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Cleaning of a Tablet Packaging Machine Validated by a Contractor - A Case Study

by Heidi Meinertz Jensen

Introduction

This case study describes a validation assignment carried out by a contractor for a client. In addition to discussing the actual assignment and how it was handled, the article includes sections that generally talk about the legislation issues involved in the assignment.

Background

A pharmaceutical company (the client) has purchased a blister packaging machine which has not yet been delivered. The intention is to use the machine for packaging of the client's own non-drug products, but preferably also for packaging of tablets under contract for another pharmaceutical company. The specific tablets fall under the category of drugs, and the other company has stipulated that the machine, in addition to qualification and validation, undergoes cleaning validation. After completion of the cleaning validation, the client would then be audited with a view to entering into a contract for packaging of the specific tablets.

The client has no experience with cleaning validation and cannot spare the resources for the task due to the tight time schedule. A contractor is hired to do the job.

The analysis part of the cleaning validation was carried out by a laboratory under contract, and is not included in the assignment. Therefore, the analysis aspects are discussed to the extent only that they relate to the assignment.

The packaging machine was to be delivered from Italy and was still being constructed when the cleaning validation assignment was started.

Contractor Assignments

21 CFR part 211.34[1] includes a description of contractor work detailing that the client must

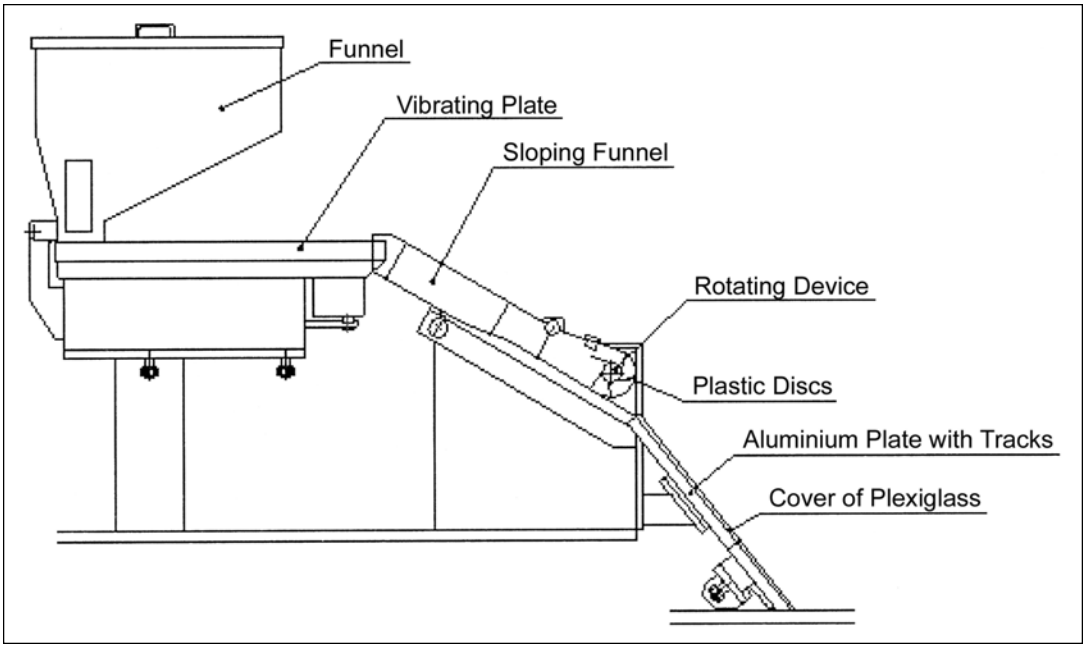

Figure 1. The infeed system of the blister packaging machine.

ensure that contractors are qualified for carrying out the specific task and that they keep records. The FDA will hold the client responsible for all work performed by contractors and will inspect these operations through the client. Furthermore, the FDA will inspect and approve contractor sites for manufacturing, packaging, testing, and holding.

EU's GMP[2] does not describe anything about contractors. The section dealing with QA responsibilities, states that QA has the overall responsibility, which means that the client's QA function must approve validation performed by the contractor. The Danish Medicines Agency will, like the FDA, hold the client responsible for all work performed by contractors and will inspect these operations through the client. Also, the Danish Medicines Agency has the option of inspecting the contractor sites for manufacturing, packaging, testing, and holding.

Consequently, the contractor cannot be directly responsible for a validation assignment performed. However, the contractor is under obligation as stated in the agreement entered into with the client. And furthermore, contractors can only be interested in performing the job to the clients' satisfaction. If they do not perform, they will soon lose their clients.

Dedicated Equipment

The client has chosen to purchase two identical sets of machine parts (those in direct contact with the product) to be used exclusively for packaging of the specific tablets. The machine parts are thus classified as dedicated equipment.

Use of dedicated equipment is normally recommended for substances that are difficult to remove, equipment that is difficult to clean, or products with a high safety risk, eg., products of a high potency which may be difficult to detect below an acceptable limit.[3] In this case, dedicated equipment is used to avoid a cleaning validation involving several non-drug products, and thus, a validation matrix that will be difficult to handle. The client chose a simpler and probably also less expensive solution by purchasing dedicated equipment for the drug products.

The two sets are labeled so that it is easy to distinguish between the two and to tell them apart from other machine parts in connection with future repairs and adjustments. The two sets are used randomly during cleaning validation, but care must be taken that the validation does indeed include both sets.

Preconditions of a Satisfactory Cooperation

The criteria for a well-run project and for good teamwork are a solid project agreement. Both the overall framework and the details must be in place. Who must do what? Who is responsible for which step of the process? The clients often underestimate the time they must spend on preparing comments, approval activities, and making decisions in cases when the preconditions or other aspects are changed. The overall and basic issues are often covered by the contract or the task specification which is a brief description of the assignment, who delivers what, specification of price and deadline. Establishing all the details during a meeting with several participants is highly recommended, particularly with participants from the client, as the client is often represented by a proportionally higher number of functions although on a smaller scale. Comprehensive and approved minutes of this meeting constitute the detailed project agreement.

The following was agreed and stipulated in the contract: the contractor was to provide and deliver a prepared protocol including rationales behind the validation concept/worst case. The contractor was furthermore to deliver a test plan, execute the tests, prepare a validation report, and prepare a final SOP for cleaning of the machine. The client was to provide the following: a validated method of analysis including sampling method, method of analysis for the detergent, execution of analyses, operator help for running the machine, product to make it possible to run campaigns that reflect the daily production, and resources for commenting on and approving protocol and report.

During the first meeting after the contract was in place, the following distribution of responsibilities was arranged: The client was to supply a copy of a validated method of analysis, secure materials for sampling, submit information about order sizes to use for calculation of acceptance criteria, obtain and submit drawings of the machine to use for calculation of surface area, prepare a draft for a SOP for cleaning of the machine, secure an adequate number of tablets for the validation, distributed on three different batches, and update the time schedule for the project.

The contractor was to prepare a protocol to be commented on within a fixed deadline and provide rationales behind selection and acceptance criteria.

The time from the first meeting after the contract was in place and until the project was to be finished and the machine ready for production was set to two and a half months. Within this timeframe, the machine was to be installed and IQ, OQ, PQ, and other activities were to take place before the cleaning validation could start. If for some reason the project exceeds timeframes, budget, or in other ways does not live up to the agreed terms, it is important to be in a position to point out changes and consequences as early in the process as possible.

In this particular case, delivery of the machine was delayed. This required revision of the time schedule, and it is especially important to note that all parties involved in commenting and approving activities, the analysis work, the actual test work, and the report preparation, etc. must be notified of the changed time schedule.

Beyond the descriptions of responsibilities included in both the agreement and in the meeting minutes, the protocol specifies the distribution of responsibilities applicable in connection with the actual validation.

Calculation of Area and Definition of Acceptance Limits

Area

The first task was to establish the acceptance limits for the active substance. The analysis laboratory had to start valida-

tion of the method of analysis as quickly as possible and therefore needed to know at what level the acceptance limit was going to be specified. To establish the acceptance limit, the total machine surface area in direct contact with the product must be estimated. All parts of the machine to be in contact with the tablets, ie, the entire tablet infeed system, must be included in the calculation.

The tablet infeed system consists of a funnel. The tablets are poured into the funnel, and the funnel directs the tablets to a vibrating plate made of steel provided with small holes. The vibrating plate leads to a sloping steel funnel, and this funnel again leads to a rotating device made of plastic and plexiglass that distributes the tablets into tracks on an aluminum plate which again leads down to the blister foil. A plate made of plexiglass covers the aluminum plate with tracks - *Figure 1.*

As already mentioned, the packaging machine is still in Italy at the start of the project. For confidentiality reasons, it was not possible to get access to detailed drawings and the exact measurements were therefore not available. The only materials available are a brochure showing parts of the design, and two drawings one of which is showing a few measurements. Together with the brochure and the other drawing, the drawing with the measurements is used for proportional calculations of measurements which can then be used for estimating the required area. This is a very uncertain method, but the only method available at this point in time.

As the total area in contact with the product is included in the calculation of the acceptance limit in the denominator, it is important to arrive at a worst case calculation to round off to the nearest high measurements and calculations so that the area gets as large as possible and the acceptance limits are tightened.

The surface area was calculated to be A cm^2.

When the machine was installed at the client's site, the client found that the estimated worst case was indeed adequately covered and that the calculated area was larger than the actual area. The actual area is estimated to be two thirds of the calculated area.

Acceptance Limits

The specific tablets are manufactured in three strengths, the lowest strength being without coloring agents whereas yellow and red coloring agents are added to the medium and highest strength, respectively. The tablets containing the three strengths have the same weight and size. The tablets with the highest strength thus contain more active substance in terms of percentages, and they therefore present the worst case for the validation.[4]

Selection of acceptance criteria included considerations to decomposition products. The client was contacted and expressed that the active substance is very stable and that decomposition of the product during the period from production start to cleaning is deemed unlikely. This also was the reason why the method of analysis was not validated in relation to decomposition products.

Material	Recovery Percentage
Plexiglass	73%
Aluminum	71%
Plastic	75%
Steel	85%
Combined recovery percentage for calculation of acceptance limit	70%

Table A. Lowest determined recovery percentages.

When approaching the client, the other pharmaceutical company had stated the acceptance criteria to be fulfilled.

The requirement for the cleanliness of the equipment is as follows: No more than 0.1 % of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product.[3] The most stringent of the following criteria must be met:

a. No more than 0.1 % of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product.

b. No more than 10 ppm of any product will appear in another product.

c. No quantity of residue should be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible.

It must be assumed that the other pharmaceutical company has calculated that (a) is the most stringent acceptance limit for this active substance.

Normal therapeutic dose and maximum daily dose are thus included in the calculation of the acceptance limit for the active substance.

The normal therapeutic dose varies from patient to patient, and the smallest possible dose is therefore used as worst case. The minimum daily dose (Lowest Daily Dose, LDD) is three tablets of the lowest strength.

LDD = 3 * B µg
= C µg and 0.1 % of C µg = D µg

The maximum daily dose (Highest Daily Dose, HDD) is eight tablets of the highest strength.[5]

The behavior of any leftover residue after cleaning is in no way predictable. The only predictable thing is that the leftover residue is not distributed evenly onto the tablets that will subsequently be in contact with the equipment. To finish the calculations, it is therefore necessary to assume that a certain, even distribution will take place.

In this case, it is assumed that any leftover residue is released in an even distribution on the subsequent tablets. In worst case, the maximum eight tablets that a patient is to take will be contaminated with tablet dust from the last packaged tablets. The smallest order packaged by the client

is for 60,000 tablets. If these 60,000 tablets have the highest strength and are taken in a maximum dose, the scenario would be as follows:

$$\text{Number of daily doses} = \frac{\text{Smallest packaging order}}{\text{Max number of tablets}} = \frac{60{,}000}{\text{eight tablets/daily dose}} = 7{,}500 \text{ daily doses}$$

The maximum allowed addition to each of the 7,500 daily doses is D µg. This means an allowed maximum of D µg * 7,500 = E µg distributed on the entire machine. This in turn assumes that the residue that might be left over on the machine is transferred and evenly distributed to the next packaging order.

