablet manufacture performed with basic equipment, which is very common in Chile, is to determine the degree of homogeneity through the mixing index. The objective of this section is to teach how to select the appropriate tracer and calculate the mixing index. The questions are the following:

1. define which component of the formulation is suitable to use as a tracer

2. calculate the theoretical standard deviations at zero time

3. calculate the mixing time using the table of data for the selected tracer

By clicking the plot base, the user can compare the curve of mixing index over time with the correct curve.

**Preliminary CD-ROM Evaluation**

A preliminary survey was given to a small number of students at the end of the course with the aim of providing a general impression regarding:

• mode of use

• design

• contents

• self-evaluation section

The students mainly used the CD at home at a frequency of two to three times/week and found the navigation easy or very easy. The general quality of design was found to be good or excellent. Some of the students experienced problems with the video sound when their computer had a processor older than a Pentium® III, 500 MHz or equivalent. Also, some found problems with the screen definition color, due to not having configured their screen appropriately (True Color (32 bit)).

With regard to content, more than 75% of those surveyed found that clarity of presentation was good or excellent, and more than 50% considered that the degree of difficulty was easy or very easy. In relation to the degree of difficulty of the self-evaluation section, the highest value for difficulty was presented by the exercise section (38.5% of the surveyed considered the section difficult). This result was expected because the lowest results in the non-CD-ROM based Unit Operations course are obtained in the exercise test, which is considered the most difficult part of the course. According to the students’ comments, the puzzle section was the most attractive section. More than 50% of those surveyed found this section easy or very easy. The multiple choice question section was considered by more than 60% of those surveyed as being of a moderate degree of difficulty.

**Conclusion**

The CD-ROM took two years to develop and is in the preliminary stages of evaluation with the students on the Unit Operations course. Based on the preliminary results of the surveys, it can be stated, in advance, that the CD may enhance the interest of the course, and it may be considered a contribution to the improvement of the traditional teaching of this discipline.

**References**


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**About the Authors**

**Cristián Tapia** is an Assistant Professor of Faculty of Chemical and Pharmaceutical Sciences at the University of Chile. He has been teaching Unit Operations for 15 years, in particular their applications in the pharmaceutical industry. He holds a BSc. (1987) in chemistry and pharmacy and a MSc. (1993) in pharmaceutical sciences both from the University of Chile. He has a diploma in multimedia and interactive video from the Tracor Institute of Spain. He is a member of the Chilean Chemical Society, ISPE, and the Controlled Release Society. He can be contacted by email: ctapia@uchile.cl.

Laboratory of Unit Operations, Faculty of Chemical and Pharmaceutical Sciences, University of Chile, PO Box 233 STGO1, Chile.

**Carlos Basualto** is an Assistant Professor of Faculty of Chemical and Pharmaceutical Sciences at University of Chile. He has been teaching Unit Operations for nine years, in particular their applications in the chemical and food Industry. He holds a BSc (1992) in Chemistry from the University of Chile. He can be contacted by email: cbasualt@uchile.cl.

Laboratory of Unit Operations, Faculty of Chemical and Pharmaceutical Sciences, University of Chile, PO Box 233 STGO1, Chile.

**Jaime Sapag-Hagar** is an Associate Professor of Faculty of Chemical and Pharmaceutical Sciences at the University of Chile. He has been teaching Unit Operations for more than 40 years, in particular their applications in the pharmaceutical and food Industry. He holds a BSc. in Chemistry and Pharmacy from the University of Chile. He is a member of the Chilean Chemical Society and the Chilean Food Society. He can be contacted by email: jsapag@uchile.cl.

Laboratory of Unit Operations, Faculty of Chemical and Pharmaceutical Sciences, University of Chile, PO Box 233 STGO1, Chile.

**Fernando Valenzuela Lozano** is an Associate Professor of Faculty of Chemical and Pharmaceutical Sciences at the University of Chile. He is the Chairman of the Food Sciences and Chemical Technology Department at the same University. He has been teaching Unit Operations for more than 25 years, in particular their applications in the chemical, pharmaceutical, and food Industry. He currently teaches a Mining and Metallurgical Chemistry course. He holds a BSc. in chemistry from the University of Chile and a Masters Degree in chemical engineering from Kyushu University, Japan. He is a member of the Chilean Chemical Society. He can be contacted by email: fvalenzu@uchile.cl.

Laboratory of Unit Operations, Faculty of Chemical and Pharmaceutical Sciences, University of Chile, PO Box 233 STGO1, Chile.

**Mauricio Muller** is a graphic designer. He has been working in multimedia for educational purposes since 1998. He has a diploma in multimedia and interactive video from the Tracor Institute of Spain. He can be contacted by email: mmuller@yahoo.com.

Faculty of Chemical and Pharmaceutical Sciences, University of Chile, PO Box 233 STGO1, Chile.

**Gian Franco Zunino** is a GMP Manager of Laboratorios Bagó. He has participated since 1993 in training programs in the pharmaceutical industry for pharmacy students. He holds a BSc. in chemistry and pharmacy from the University of Chile. He is a member of ISPE. He can be contacted by email: gzunino@bago.cl.

Laboratorios Bagó, PO Box 3381 STGO, Chile.