As one of the first tasks, the analysis laboratory performed a recovery test of the active substance on the four materials that are covered by the tablet feeding system. 100 cm^2/15.5 $inch^2$ are applied with a known quantity of active substance in a given concentration. The lowest determined recovery percentages for the four materials are shown in Table A.

The test area is 100 cm^2, standard size for sampling areas. A cotton roller moistened with methyl alcohol is used for swabbing the test area which is the same method used for validation of methods of analysis for active substances.

As a result, the final calculation of the acceptance limit is:

$$\frac{\text{qty. active substance distributed on the machine * recovery percentage * test area *}}{\text{Surface area}} = \frac{\text{E µg * 0,7 * 100}}{\text{A}} = \text{F}$$

= the maximum substance quantity allowed in a single sample. Consequently, the acceptance criteria for the test are that all results must be ≤ F.

The results of the chemical tests all fell under the detection limit.

Hot Spots

The fact that the machine is still in Italy at the start of the project also makes determination of hot spots difficult. Hot spots are defined as places where residue tends to collect or as places that are difficult to reach during cleaning. The tablet residue is expected to settle on and in the edges and corners of the vibrating plate. The vibrating plate is provided with holes and the dust from the tablets falls through these holes and is collected in a dust tray.

The dust tray is not covered by the validation, since it is not in contact with the product. The device used for distributing tablets in the tracks is a rotating cylinder on which four flat rectangular plastic discs have been firmly affixed. This device is definitely expected to collect dust and to be difficult to clean. It was not the immediate intention to disassemble the device for distribution of the tablets prior to cleaning if at all avoidable, but it was definitely something that might become necessary. The tracks in the aluminum plate are not expected to be especially dust-collecting as the plate is sitting at a sloping angle, the tracks may on the other hand be difficult to clean and inspect for visual cleanliness. Ten hot spots are selected, covering all four material types.

When the machine was installed at the client's site and the machine was put in operation, a pretest was performed and the client ascertained that the anticipated dust-collecting spots do indeed match reality. The client furthermore ascertained that it is necessary to completely disassemble the device for distribution of the tablets to obtain an acceptable cleaning result. It was clear that dust collected between the rotating cylinder and the four plastic plates attached to the cylinder. The dust could not be removed without disassembly of the four plastic plates.

Detergent Residue

As the active substance is not soluble in water or ethyl alcohol, a detergent must be used for cleaning. To this end, a detergent is used containing a quaternary ammonium compound that is very surface-active.

Using a detergent adds a new aspect to the process, ie., the risk of transferring detergent to the tablets and resulting ingestion of detergent in connection with intake of the tablets. When a detergent is used, the validation must thus include inspection of the removal of detergent residue.

The client was in charge of a test for removal of the detergent. A "Test kit for determination of cationic detergents (surfactants)" was used. The acceptance criteria and the rationale behind the criteria were included in the overall protocol.

Cleaning

To be in a position to clean the machine and to validate the cleaning, the equipment must be used and contaminated with the active substance. It was discussed how many tablets were needed for the validation. The tablets are relatively expensive and the client therefore wished to minimize the quantity and reuse the tablets instead.

The contractor preferred to have a sufficient quantity available, and did not want to reuse the tablets. The maximum speed of the machine is 270 blister cards per minute. Each card contains 15 tablets, which corresponds to 4,050 tablets per minute or 243,000 tablets per hour.

The quantity of the tablets used for the validation is equal to running the tablets through the machine three times. A test was not performed to show that the tablets gave off as much dust during the third run as they did during the first run. To avoid puncturing the blister packages to get the tablets out, the tablets are transported without the top foil and in such a way that after they have been placed in the

bottom foil they are poured out of the foil and collected. The tablets are then poured into the funnel again and reused for contaminating the machine. The tablets are run through the machine for one hour.

Prior to cleaning with water and detergent, all components are vacuumed for tablet dust as thoroughly as possible. A vacuum cleaner has been purchased for this purpose, dedicated to use for runs with the specific tablets. As vacuum cleaning removed practically all the dust anyway, the amount of dust given off by the tablets was of no importance. And it would therefore have made no difference if a test had been performed to show how much dust the tablets gave off during a third run.

In addition, all equipment components are vacuum cleaned at the end of the work day if the machine is to continue packaging tablets from the same batch on the following day.

The client and the contractor had agreed that the cleaning method for the new equipment must resemble the method already being used by the client. The client uses manual washing processes, soap water, and rinses the equipment with running water and a hand shower. It can be difficult to adapt a non-validated washing process like that to a controlled situation.

First of all, the solution of the detergent to be used on the new equipment must have a predefined concentration. This was solved with the use of a measuring cup for measuring out the detergent. A large sink was marked to indicate the filling level of the water. As both the processes of measuring out the detergent and the water involve a certain degree of uncertainty, the validation demonstrates that the machine can be cleaned adequately even with a short measure of detergent and can be rinsed adequately after an excess of detergent.

Secondly, the process of rinsing with running water is difficult to control. There may be differences in how hard the water is turned on, the duration of the rinse, and how the equipment is moved around under the water. The temperature of the water may also have an influence on how easy or difficult it is to rinse the equipment to get it clean. It is furthermore necessary to collect the rinse water for purposes of measuring potential left-over residue. Filling the sink with a defined measure of water, rinsing, and repeating the process solved this problem. The last batch of rinse water was used for measuring detergent residue.

Apart from the last batch of rinse water, the water used for cleaning and rinsing is city water from a tap producing water with a permanent temperature of approximately 40°C. The last rinse uses RO water that also has a permanent temperature of approximately 40°C. The client's internal monitoring system generates a warning if the temperature goes below or above the specified limits.

Thirdly, the human factor must always be allowed for when manual procedures are included in the process. The human factor is difficult to handle. It cannot be measured and it may not be the same every day. There are both disadvantages and advantages to manual wash processes. When people performing a task know that they are being watched or supervised, one of two things usually happens. They either get nervous and start fumbling and do things in the wrong sequence, and the result is not necessarily the same as if they had not been watched and could perform the task at their own pace. Or they become very thorough and do things more meticulously than they would under normal circumstances.

Experience shows that skilled operators tend to fall under the latter category, whereas a relatively new and inexperienced operator is likely to fall under the first category.

Watching or supervising people during such processes also may reveal missing SOP compliance. An operator is well into a wash process, stops, and hesitates a little: "I know that the SOP specifies that I must ..., but that is not possible because ... So I will ..." A variation of this could be: "I know that the SOP specifies that we must ... but we will ..."

The first scenario is relatively easy to handle. The SOP must be revised to match the real world if the real world complies with cGMP. This involves simply asking the operators to draw attention to such instances.

The second scenario is a bit more difficult to handle. Why does the SOP and reality not match, when, how, and why did reality change into something other than what is described in the SOP. And last but not least, where else are discrepancies between the SOP and reality likely to be found?

The time of day when the cleaning is performed also influences the cleaning process. If the cleaning takes place close to the end of the work day, the operator may tend to be sloppy with the cleaning. Under normal circumstances, two to three operators can easily perform a demanding task and carry on a conversation at the same time. They do not look at each other while they perform the task, but at the task at hand. When an outsider talks to them while they perform the task, they often have eye contact with the person they are talking to out of politeness.

These disturbances and stress factors are used to influence the manual cleaning procedure to arrive at worst case.

The client had selected a number of operators who were to be permanently assigned to this blister machine. The operators were chosen based on their knowledge and experience, and they were all good at their work. Subsequently, no new or inexperienced personnel could be engaged in the validation process, but handling of these specific machine parts was relatively new for all involved. During all three cleaning processes, the operators were distracted and stressed caused by questions asked by the contractor and by other interruptions. One of the cleaning processes with subsequent tests took place on a late Friday afternoon just before the operators were to go home for the weekend. (As a minimum, three different operators must clean and rinse the equipment with the tasks preferably distributed on experienced and less experienced/relatively new operators in connection with the three subsequent runs/cleaning processes).

Microbiological Cleanliness

Neither the FDA nor the EU specifies room classification for packaging of tablets. The closest we can get is 211.46 and 3.12.

Under normal circumstances, packaging takes place in controlled areas corresponding to class D/100,000.

In class D/100,000 rooms, 50 cfu/plate is the allowed maximum on 55 mm/2.2 inches. contact plates. When working in class D/100,000 rooms, the personnel must cover their hair and beards. Suitable clothing and shoes must be worn. These unwritten rules are followed at the client's site.

The staff changes to work clothes, including caps, before entering class D production areas. When their work involves physical contact with the equipment, they also put on gloves.

The room is monitored at suitable intervals for compliance with class D/100,000. The equipment also must live up to class D/100,000 after completed cleaning. Samples are taken on the equipment equal to one sample on each of the four materials.

The results for microbial cleanliness must be ≤ 50 cfu/plate when the plate has a diameter of 55 mm/2.2 inches.

The other pharmaceutical company mentioned at the beginning of the article expressed their concern in connection with vacuum cleaning being carried out at the end of the work day if the machine was to continue packaging tablets from the same batch on the following day. The concern was directed at microbiological contamination of the equipment from the vacuum cleaner.

Microbiological tests were performed on the equipment before and after the vacuum cleaning and the concern was documented as being unfounded.

The results of all microbiological tests were found to be below the acceptance limit.

Revalidation

The cleaning validation is valid as long as the same cleaning procedure is used for cleaning as was used for the validation. The smallest packaging order of 60,000 tablets is included in the calculation of the acceptance limit and can therefore not be changed to a smaller quantity without revalidation.

In principle, there is no upper limit for the size of the packaging order as it is not included in the calculation of the acceptance limit. But that does not mean that this aspect should not be considered if very large quantities are scheduled for packaging.

The condition of the equipment and the manual cleaning process should be evaluated regularly. New equipment is smooth and polished. During use, the surfaces get worn and may be scratched in connection with handling the packaging processes. Changes may creep in during manual processes.

For a start, these changes may be barely discernible, but in the long run, they can change a process completely. Regular tests for verification are recommended.

Conclusion

To perform a validation for a client is not always without problems. For one thing, it is not possible to obtain all relevant information, and information and statements must therefore be used in good faith. The reason for this might be that the client is not interested in revealing sensitive information, that the client does not set sufficient time aside for passing on information to the contractor, or that the client takes things for granted.

The situation does not get easier in this case by a third party being involved, a third party who owns the main part of the information that might be of interest to the project. The client wants to meet the demands made by the other pharmaceutical company, but on the other hand does not want this to cost more than absolutely necessary, as a satisfactory cleaning validation does not automatically lead to a contract with the other pharmaceutical company.

The client does not have the experience or the resources to solve the task within the strict timeframe. By hiring a contractor, the client buys the experience that the client does not have available, at the same time binding the contractor to deliver a validation that complies with current requirements, meets a deadline based on certain assumptions, and keeps within a fixed price, also based on certain assumptions.

The contractor possesses the knowledge and experience needed to solve such tasks within the given framework.

References

1. FDA: Code of Federal Regulations 21 Part 211 "Current Good Manufacturing Practices for Finished Pharmaceuticals," US Food and Drug Administration.
2. EU: The Rules Governing Medicinal Products in the European Community, Volume IV, "Good Manufacturing Practice for Medicinal Products."
3. PIC/S, Recommendations on Cleaning Validation, August 2001.
4. LeBlanc, D.A., "Establishing Scientifically Justified Acceptance Criteria for the Cleaning Validation of APIs," *Pharmaceutical Technology,* October 2000, pp 160-68.
5. Danish Catalogue listing pharmaceutical products, 2000.

About the Author

Heidi Meinertz Jensen graduated from the Danish University of Pharmaceutical Sciences in 1993. Immediately afterwards, she started working at Novo Nordisk A/S in Copenhagen in an aseptic filling department. During the years at Novo Nordisk A/S, Jensen was responsible for daily production and release, optimizing and validation, audits and inspections, integration and implementing ISO 9001:1994 into an already existing quality system and training and education. In 2001, Jensen changed employment to NNE A/S and is now working in the department for GMP and Validation Services. In autumn 2002, Jensen was promoted to Specialist. Jensen is working with consulting as well as preparing documents and hands on testing in relation to GMP, primarily finished drug products. Jensen's specialties are cleaning validation and aseptic filling. She can be contacted by email: hmje@nne.dk.

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Design Considerations for Aseptic Liquid Vial Filling and Lyophilization Operations Within High Containment Isolators - Part 1

by Michael P. DeBellis

This article discusses the many design considerations involved with interfacing a high containment isolator with an aseptic liquid vial filling and lyophilizer operation.

Part 2 will present lyophilizer and loading operations, and isolator integration.

Overview

Enclosing critical highly potent or toxic products within a high containment or barrier isolator, regardless of whether you are protecting the product from contamination or the operators from exposure or both, has become increasingly more commonplace. In pharmaceutical manufacturing, isolation technology is gaining acceptance, the equipment operations housed within them are getting more varied, and the mystique around validating these isolator enclosures is becoming better understood. The industry as a whole is enjoying more and more success stories and acceptance. Many of the design features utilized in isolator/glove box designs are mature designs. However, there is still some room for improvements. Access through glove ports and half suits to perform even the simplest of operations can become very cumbersome and difficult when interfacing isolators with pharmaceutical and biotechnology process equipment. This article discusses the many design considerations involved with interfacing a high containment isolator with an aseptic liquid vial filling and lyophilizer operation - *Figure 1*.

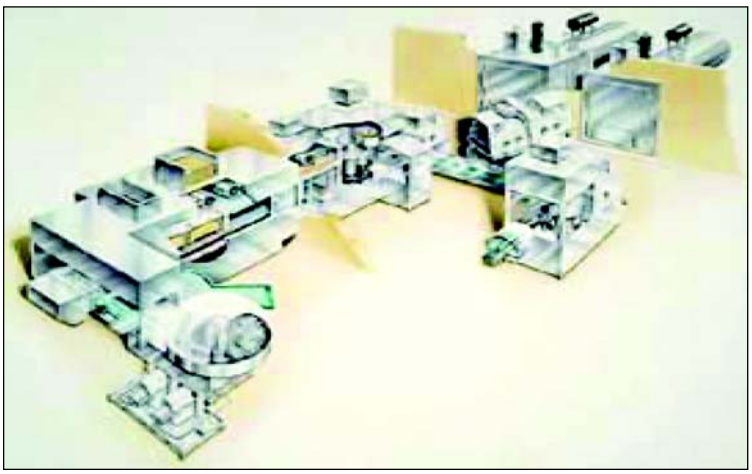

Figure 1. Vial filling Line and lyophilizer operations.

Introduction

Due to the high costs of filling equipment and the high value of the products, special considerations must be given to designing a filling line. Conventional filling operations are performed under unidirectional flow in Class 100 (Grade A) fully HEPA filtered processing suites. Access to the room is limited during the filling operations to minimize disturbance in the airflow patterns.

Protein products are heat sensitive and cannot be terminally heat sterilized; therefore, they must be sterile filtered prior to liquid filling and/or freeze drying (lyophilization). All components including tanks, piping/tubing, filters, and filling equipment must be separately heat sterilized. For aseptic processes, the components are required to be assembled under laminar (unidirectional) airflow.

Aseptic processing requires special precautions in formulation as well as in the downstream operations until the product is completely enclosed and sealed. For example, a protein product being heat sensitive,

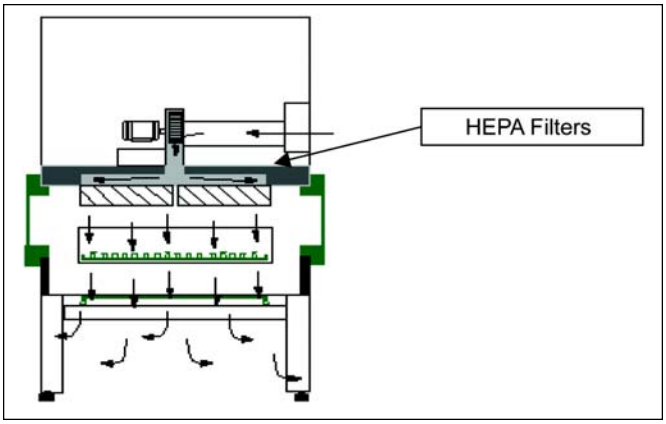

Figure 2. Class 100 preheat zone. (Depyrogenation Tunnel)

typically would be formulated in a clean bulk preparation tank and then sterile filtered through a 0.22 micron filter which provides a Sterility Assurance Level (SAL) of 10^{-3}. Terminally sterilized products achieve an SAL of 10^{-6}. In general, a terminally sterilized product offers a higher degree of assurance of sterility than aseptic processing. The US FDA requires that filled containers must be terminally sterilized unless the product is altered by heat and is referred to as being thermolabile. Because the product itself is terminally sterilized, the container and closures are of high microbiological quality, but not necessarily sterile. Containers and closures are required to only be washed, not sterilized, but must be pyrogen free. However, most biologics and vaccines are heat sensitive and must be filled aseptically and lyophilized to improve their stability by removing the water content from the product. The filling, stoppering, and also capping environments must be of high quality in both cases, i.e., Class 100 until a completely sealed container is established.

For antibiotics and other in-vitro type drug products, they must be produced in an aseptic manner in order to prevent the product from contamination. Most contamination can be controlled to acceptable limits through such means as good people and material flow design, planning, cleaning processes, and good personnel training and gowning practices. Typically, filtration is used to reduce particulates, sterilization is used to reduce the microbial contamination, and depyrogenation is used to remove endotoxins. The concern is to minimize the bioburden on these formulations during the process steps; such as batching, compounding, and storage in bulk tanks, where sterile filtering prior to vial filling operations is required.

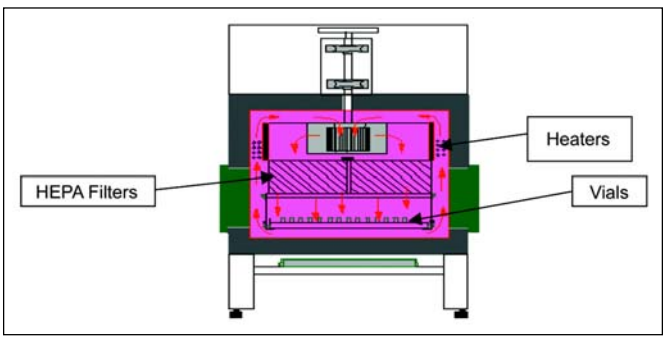

Figure 3. Class 100 heating zone. (Depyrogenation Tunnel)

Operator exposure may be a concern for certain drug products such as cytotoxics and other hazardous, highly potent type drug products. These products cannot be handled in the usual manner and require a higher degree of protection to the operator. Some of these highly potent lethal drugs may have an Operator Exposure Limit (OEL) down in the nanogram/cubic meter/8 hrs range. Even with today's detection methods, these levels are low enough to pose a serious challenge to any containment isolator system design and fabrication. Techniques used to introduce and remove equipment and components from the isolator should be reviewed so that it does not compromise containment design. These activities should be minimized during the process operations. Surrogate testing using safer non-toxic materials that behave similarly to the drug product must be determined and testing must be developed for this material as well, in order to perform leakage tests on the isolator system for its validation.

Overview of Vial Filling and Lyophilization Operations

In a typical aseptic liquid vial filling line and lyophilization operations, virgin glass vial bricks are received on shrink-wrapped pallets. The pallets are broken down to individual vial bricks and must be taken to a clean area to be unwrapped and de-cartoned for preparing the vials for aseptic filling. The vials are rinsed, inside and out, to remove any packaging debris and then they are properly configured for depyrogenation (sterilization). There are many issues of concern such as: variations on material handling methods, HEPA filter particle shedding issues, the type of depyrogenation equipment (batch oven vs. continuous tunnel) and operations, available floor space and layout, utilization, flexible design, future expansion, multiple vial sizes, multiple products, and cost issues are just some of these. These issues must be thoroughly reviewed when determining the correct equipment line for your facility.

Preparation in support of a typical filling and lyophilization operation for an aseptic liquid filling operation begins with the cleaning and sterilization of the glass vials, stoppers, caps, filling change parts, product head tanks, tubing, stoppers bowls, capping feed bowls, feed conveyors, rails, and other product contact parts necessary for the filling line.

In a containment isolator filling line, the following additional activities need to be performed: pre-sterilized bagged items are transferred into the isolator in a contained manner via alpha-beta type ports. These items are placed inside the isolator and along with other permanently fixed components within the isolator are decontaminated. Decontamination is most commonly done with sterilants such as formaldehyde, Vaporous Hydrogen Peroxide (VHP), or chlorine gas. When comparing the different methods, most commonly used is the VHP. It is relatively fast acting, has been validated, has a broad spectrum efficacy, good material compatibility, rapidly degrades to water and oxygen, and there are automated

controlled systems available. Some materials will absorb the VHP and may require longer aeration times to reduce the VHP concentrations to acceptable levels. VHP may cause some cosmetic surface changes; however, consideration should be given to these effects during the design and selection of the isolators, accumulator, filler and accessory items, conveyors, lyophilizer, and capping equipment. The typical VHP cycle is made up of four different phases: dehumidification, conditioning, sterilization, and aeration. Relative humidity is reduced by 10 to 30% by drying circulated air in a closed loop during dehumidification. During the conditioning phase, VHP is produced by vaporizing 30 - 35% liquid hydrogen peroxide and introducing it into the recirculated air stream to achieve the desired concentration. During the sterilization phase, the VHP concentration is maintained for the desired exposure time to establish sporicidal kill. VHP concentrations are typically low between 1-2 mg/L at 25°C. During the aeration phase, the residual peroxide vapor is decomposed into water vapor and oxygen byproducts by recirculating the VHP through a catalytic converter. Using an exhaust fan can reduce the aeration times. (Operating above or below the dewpoint is a topic for debate between VHP generator manufacturers, as both the dry and wet processes should be understood before selecting a VHP generating system.) Using chemical and biological indicators, the surfaces of the isolator can be validated to show up to a 10^5 bacillus stearothermophilus spore reduction. Good airflow from the isolator ventilation and filtering systems is key to establishing good distribution and surface contact with the VHP. The ventilation and filtering systems need to be designed for the higher aeration airflows required and optimize the cycle times.

Once the filling equipment has been sanitized, assembled inside the isolators, and the proper isolator environment is established (airflow rates, pressurization, particle counts), the washing and depyrogenation of the virgin glass vials can begin. (The formulation process also would precede the filling. The stability level of the product would determine how soon after formulation the filling operations begin).

Vial Preparation and Depyrogenation

The washing operation of virgin glass vials poses no hazardous exposure risk to the environment or personnel, and occurs outside of the isolators in a clean process area. The vials are rinsed primarily to remove packaging debris. Vial washers are manufactured in basically two configurations: batch units and automated continuous units. Vials are depacked and manually loaded onto an accumulation table where they are trayed for batch washing or pushed onto a conveyor for a continuous type washing operation. In a continuous process, the clean glass vials exit the washer and are staged and oriented for depyrogenation.

The depyrogenation of the glass vials removes and destroys endotoxins on the surfaces of the glass and prepares it for the aseptic filling operation. A key concern in any depyrogenation operation is contamination. A potential area for contamination can come from the oven itself. HEPA filters are utilized in generating the Class 100 quality air in the

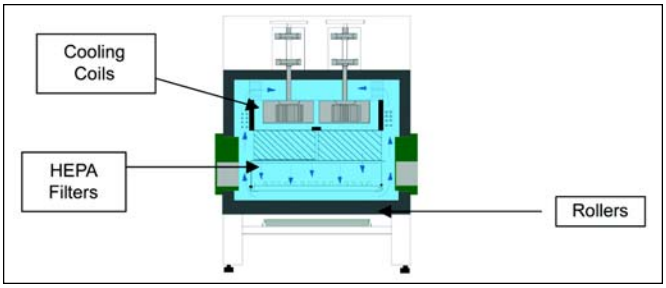

Figure 4. Class 100 cooling zone. (Depyrogenation Tunnel)

ovens or tunnels. In batch type depyrogenation ovens, the HEPA filters are repeatedly heated up and cooled down after each cycle. This cyclic thermal expansion and contraction of the HEPA filters causes the filter material to flake and fluff off in small particles which get entrained in the hot air stream. These particles can potentially contaminate the interior and exterior surfaces of the vials. Trays are sometime used with lids to protect the inside of the vials in batch ovens. The glassware handling methods required for this type of operation are very cumbersome. When integrated into a gloved isolator operation, this gets very difficult to safely manage. Glove tears, heavy tray lifting and handling, broken glassware, and longer set up times are inherent difficulties for this type of operation. For larger manufacturing operations, continuous depyrogenation tunnel operations are best suited for fully integrated filling and lyophilization operations, while minimizing HEPA filter particle shedding.

Depyrogenation tunnels typically have three Class 100 zones: preheating, heating, and cooling zones. The preheat zone (Figure 2) transfers glassware from the washer to the tunnel under a Class 100 air shower. (This section is closed off during the heating cycle so as to not expose the washer to the high temperature air associated with the depyrogenation process.)

The hot zone (Figure 3) heats the glassware to depyrogenation temperatures (approximately 400°C maximum) as fast as possible without causing cracking of the vials due to excessive thermal stresses. The glass remains at the required temperature for the pre-determined time to provide a three log reduction, or greater, in endotoxins. The entrance and exit to the hot zone is typically equipped with adjustable profile plates to minimize the height needed for the glass

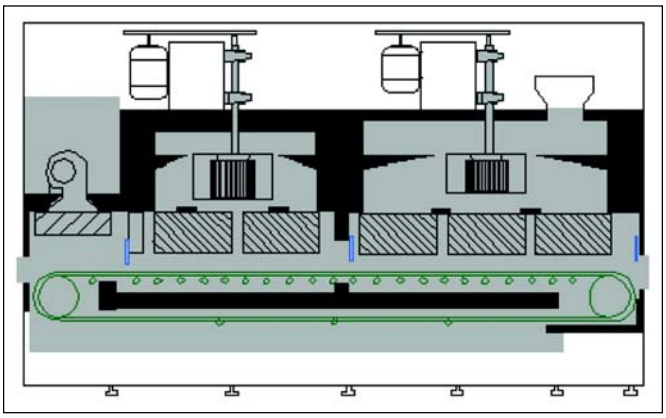

Figure 5. Class 100 tunnel. (Depyrogenation Tunnel)

Figure 6. Depyrogenation tunnel interfaced with an isolated filling line.

vials to pass through and into the next zone.

The cool zone (Figure 4) uniformly cools the glassware to optimal temperature without causing cracking due to thermal stresses for entry into the filling operations while maintaining Class 100 conditions. The cool zone is typically sterilized before beginning the depyrogenation operation of glass vials. This sterilization cycle is necessary to assure all surfaces in the cool zone are sterilized (maximum temperature approx. 260°C) because this is where the isolator environment interfaces with the tunnel environment.

Heating and cooling rates are critical as high stresses in glassware during both operations may cause the vials to develop cracks and break.

Figure 5 illustrates sterile vials exiting the tunnel. The tunnel pressurization system should be dynamically balanced to compensate for the changing pressures in the surrounding areas, whether that is a cleanroom or an isolator, as in our case. Isolator pressures may range from 0.05 to 0.5 inches of water column. The vials are then conveyed into the first chamber of the filling line isolator. This chamber would typically be an accumulation section for a continuous filling operation. The sterile vials are now isolated from the process room environment and maintained in a Class 100 environment throughout the remainder of the line until after the vials are capped and sealed. Cascading pressurization of the different isolator chambers that enclose the filling operation, lyophilizer loading, capping, and external vial washing, if required, prevents potential cross-contamination between chambers.

Figure 6 shows a depyrogenation tunnel interface between the cool down zone of the tunnel and the accumulation isolator. During the depyrogenation of the glass vials, a Class 100 or Grade A environment must be maintained through the tunnel including the cool down zone. During factory acceptance testing (pre-validation), the depyrogenation unit should be operated through its full typical cycles. Particle testing ensures full Class 100 compliance (< 100 - 0.5 micron particles per cubic foot).

The vials are typically transported onto an accumulator table for disciplining the vials for single file transport onto the filling machine. Prior to the filling operation, the lyophilizer also needs to be preconditioned. The lyophilizer should be cleaned after each batch of vials has been processed; however, if the unit has remained idle for extended periods of time, it is a good practice to initiate a cleaning cycle prior to the start of the next run as well. Once the lyophilizer is verified as being clean (via testing), the lyophilizer chamber and condenser are steam sterilized and tested for leakage to assure the unit will hold vacuum. If the unit develops a leak after introducing the vials, and it goes undetected or untested, the entire batch could be at risk. Therefore, it is very important to perform this test before loading the lyophilizer and putting valuable products at risk. After leak testing, the chamber environment also may require pre-cooling for cold shelf loading. If the product is solvent based, an inert gas such as nitrogen may be introduced into the chamber and any associated isolator system.

Figure 7. Filling isolators.

Figure 8. Sidewall mounted filling machine provides outside access to mechanical components.

Filling

After the vials are washed, depyrogenated, cooled, accumulated, and disciplined into a single file, they are filled and partially stoppered and transported to the lyophilizer for the freeze-drying process. Up to this point, this process is fairly straightforward. But now consider that you have a high potent liquid, which has to be aseptically filled into vials and may be either aqueous or a solvent based liquid drug product. When dealing with all of this in isolators, the handling issues get complicated. It is crucial that the vials are filled and partially stoppered under Class 100 (Grade A) conditions for all aseptic processes. Maintaining aseptic Class 100 environments within high containment isolators, allowing for sampling, breakage, spillage, cleaning, sterilization, set-up, microbial testing, etc., all contribute to these complications. Knowing what to consider is the key to the design of the equipment, layout, operations, containment, properly controlled environment, and the successful validation of this type of process.

Today's filling machines offer a range of filling methods over a wide range of operating speeds. According to a study by Jack Lysfjord and Michael Porter presented in their article titled "Barrier Isolation and Trends," previously published in *Pharmaceutical Engineering*, the trend in isolated filling lines is toward liquid filled vial operations at speeds less than 100 vials per minute. For small clinical trial batches, filling speeds may be even lower at less than 50 vials per minute. This is typical to minimize mishaps such as breakage, jamming, and mis-fills, which would require delicate corrective actions to be performed through cumbersome glove ports. In clinical operations, campaigns for a particular filling operation may occur once every few months and systems are often kept idle in between filling runs. Operators of these filling lines tend to be scientists and are not operations people who are familiar with these types of operations. They often need to be re-trained from run to run, re-acquainting themselves with the equipment and procedures each time. The slower speed operations provide a greater level of comfort ensuring hazardous and expensive products are filled safely, with a high degree of quality, containment, and the assurance that the batches will be consistent and can be validated.

Today's filling machines are equipped with the following features, which better integrate with an isolator enclosed filling operation:

- free-standing, through-wall mounted and isolated configurations
- pre-engineered modular construction to minimize production lead time
- integrated barrier isolation technology may be supplied initially or easily retrofitted at a later date
- simplified maintenance, often without entering the aseptic area
- VHP compatible
- CIP/SIP of product path for liquid and powder filling applications
- unique transport mechanism eliminates conveyors from the filling zone
- statistical and 100% check weighing systems

The filling operation with an isolator has its own unique set of concerns, in addition to those that are typical for a filling operation. Some of these key issues are, but not limited to, the following:

- future expandability of capacity, i.e., additional filling heads and pumps
- bottom up filling (minimizes aerosol generation)
- liquid path (bulk tank, head tank, sterile filters, tubing, instrumentation and controls)
- gas injection (inert gas applied to vials/isolator for extremely low residual oxygen levels)
- check weighing (manual or automatic)

- sampling (isolator atmosphere and product)
- reject paths (for fallen vials, broken vials, or mis-filled vials)
- conveyor interfacing and controlled pass-through ports
- stopper feeding (stoppers must be provided pre-washed, siliconized (if required) and sterilized.

Stopper sizes and types vary, and it is important to understand the many different stoppers that will need to be used in your filling operation. Stoppers for lyophilization are different from normal liquid filled vial stoppers. A notch is formed into the stopper to allow the release of moisture during the freeze drying cycle. Fitted stoppers to accommodate thermocouples used in cycle development, feeding of stoppers, bowl sizes, getting these materials inside and out of the isolators for cleaning and sterilization, etc., are all factors which will impact the ergonomic issues to be addressed in the final design and layout of the isolator enclosures.

Another important feature offered by today's designed filling machines are their ease of integration with an isolator. Motor drives, belts, seals, and electrical power connections are separated from the interior of the isolator. Sealed penetrations through the isolator filler base plate or a sidewall for vertically oriented fillers are necessary when integrating a filler with an isolator to accomplish the proper leak tightness of the enclosure and eliminate all particle shedding and spark generating type equipment from the interior space of the isolator. Vertically oriented fillers, allow for free draining during the CIP of the filler and its many component parts. Routine maintenance, repairs, and replacement of these parts can be addressed from outside the isolator chambers. As for the sidewall mounted filler and components, these can even be accessed from a sealed mechanical area where no special gowning would be required as depicted in Figure 8.

Once the vials have been properly filled, partially stoppered (for lyophilization) or fully stoppered, check weighed, and sampled they are conveyed in a single file orientation and transported under unidirectional air flow and remain in a Class 100 environment all the way through to the capping operations. The FDA does not consider the vials sealed until an over cap has been placed over the stopper.

References

1. PDA Draft Technical Report No. 34, Design and Validation of Isolator Systems for Manufacturing and Testing of Health Care Products.

2. Lysfjord, J., Porter, M., "Barrier Isolation History and Trends," *Pharmaceutical Engineering*, Volume 23, No.2, 2003, pp 58-64.

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Pharmaceutical Drug Substance Due Diligence - A CMC Technical Assessment - Part 1

by Thomas J. DiFeo, PhD

This article provides an overview of the Chemistry, Manufacturing, and Controls (CMC) information which should be reviewed as part of due diligence activities for drug substance.

Part 2 of this article will include a review of controls associated with the manufacturing process, process development and validation, elucidation of structure, control of the drug substance, the container closure system, and stability.

Introduction

Due diligence is a vital activity in the acquisition or in-licensing of pharmaceutical compounds for market commercialization. Pharmaceutical product due diligence is a detailed investigation of the Chemistry, Manufacturing, and Controls (CMC) information associated with a drug substance and/or drug product. The investigation provides assurance that a given compound meets requisite technical and quality elements to allow for successful commercialization of the drug. This article provides an overview of CMC information which should be reviewed as part of due diligence activities for drug substance. This review follows the format of the Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use: Module 3, Quality, of the ICH Harmonized Tripartite Guideline[1] with some sections of the CTD template combined in order to simplify the presentation. Part 1 of this article includes a review of the nomenclature, structure, general properties, manufacturer and description of the manufacturing process.

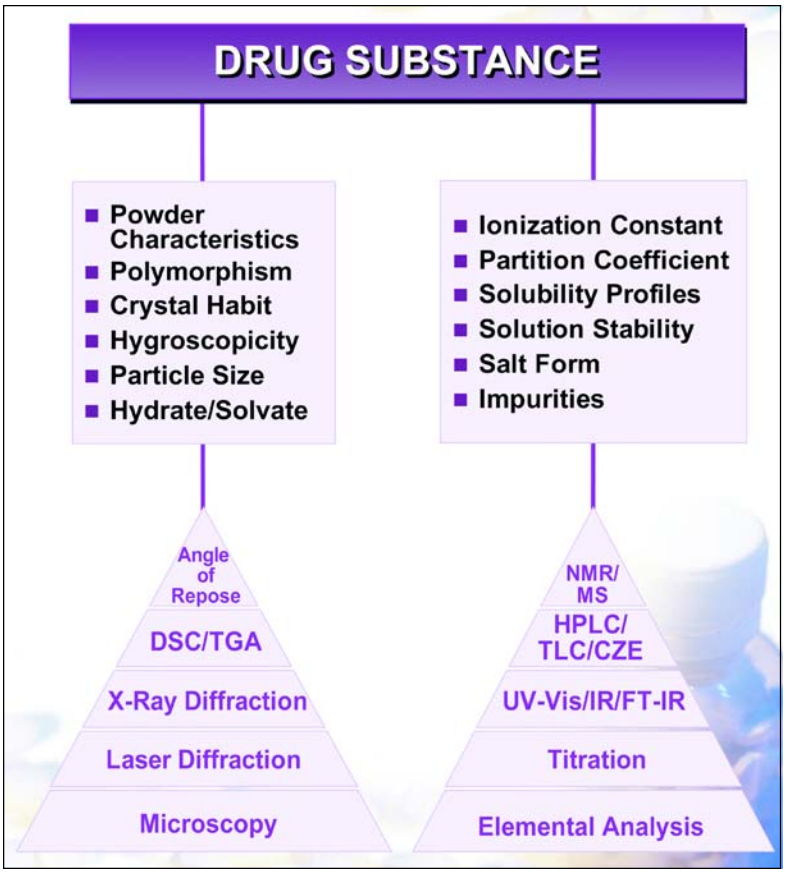

Figure 1. Drug substance assessment - an overview of key characteristics and investigative tools.

Drug Substance

Nomenclature

The chemical name of the drug substance is provided. International Union of Pure and Applied Chemistry (IUPAC) nomenclature should be employed. The laboratory code name or other non-proprietary names are noted in order to cross-reference information from various due diligence reports.

- IUPAC name
- Non-proprietary name
- Laboratory codes

Structure

The structural formula, including the relative and absolute stereochemistry, the molecular formula, and the molecular mass should be provided.

Structural elucidation studies may include elemental analysis, mass spectrometry, liquid chromatography/mass spectrometry (LC/MS),[2] NMR spectroscopy, UV-vis spectroscopy, IR spectroscopy, FT-IR spectroscopy, stereochemical analysis, configurational/conformational analysis, X-ray analysis, degradative analysis, and chromatographic analysis.[3] A careful review of the spectroscopic data used to demonstrate the structure of the drug substance is applied. The complexity of the spectroscopic techniques requires data review by specialists in spectroscopy to assure the accuracy and adequacy of the studies. Elemental analysis is used to confirm the theoretical formula. Mass spectrometry studies provide structural information based upon the various fragmentation patterns of the molecule. NMR studies can be performed on the drug substance in the solid state or in solution. Typically, ^{1}H and ^{13}C probes are used and give specific spatial information on the chemical structure. The literature is replete with references to structure elucidation using NMR techniques including specific references to pharmaceutical compounds.[4,5]

More complex molecules such as synthetic peptides are characterized by amino acid analysis and peptide sequencing. Mass spectrometry of peptides includes techniques such as fast atom bombardment, electrospray, plasma desorption, or laser desorption which may be used to provide the molecular weight or sequence information.[6]

Structural Elucidation

- Elemental Analysis
- Nuclear Magnetic Resonance (NMR)
- Mass Spectrometry (MS)
- Ultraviolet-Visible Spectroscopy (UV-vis)
- Infrared Spectroscopy (IR)
- Fourier Transform Infrared Spectroscopy (FT-IR)
- X-ray Diffraction Analysis

General Properties

The physical and chemical properties of the drug substance must be understood in order to develop an adequate formulation. The rationalization of the selection of the salt or free acid/base should be given with regard to the resultant quality of the drug substance and the ability to handle/process the drug product. Typically, the physico-chemical properties of the salts and free acid/base are compared and assessed with regard to formulation needs, process chemistry capabilities, and clinical requirements.[7] The difference in pKa values between the parent molecule and that of the counterion is usually 3 pK units or more for the formation of a stable salt. The ionization constant, pH dependence of the partition coefficient and solubility in aqueous and non-aqueous media of the chosen salt should be well-characterized. The resultant chemical and physical characteristics of the selected salt are examined with regard to ease of processing as well as any potential impact on drug product processing equipment. For example, HCl salts of weak basic drugs can produce corrosion and negatively impact the tableting equipment.

The purity profile for multiple lots is examined. Reversed-phase High Performance Liquid Chromatography (HPLC) is typically employed for the analysis. Is the purity profile reproducible? Are impurities at ICH thresholds[8] appropriately reported, identified, and qualified? It is recommended to use complementary detection techniques to verify the purity of the drug substance. In particular, impurities with weak chromophores may not be detected by conventional UV detection techniques. Alternative detection techniques can be employed including LC-MS, LC-NMR, refractive index, and evaporative light scattering.[9] Alternative separation techniques also should be employed and may include normal-phase HPLC, Thin Layer Chromatography (TLC) and Capillary Zone Electrophoresis (CZE).[10]

An examination of the solution stability of the drug substance in various solvents also may provide an indication of the propensity for the drug substance to degrade in liquid formulations or during wet processing steps.

Physical properties such as hygroscopicity, polymorphism, hydrate/solvate formation, solid-state stability, and powder characteristics must be documented. The particle size distribution of multiple lots should be examined as an indicator of processing robustness. Special attention should be given to the reproducibility of the particle size distribution since the particle size may impact homogeneity of a tablet formulation.[11] A variety of particle size techniques exists including laser light scattering, sieve analysis, and optical microscopy. Additional powder characteristics include density, angle of repose, and compressibility[12] and are important indicators of drug substance behavior. For example, the difference between aerated bulk density and packed bulk density can be used to determine the compressibility of the drug substance. While highly compressible powders may be likely candidates for a direct compression process, the flow of the drug substance decreases as the powder becomes more compressible and may lead to product flow limitations during the manufacture of the drug product.

Other physical characteristics may be determined by x-ray powder diffraction, thermal analysis – Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA), and hot stage microscopy. A recent example of a literature review of solid state characterization details several quantitative methods of analysis.[13]

Crystal polymorphism is an essential characteristic needed to be fully understood in the drug development process. Polymorphism entails different arrangements of the molecule in the solid state. Crystalline polymorphs differ in crystal structure (internal structure), but are chemically identical having the same liquid and vapor states. The propensity for the drug substance to form polymorphs should be studied extensively in a variety of crystallization solvents. These studies also may include freeze drying and evaporative studies in order to induce polymorphic transformations.[14] Where polymorphs exist, the relative difference in energies (and hence the propensity for conversion) may be studied via solution solubility studies. An examination of the solution solubility data is made to assure that no solvent-mediated transformations occurred during the solubility study[15,16] thereby affirming the validity of the experiment. It is impor-

Figure 2. Overview of key review aspects of the manufacturing process from receipt of raw materials through testing of the drug substance.

tant to note that the most thermodynamically stable polymorph may not necessarily represent the most chemically stable drug substance crystal form.[17] Selection, therefore, of the polymorph to be developed should not be based solely on thermodynamic considerations and must include an assessment of the kinetic behavior of the solid. When testing polymorphs, it has been noted that some polymorphs may not show differences in either IR or Raman spectroscopic results[18] and thus complementary techniques are employed including techniques such as two-dimensional solid-state NMR.[19]

Polymorphs may have solid state characteristics which impact the stability and robustness of the ultimate drug product process. A classical publication on the early study of polymorphism in pharmaceutical products describes the fundamental issues impacting drug products.[20] Brittain et al. have studied the physical characterization of pharmaceutical solids and they provide a general review of the methods available for the physical characterization of polymorphs.[21] ICH Q6A discusses the regulatory aspects of polymorphism control in drug substance and drug products.[22] Multiple techniques are available to study the physical characteristics of polymorphs. These techniques include intrinsic dissolution rate studies[23] which may be indicative of differences in bioavailability among the polymorphs.

Finally, the crystal habit of the drug substance details the various forms in which a solid may appear (a reflection of external structural differences). Crystal habit can influence the flow and compaction properties of a drug substance formulated in the solid state.[24,25] The influence of crystal habit on suspension formulations can be seen in the stability, sedimentation volume, and redispersibility of the drug product. Photomicrographs[26] of multiple lots can demonstrate the reproducibility of the drug substance synthetic process with regard to specific habit formation. The type of crystal habit produced can be affected by the degree of impurities found in the drug substance[27] again underlining the importance of determining the reproducibility of impurity profiles for multiple lots. Figure 1 highlights the building blocks of the database used to support drug substance assessment during a due diligence review.

Physicochemical Characteristics

- Ionization Constant
- Partition Coefficient
- Solubility Profile
- Solution Stability
- Hygroscopicity
- Polymorphism
- Hydrate/Solvate Formation
- Particle Size Distribution
- Adsorption/Desorption Isotherms
- Density
- Angle of Repose
- Compressibility
- Crystal Habit

Manufacturer

The name, location, and current Good Manufacturing Practice (cGMP) status of the manufacturer of key starting materials and drug substance is provided. An overview of the quality assurance aspects of the manufacturer(s) may provide insight into the viability of the process. A request from the manufacturer for the report of the most recent cGMP manufacturing inspection from the United States Food and Drug Administration (FDA) or European Union (EU) authority enables a broad overview of the cGMP compliance aspects of the facilities. Specific indications of issues concerning testing practices or general cGMP compliance may help determine the reliability of the various data supplied by the manufacturer. If testing is performed at another facility, an investigation as to the cGMP status of the testing facility is pursued.

An inventory of available drug substance (suitable for clinical supplies) and critical raw materials is obtained. A review of supply agreements and contractual obligations for critical raw materials is performed to assure the availability of future supplies. In addition, alternate suppliers for critical materials should be identified and qualified. The discussion below on the manufacturing process and process controls generally applies to the drug substance although some aspects may be applicable to critical raw materials as highlighted in Figure 2. Figure 3 provides a summary check list for review of items concerning structure, general properties, and the manufacturer.

Description of Manufacturing Process

Process Flow Diagram

A flowchart summary of the process should be provided with the molecular formulas, reactant quantities, yields, operating conditions, solvents, and Critical Quality Attributes (CQAs) for each intermediate indicated. The flowchart allows for an overview of the process and an outline for ease of review of the various synthetic steps.

Figure 3. A Summary Check List of Key CMC Review Aspects of Drug Substance - Structure, General Properties, and Manufacturer.

Description

- Batch records
- Critical Quality Attributes
- Scale-Up
- Process Controls
- Safety

A detailed narrative description of each step in the manufacturing process is typically available from early phase regulatory documents. This narrative is compared with actual batch records from the manufacturing facility. A detailed analysis of the manufacturing process includes a review of quantities of raw materials, solvents, catalysts, reagents, identification of critical steps and process controls, the type and size of processing equipment, and operating conditions, such as temperature, pressure, pH, and mixing time. If the process has been scaled-up from earlier batches used in toxicological studies, the impurity profile is compared with the earlier toxicology study batches. A review of the raw materials includes the availability of reagents and safety concerns (handling and need for special processing equipment and protective requirements for the operator). Some questions that should be asked include:

1. What is the robustness of the process (are re-works common)? How do the physicochemical profiles of multiple lots compare?

2. Are the reagents commonly available or cost prohibitive?

3. Have critical quality attributes for critical intermediates and final drug substance been determined?

4. Have Critical Processing Parameters (CPPs) been associated with critical quality attributes (are there data to support the association)?

5. If the current process is lab-scale or pilot-scale, can the process batch size be increased using the current synthesis technology (has a commercial synthesis been defined)?

6. Is the batch yield acceptable relative to cost? This analysis will entail reviews with marketing to determine the acceptable cost of goods for the drug substance.

7. Are there any environmental or safety concerns? A review by the corporate environmental group of the list of materials used in the synthesis should be performed to provide an indication of any environmentally problematic substances used in the current synthesis. The American Conference of Governmental Industrial Hygienists (ACGIH) publishes guidelines for repeated exposure to chemicals and is a good source for exposure limits in manufacturing.[28]

8. Is the current synthesis amenable to manufacturing capabilities at existing plants? Are the technologies used in the process common; is special equipment required?

9. Is the cycle time for processing of the drug substance acceptable?

10. Have suitable process hold points been determined? What is the impact on quality/stability of drug substance?

11. Are the crystallization procedures well defined and what is the risk of polymorph formation considering the results of polymorph screening studies?

12. Are micronization techniques employed? Does the micronization impact the quality (e.g. formation of degradation products or amorphous material[29] from crystalline solids) of the final drug substance?

13. Are any of the reagents of animal origin? If so, is their Transmissible Spongiform Encephalopathy (TSE) status documented?[30]

14. Are any of the process steps patent protected?

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality - M4Q, Quality Overall Summary of Module 2, Module 3: Quality, *Step 4* of the ICH Process, 9 November 2000.
2. Lim, C-K. and Lord, G., "Current Developments in LC-MS for Pharmaceutical Analysis," *Biological and Pharmaceutical Bulletin,* Vol. 25, No. 5, 2002, pp. 547-557.
3. Food and Drug Administration, Department of Health and Human Services, Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Center for Drug Evaluation and Research, February 1987.
4. Reddy, K.V.S.R. et al., "Isolation and Characterization of Process-Related Impurities in Linezolid," *Journal of Pharmaceutical and Biomedical Analysis,* Vol. 30, 2002, pp. 635-642.
5. Streng, W. H., "Physical Chemical Characterization of Drug Substances," *Drug Discovery Today,* Vol. 2, No. 10, 1997, pp. 415-426.
6. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, November 1994.
7. Bastin, R.J., Bowker, M.J., and Slater, B.J., "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities," *Organic Process Research & Development,* Vol. 4, 2000, pp. 427-435.
8. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q3A(R), Impurities in New Drug Substances, *Step 4* of the ICH Process, 7 February 2002.
9. McCrossen, S.D. et al., "Comparison of LC detection methods in the Investigation of non-UV Detectable Organic Impurities in a Drug Substance," *Journal of Pharmaceutical and Biomedical Analysis,* Vol. 17, 1998, pp. 455-471.
10. Hilhorst, M. J., Somsen, G.W., and de Jong, G.J., "Capillary Electrokinetic Separation Techniques for Profiling of Drugs and Related Products," *Electrophoresis,* Vol. 22, 2001, pp. 2542-2564.
11. Sallam, E. and Orr, N., "Studies Relating to the Content Uniformity of Ethinyloestradiol Tablets 10 µg: Effect of Particle Size of Ethinyloestradiol," *Drug Development and Industrial Pharmacy,* Vol. 12, No. 11-13, 1986, pp. 2015-2042.
12. Carr, R.L. , "Particle Behavior, Storage and Flow," *British Chemical Engineering,* Vol. 15, No. 12, 1970, pp.1541-1549.
13. Stephenson, G.A., Forbes, R.A., and Reutzel-Edens, S.M., "Characterization of the Solid State: Quantitative Issues," *Advanced Drug Delivery Reviews,* Vol. 48, 2001, pp. 67-90.
14. Otsuka, M., Ofusa, T., and Matsuda, Y., "Physicochemical Characterization of Glybuzole Polymorphs and Their Pharmaceutical Properties," *Drug Development and Industrial Pharmacy,* Vol. 25, No. 2, 1999, pp. 197-203.
15. Bartolomei, M. et al., "Physico-Chemical Characterisation of the Modifications of I and II of (R,S) Propranolol Hydrochloride: Solubility and Dissolution Studies," Journal of Pharmaceutical and Biomedical Analysis, Vol. 21, 1999, pp. 299-309.
16. Jahansouz, H. et al., "Investigation of the Polymorphism of the Angiotensin II Antagonist Agent MK-996," *Pharmaceutical Development and Technology,* Vol. 4, No. 2, 1999, pp. 181-187.
17. Matsuda, Y. et al., "Pharmaceutical Evaluation of Carbamazepine Modifications: Comparative Study for Photostability of Carbamazepine Polymorphs using Fourier-transformed Reflection-Absorption Infrared Spectroscopy and Colorimetric Measurement," *Journal of Pharmacy and Pharmacology,* Vol. 46, 1994, pp. 162-167.
18. Burger, A. and Koller, K.T., "Polymorphism without IR and Raman-spectroscopic Differences: Tiaprofenic Acid, Three Modifications," *Pharamzie,* Vol. 54, No. 5, 1999, pp. 365-368.

19. Smith, J. et al., "Application of Two-Dimensional ^{13}C Solid-State NMR to the Study of Conformational Polymorphism," *Journal of the American Chemical Society,* Vol. 120, 1998, pp. 11710-11713.

20. Haleblian, J. and McCrone, W., "Pharmaceutical Applications of Polymorphism," *Journal of Pharmaceutical Sciences,* Vol. 58, No. 8, 1969, pp. 911-929.

21. Brittain, H.G. et al., "Physical Characterization of Pharmaceutical Solids," *Pharmaceutical Research,* Vol. 8, No. 8, 1991, pp. 963-973.

22. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 of the ICH Process, 6 October 1999.

23. Kushida, I. and Ashizawa, K., "Solid State Characterization of E2101, A Novel Antispastic Drug," *Journal of Pharmaceutical Sciences,* Vol. 91, No. 10, 2002, pp. 2193-2202.

24. Tiwary, A.K. and Panpalia, G.M., "Influence of Crystal Habit on Trimethoprim Suspension Formulation," *Pharmaceutical Research,* Vol. 16, No. 2, 1999, pp. 261-265.

25. de Villiers, M.M. et al., "Correlation Between Physico-Chemical Properties and Cohesive Behavior of Furosemide Crystal Modifications," *Drug Development and Industrial Pharmacy,* Vol. 21, No. 17, 1995, pp. 1975-1988.

26. Carlton, R. A. et al., "Preparation and Characterization of Polymorphs for an LTD4 Antagonist, RG12525," *Journal of Pharmaceutical Sciences,* Vol. 85, No. 5, 1996, pp. 461-467.

27. Byrn, S.R., et al., "Solid-State Pharmaceutical Chemistry," *Chemistry of Materials,* Vol. 6, 1994, pp. 1148-1158.

28. American Conference of Governmental Industrial Hygienists, Guide to Occupational Exposure Values, Publication #0380, Cincinnati, OH: ACGIH Signature Publications, 2002.

29. Mura, P. et al., "Investigation of the Effects of Grinding and Co-grinding on Physicochemical Properties of Glisentide," *Journal of Pharmaceutical and Biomedical Analysis,* Vol. 30, 2002, pp. 227-237.

30. Committee for Proprietary Medicinal Products (CPMP), Committee for Veterinary Medicinal Products (CVMP), Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, 31 May 2001.

31. Zdrojewski, T. and Jonczyk, A., "Application of ^{13}C NMR Spectroscopy and ^{13}C-Labeled Benzylammonium Salts to the Study of Rearrangements of Ammonium Benzylides," *Journal of Organic Chemistry,* Vol. 63, 1998, pp. 452-457.

32. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q2B, Validation of Analytical Procedures: Methodology, *Step 4* of the ICH Process, 6 November 1996.

33. DiFeo, T. J. and Shuster, J. S., "Mixed-mode Gradient HPLC Analysis of a Tyrosine Kinase Inhibitor, its Isomers and Other Potential Impurities," *Journal of Liquid Chromatography,* Vol. 16, No. 18, 1993, pp. 3903-17.

34. Shah, R.D. and Nafie, L. A., "Spectroscopic Methods for Determining Enantiomeric Purity and Absolute Configuration in Chiral Pharmaceutical Molecules," *Current Opinion in Drug Discovery and Development,* Vol. 4, No. 6, 2001, pp. 764-775.

35. Haginaka, J., "Pharmaceutical and Biomedical Applications of Enantioseparations using Liquid Chromatographic Techniques," *Journal of Pharmaceutical and Biomedical Analysis,* Vol. 27, 2002, pp. 357-372.

36. McWilliams, M. L., Chen, G-D., and Fechter, L.D., "Characterization of the Ototoxicity of Difluoromethylornithine and its Enantiomers," *Toxicological Sciences,* Vol. 56, No.1, 2000, pp. 124-132.

37. Mayer, J.M. and Testa, B., "Pharmacodynamics, Pharmacokinetics and Toxicity of Ibuprofen Enantiomers," *Drugs of the Future,* Vol. 22, No. 12, 1997, pp. 1347-1366.

38. Brittain, H.G., "Applications of Chiroptical Spectroscopy for the Characterization of Pharmaceutical Compounds," *Journal of Pharmaceutical and Biomedical Analysis,* Vol. 17, 1998, pp. 933-940.

39. Anderson, N., (ed), Practical Process Research and Development, San Diego, CA: Academic Press, 2000.

40. Committee for Proprietary Medicinal Products (CPMP), Note for Guidance on Specification Limits for Residues of Metal Catalysts, London, 27 June 2002.

41. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q7A, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 of the ICH Process, 10 November 2000.

42. Committee for Proprietary Medicinal Products (CPMP), Committee for Veterinary Medicinal Products (CVMP), Note for Guidance on Process Validation, London, 1 March 2001.

43. Center for Food and Drug Evaluation, Center for Biologics Evaluation and Research and Center for Devices and Radiological Health, Guideline on General Principles of Process Validation, May, 1987.

44. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline,

Q3A(R), Impurities in New Drug Substances, Step 4 of the ICH Process, 7 February 2002.

45. Lee, R., "Identification and Determination of Impurities in Drugs," *Progress in Pharmaceutical and Biomedical Analysis,* Vol. 4, 2000, pp. 23-37.

46. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q3C, Impurities Guideline for Residual Solvents, Step 4 of the ICH Process, 17 July 1997.

47. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 of the ICH Process, 6 October 1999.

48. Laasonen, M. et al. "Near infrared Reflectance Spectroscopy for the Fast Identification of PVC-based Films," *The Analyst,* Vol. 126, 2001, pp. 1122-1128.

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Installation of Pharmaceutical Process Piping - A Case Study

Part 1 - Planning and Preparation

by Barbara K. Henon, PhD, Stephan E. Muehlberger, and Gene DePierro

This two-part article is a case study tracking the installation of process piping for (product) filling lines 7 and 8 in Building 21 at the Sicor, Inc. (formerly Gensia Sicor Pharmaceuticals) plant in Irvine, California.

Part 1 includes planning, demolition of existing structures, and preparation for the new installation.

Introduction

Good process piping is fundamental to the success of any pharmaceutical or biopharmaceutical installation. All systems including process equipment and piping, must be fully drainable, cleanable, and sterilizable for the successful production of pharmaceuticals. Over the past decade, advances on several fronts have contributed to make the installation of process piping more efficient and with fewer delays.

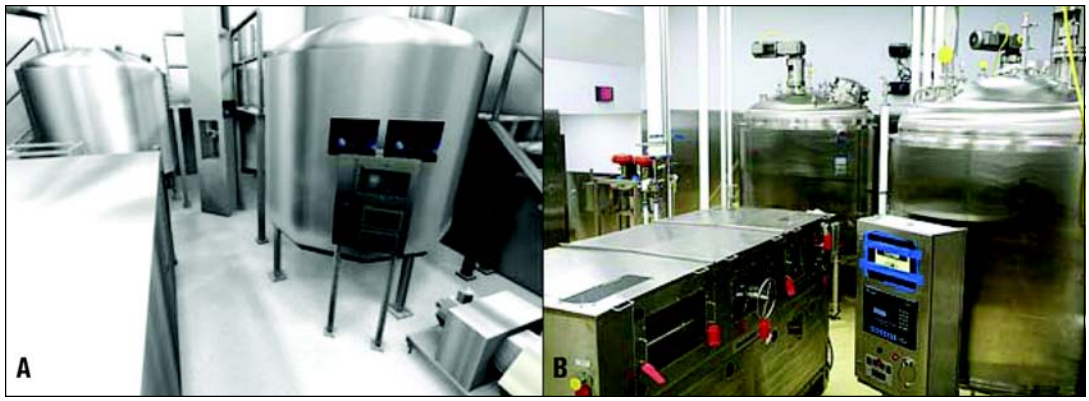
As an example of current installation practices, this article is a case study of a process piping installation at a project for Product Filling Lines 7 and 8 in Building 21 at the Sicor Inc. Pharmaceutical Plant in Irvine, California from the summer of 2002 until its completion in March, 2003. In support of the product lines, piping systems for nitrogen, Clean-In-Place piping (CIP), Water For Injection (WFI), Reverse Osmosis (RO) water, Deionized (DI) water, product clean steam, and clean steam condensate were installed.

Projects such as this must be planned in advance by the owner and activities coordinated between the design engineer, general contractor, installing contractor, third party QA (also referred to as the inspection contractor), and the validation team.

Before beginning construction, the owner must have a very clear idea of exactly what he wants the system to look like and how he wants it to function. Computer simulations help to visualize the project before the engineers and vendors are called. Mechanical contractors have greatly improved their fabrication technology for installing process piping. They now have better defined procedures and fewer "cut- outs" of welds which has meant "cleaner" documentation submitted for FDA approval. As a result, productivity is higher.

This is partly due to the widespread use of orbital welding and the development by the installing contractors of orbital welding Standard Operating Procedures (SOPs). These SOPs are written procedures followed by welding personnel so that everyone follows the same series of steps in the same order for handling materials, cutting and end-prepping of tubing for welding, inert gas purging, and welding, etc.

Improved standards and guidelines such as the ASME Bioprocessing Equipment Standard



Figures 1A and 1B. "Before" and "after" pictures show renderings of the desired "look" as a pre-construction Computer Graphic Image (CGI) on the left, while the actual appearance of nearly completed room is shown in the photo on the right. *CGI and photo courtesy of Sicor Inc.*

"On a similar project, computer simulations saved an estimated 10% of the project cost and helped the owner to get what they wanted."

(BPE-2002) originally published in 1997, and the ISPE Baseline® Guides[1,2] also have driven the quest for quality in pharmaceutical piping systems. These standards were developed by industry leaders who recognized that good design and efficient installation procedures are important for containing costs both during construction and for the service life of the systems.

This installation would be considered a "small" process piping project with about 2,500 feet of stainless steel tubing with a total of approximately 600 orbital welds. This works out to be a weld every 4 to 5 feet. Sicor Inc. is nearly unique in the number of products they produce with more than 100 different drugs made at this facility. Their products include Active Pharmaceutical Ingredients (APIs) for use in various products, Finished Dosage Products (FDP) (injectables), and biopharmaceuticals such as human growth hormone and human insulin.

Defining User Space

Senior Project Manager for Sicor, Stephan Muehlberger, begins a project by defining the user space. He develops computer simulations of the proposed spaces using software which provides extremely accurate visualizations of how the completed rooms and suites will appear when finished. The end-user is most concerned with the appearance of those areas with the highest requirements for cleanliness. He has a certain "look" in mind for the high-visibility areas which include the filling suite, the area of compounding, and the component preparation area. Not coincidentally, these happen to be the areas with the highest ratio of process piping.

Once the location of equipment in these areas is established, engineers can concentrate on how to get the utilities to the spaces. Computer simulation is a very powerful tool that allows the viewer (engineer or contractor) to virtually open doors and walk through a series of proposed areas and to view the spaces from above to see how various pieces of equipment will be placed in a room. From this perspective, they are able to gauge the amount of walk-around space that should be available around each component. The work space must be uncrowded, clean, and orderly with everything in its proper place.

The filling lines project has 20 cleanrooms ranging from Class 100 up to Class 10,000. The number and location of sinks and use points must be detailed in advance. Arrangements must be made for HEPA filters, HVAC, temperature controls, and piping. To prevent crossing of piping and ducting or similar disorderly arrangements, the areas to be left clear must be specified. A computerized presentation can provide sufficient detail to serve as a guide for writing the job specification and help to keep change orders to a minimum. If a particular computer drawing of a process panel shows the exact position of a valve with respect to the piping, this can help serve as a guide for the installing contractor - *Figures 1A and 1B*. On a similar project, computer simulations saved an estimated 10% of the project cost and helped the owner to get what they wanted.

General Contractor

The general contractor specializing in construction projects for the Biotech and Pharmaceutical Industry was the liaison between the architect engineering firm, the end user, and the construction team. Project Executive, Larry Moore, was responsible for overseeing the entire project. The general contractor prepared the master document for the installation called the *Construction Qualification Program* (CQP). The CQP consisted of a set of written SOPs and guidelines for the purpose of controlling the construction process. The procedures covered documentation compiling, system and equipment testing, and the requirements for Turnover Package preparation.

Written procedures are considered to provide the best assurance that the important systems and components of a pharmaceutical manufacturing facility are installed in accordance with the specifications and that the proper installation has been documented giving a high level of assurance that the principles of current Good Manufacturing Practices (cGMP), as interpreted and enforced by the United States Food and Drug Administration (FDA), have been met.

The FDA does not tell people how to build a facility, but rather checks to see that all the documentation is correct. End users and their validation and QA people must demonstrate that they are in compliance with 21 CFR 211.65 paragraph (a) which states "*Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.*"[3] If any of the documentation submitted to the FDA is found to be out of order, the FDA will start "pulling at threads" to get at the root of the problem.

Installing Contractor

Project Manager Stephan Muehlberger said that in a perfect world he would be able to just tell the vendor to "install the process pipe" and it would be done not just to the standard, but exactly the way he wanted it. Since it is not a perfect world, he must have a relationship with the vendor and know their level of experience and expertise. The installing contractor, who has done previous work for Sicor and are an approved and preferred vendor, did design-assist and project

coordination and execution. Their welders are experienced in the use of orbital welding equipment - *Figure 2.* They understand what's required in terms of how the system should look, how to do the isometrics, and the best way of supporting the piping. Proper pipe support is important since the plant is in California and must conform to requirements for seismic zone 4.

IQD Turnover Package

In preparation for Phase I construction, the installing contractor prepared an IQD Turnover Package for each system that was to be relocated including process gases, clean steam, etc. The IQD Turnover Packages each contained a Scope of Work statement, a list of project personnel and their brazing certificate, or for welded systems, welder performance qualifications, Weld Procedure Specifications (WPS), and Procedure Qualification Records (PQR) in compliance with ASME Section IX of the Boiler and Pressure Vessel Code.[4] Also included were welding equipment certifications, receiving logs for materials, critical system isometric (ISO) drawings for each of the systems, certificates of cleaned material, and pressure test reports for various system components.

Welded systems had coupon logs, weld logs, borescope logs, and passivation procedures and certificates. At the end of the IQD Turnover Package, there was a sign-off sheet to be turned over at the end of the shutdown for acceptance of the work by the client. The Scope of Work for the shutdown was to isolate and remove process gas lines from the first floor labs in the demolition area and tie-in and re-route process piping systems.

The installing contractor translated engineering drawings from the architect engineer from two- dimensional to three-dimensional isometric construction drawings and then verified that the drawings were "constructible." The general contractor obtained the necessary permits from the city to do the work.

Phase I, June 14 - July 30, 2002, Demolition and Re-Installation of Existing Systems

The first phase of the piping installation was a shut-down to accommodate a "Tenant Improvement" (TI) situation. This involves relocation of the existing equipment and utilities in the area where the new product lines were to be installed in order to avoid interruption of the then-current production schedule. The demolition phase was on a very tight schedule with crews working around the clock. Bulldozers were used for demolition of walls which were cut down and moved out in large chunks; utilities, lights, phones, fire alarms, etc. were all cut out and then equipment was relocated and re-installed. All process equipment, utilities, and piping had to fit within very confined spaces and there could be no interference among the plumbing, electrical, concrete, carpenters and other trades who had to work in the same space at the same time to complete this phase within the allotted time.

Figure 2. Welding operator installs an electrode in the orbital weld head which is connected to an orbital welding power supply. A water cooling unit is situated beneath the power supply. *Photo courtesy of Pro-Tech Process, Inc.*

Phase II

In preparation for Phase II, the installing contractor prepared a separate submittal package for each of the piping systems which included the product lines and piping systems for nitrogen (N_2), Clean Air (CLA), Clean-In-place (CIP), Water For Injection (WFI), Reverse Osmosis (RO) water, Deionized (DI) water, product clean steam, and clean steam condensate. For example, the WFI submittal package contained a specification for stainless steel piping materials, such as tubing and fittings, and methods of attachment which included flanges and gaskets, orbital welding, and valves. The remainder of the book contained vendor product information and specifications for the above items as well as for piping insulation material and instrumentation. An orbital Weld Procedure Specification (WPS), qualifying the welding procedure to ASME Sect. IX of the Boiler and Pressure Vessel Code[4] and Procedure Qualification Records (PQRs) for each of the welders and isometric drawings for routing the WFI system also were included in the package.

Typically, material availability drives the schedule which means that items with long lead times must be ordered as soon as possible. For this project, the long lead time items are one-of-a kind custom pieces of equipment such as WFI heat exchangers, valve clusters, and other process equipment.

Orbital Welding

During the past decade, the ratio of orbital welds to manual in biopharmaceutical systems has increased to the point that presently very few manual welds are done. Dr. Richard Campbell of Purity Systems, Inc. reported at a recent ASME BPE Standards meeting that about 99% of welds in biopharmaceutical installations are now done with orbital welding. The BPE standard requires that, if a manual weld is done, it must be with the owner's permission and it must be inspected on the inside (ID) with a borescope as shown in Figure 3.

Figure 3. Video borescope display showing I.D. weld bead from a field weld and information recorded for each weld. *Photo courtesy of Purity Systems, Inc.*

The welding used in hygienic biopharmaceutical applications is autogenous orbital GTA welding. In this process, an arc is struck between a non-consumable tungsten electrode and the weld joint. This takes place inside an enclosed weld head in an inert gas atmosphere. The tube or fitting being welded remains in place while the electrode in the weld head rotor moves around the joint circumference to complete the weld. Weld parameters such as welding current, electrode travel speed, and pulse times are programmed into the microprocessor-controlled power supplies (Figure 2) and stored as weld programs or weld schedules for each size of tubing, pipe, or component to be welded. Print-outs of weld schedules are included in the weld qualification documents. The weld joint configuration is a square butt preparation in which the tube ends are cut square and machine-faced to fit together without a gap.

The goal of orbital welding is to achieve a very high degree of repeatability from weld to weld, not only to get high productivity, but to provide the best quality system possible. The welding power supply executes the weld parameters with a high degree of accuracy weld after weld. It is up to the installing contractor and his operators to control other factors that could affect weld repeatability. The welding operators received training in operation of the equipment and are proficient at developing weld schedules for each size of tubing and know how to cope with heat-to-heat variation in weldability. Installing contractors have developed Standard Operating Procedures (SOPs) detailing every aspect of the orbital welding process.

ASME BPE Standard

Sicor Inc. hired a third-party QA company to inspect their welds. In addition to weld procedure qualification to ASME Sect.IX and B31.3[5], inspectors used the visual criteria for weld acceptance from the Materials Joining part of ASME Bioprocessing Equipment Standard (BPE-2002).[1] The BPE Standard was originally published in 1997 and was revised in 2002. The BPE Standard was the first standard written for the biopharmaceutical industry that specifically recommends the use of orbital welding.

The Dimensions and Tolerances (DT) Part of the BPE Standard has contributed to improved consistency of orbital welding by specifying acceptance criteria for wall thicknesses and ovality of weld ends of fittings and other components for bioprocess systems. Since the welding current for orbital welding is roughly proportional to wall thickness with about 1 amp of welding current for each 0.001 inch, a variation of more than a few thousandths of an inch in wall thickness could make a difference in weld bead penetration. Similarly, the squareness of the weld end is controlled so that there will be no significant gap between parts when secured in the weld head. Good fit-up and alignment of parts for welding is essential.

The material generally used in high purity biopharmaceutical applications is 316 or 316L stainless steel.[6] For welding, the reduced carbon content of 316L is preferred. With higher carbon levels (0.080 wt.% in 316 compared to 0.035 wt.% in 316L), there is a chance of carbon migrating to the grain boundaries in the area immediately adjacent to the weld during welding, combining with chromium and precipitating as chromium carbide leaving the grain boundaries in the Heat-Affected Zone (HAZ) reduced in chromium, and thus subject to intergranular corrosive attack. However, since the formation of chromium carbide is time and temperature dependant, the precisely controlled heat input of orbital welding makes this occurrence less likely than with manual welding.

In the interest of weldability, the DT Part of the BPE standard has limited the sulfur range of type 316L stainless steel used for fittings and weld ends of components to 0.005 to 0.017 weight% and recommends the use of tubing specified to ASTM A270 S-2 Pharmaceutical Grade which has the same sulfur range as the BPE. This is in contrast to the AISI specification which lists a maximum sulfur concentration of 0.030 weight%, but no minimum. Heat-to-heat variation in base metal chemistry of stainless steels results in differences in weldability and is a major cause of weld inconsistency. The limited sulfur range has eliminated much of the uncertainty in fabrication and greatly increased the consistency of orbital tube welding for those using this standard.[7]

When materials arrive on site, they are received and logged by the installing contractor and then inspected and logged by third-party QA. ASME B31.3 Process Piping Chapter VI distinguishes between *examination* and *inspection*. *Inspection* applies to functions performed for the owner by the owner's inspector or the inspector's delegates (QA), while *examination* applies to quality control functions performed by the manufacturer, fabricator or erector, in this case the installing contractor (QC). Weld criteria are detailed in the Materials Joining part of the BPE Standard.

References

1. ASME Bioprocessing Equipment Standard (BPE-2002), American Society of Mechanical Engineers, Three Park Ave., New York, NY 10016.

2. *ISPE Baseline® Pharmaceutical Engineering Guide: Volume 4 - Water and Steam Systems,* First Edition/January 2001, ISPE, 3109 W. Martin Luther King, Jr. Blvd., Suite 250, Tampa, FL 33607.

3. Code of Federal Regulations - Food and Drug Administration - Current Good Manufacturing Practice for the Manufacture, Processing, Packing, or Holding of Drugs - 21 CFR- Parts 210 & 211, Revised as of November 4, 1998.

4. ASME Sect. IX. Boiler and Pressure Vessel Code, American Society of Mechanical Engineers, Three Park Ave., New York, NY 10016.

5. ASME B31.3 Process Piping 1999 Edition. American Society of Mechanical Engineers, Three Park Ave., New York, NY 10016.

6. Gonzalez, Michelle M., "Stainless Steel Tubing in the Biotechnology Industry," *Pharmaceutical Engineering,* Vol. 21, No. 5, 2001, pp.48-63.

7. Henon, Barbara. "Specifying the Sulfur Content of Type 316L Stainless Steel for Orbital Welding: Weldability vs. Surface Finish," *Tube and Pipe Journal (TPJ),* Vol. 14, No.2, 2003, pp. 46-49.

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This article describes the basis and development of the solid dosage form section of an educational CD-ROM, including both the theoretical and self-evaluation sections.

Note: English translations of figures are shown in yellow.

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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.[1] 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:[2]

1. Solids
2. Liquids
3. Semisolids

Figure 1. Menu of the solid dosage forms.

Figure 2. Equipment used in the tablets coating process.

4. Services

5. Library

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.[3] 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.[4]

Powders are the oldest of the solid dosage forms; their use has diminished as oral powders, but they are still used as topical powders.[5]

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.[6]

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.[7] 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)[8a]

Capsules

Capsulas 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.[9] The type of gelatin used is explained as well as the process for obtaining the gelatin from dry bone, calf, and pork skin.[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

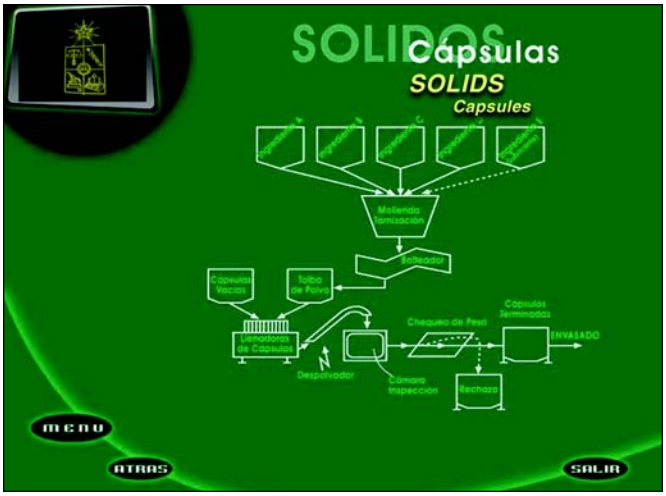

Figure 3. Basic operations involved in capsules production.

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.

Figure 5. Puzzle designed for tablet manufacture by wet granulation.

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,[10] 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:

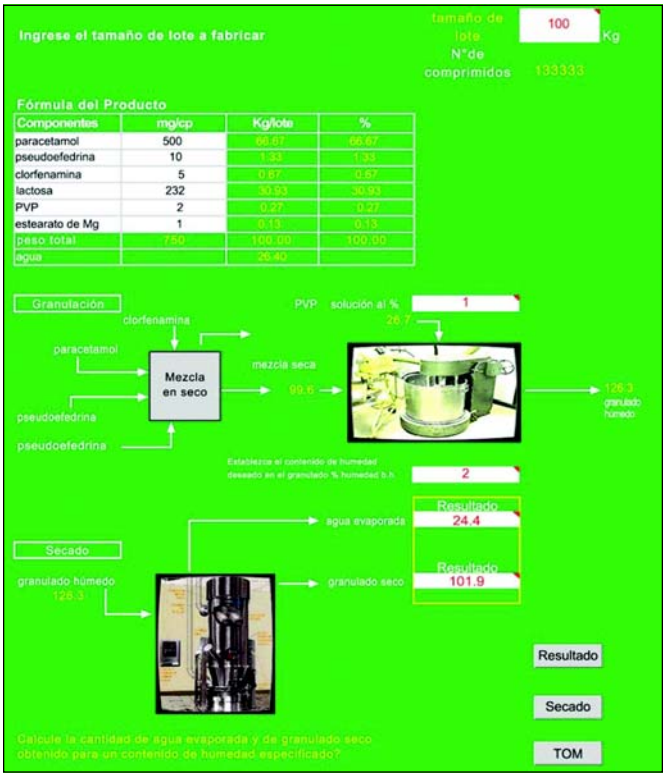

Figure 6. Examples of mass balances involved in tablet manufacture by wet granulation.

a. Size reduction (energy requirements in comminution, key factors in the ball mill operation, solid properties that influence the size reduction operation)

b. Mixing of powders (selection of mixers for specific applications, 'Mixing Index')

c. Humidification operations (estimation of air humidity from water vapor pressure, using a psychometric diagram)

d. Drying of solids (selection of drying equipment, use of drying curves). Figure 4 provides an example of the multiple-choice section of the CD-ROM.

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/cm^2), 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. m^3 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.[2]

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

1. Tashijan, J., "The Problem of Over Regulation, Over Engineering and Over Validation," **Pharmaceutical Engineering**, Vol. 20, 2000, pp. 8-14.
2. Tapia, C., Sapag-Hagar, J., Muller, M., Zunino, G., Valenzuela, F., Basualto, C., "Development of an Interactive CD-ROM for Teaching Unit Operations to Pharmacy Students" **Am. J. Pharm. Educ.,** Vol 66, 2002, pp.280-287.
3. Alderborn, G., and Wikberg, M., **Pharmaceutical Powder Compaction Technology**, Marcel Dekker, Inc., NY, 1996 p. 322.
4. www.capsugel.com.
5. Allen, L. **Comprehensive Pharmacy Review**, 3rd Ed., Williams & Wilkins, MD, 1997 pp. 97-98.
6. Reddy, I.K., "Implementation of a Pharmaceutics Course in a Large Class through Active Learning Using QuickThinks and Case-Based Learning," **Am. J. Pharm. Educ.,** Vol. 64, 2000, pp. 348-355.

7. McCabe, W., Smith, J., and Harriott, P., **Unit Operations of Chemical Engineering**, 5th Ed., 7. Mc Graw-Hill, Singapore, 1993 pp. 954-956.

8. Lachman, L., Lieberman, H., Kanig, J. **The Theory and Practice of Industrial**, 3rd Ed., Lea & Febiger, Philadelphia, 1986 a) p. 359 b) p. 375.

9. **US Pharmacopeia 24.,** United States Pharmacopeial Convention, Inc., Rockville, MD, 2000 p. 2110.

10. Edwards, D.W., Lamb, F.M., Ahmed, V.S., Rothberg, S.J., "ASTutE: Computer-Aided Teaching of Materials Balancing," **Chem.Eng. Ed.,** Vol. 34, 2000, pp. 258-263.

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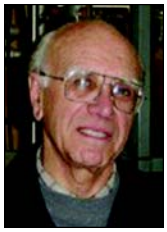

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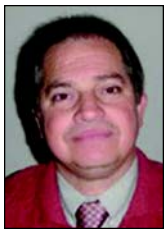

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This article discusses the comparison of Multiple Effect and Vapor Compression for USP Purified and WFI quality water for the pharmaceutical industry.

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Water Systems Utilizing Multiple Effect and Vapor Compression Technologies Compared

by George Gsell

Introduction

The critical nature of water systems within the biotech and pharmaceutical industries brings them under scrutiny from a variety of perspectives. This scrutiny is to ensure the quality of water is available to meet the requirements of the U.S. Pharmacopoeia as it relates to the product being manufactured. A clear understanding of the processes that go into a water system, and how they compare to and interact with one another, can aid us in developing systems that produce a high quality of water in a reliable and cost effective manner. All too often, additional processes are installed within a water system with the intent of improving upon the quality of the system. Overly complex systems typically generate additional costs through validation, testing, plant space, utilities, maintenance, and operations staff. The reliability of these systems diminishes as the number of components within them increases. In addition, there is tremendous focus on general issues such as validation, welding, surface finish, software development, factory and site acceptance testing. This focus further highlights the need to develop water systems that are concise and effective.

Where Water For Injection (WFI) is required within a system, it is common practice to produce this water via distillation. The method of distillation used to produce WFI often drives a number of other issues, such as the system of pretreatment and whether or not this system can be used for any other form of water production, such as USP purified or perhaps boiler feedwater, as examples. Distillation of pretreated water for WFI production is commonly done by way of multiple effect or vapor compression evaporation.

Multiple Effect (ME) and Vapor Compression (VC) distillation plants both produce water of WFI quality. As a manufacturer of both processes, we are often asked to explain the differences. Why would one choose one system over the other? The answer lies in the fact that they are both fundamentally different thermodynamic processes well documented in various text.[1,2] Each process dictates its own requirements, some of which may not be readily apparent. The feedwater pretreatment requirements for each process may be substantially different. The utilities, footprint, maintenance and operating parameters are different. The intent of this article is to provide information so that the reader can have a broader perspective of issues in determining which process is best for a particular application. The theory of each process will be reviewed along with utility requirements, feedwater requirements, misconceptions within the industry, system design, and economics.

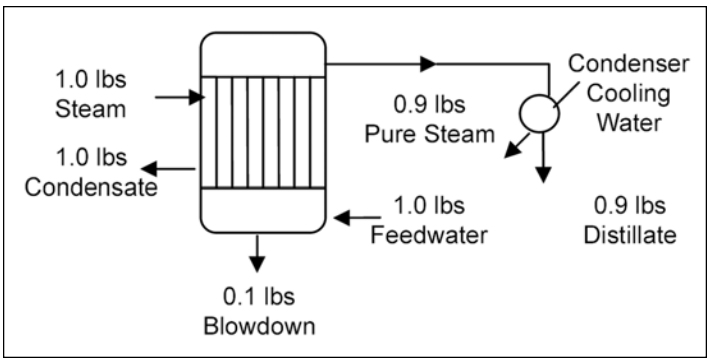

Figure 1a. 1.0 lbs of steam produces 0.9 lbs of distillate in a single effect evaporator.

Basic ME Theory

Consider the basic ME process. "If a pound (lb) of steam is sup-

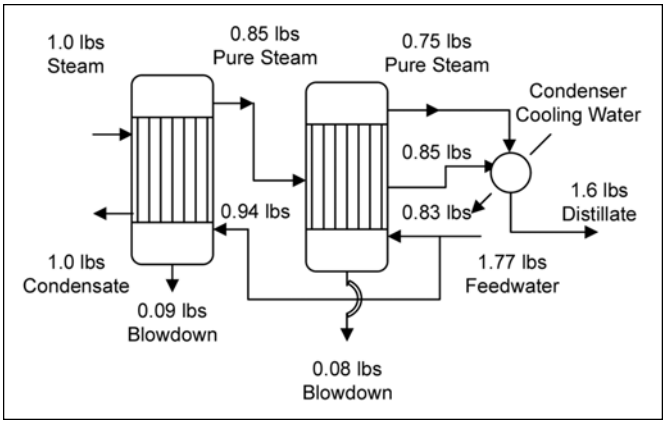

Figure 1b. 1.0 lbs of steam produces 1.6 lbs of distillate in a double effect evaporator.

plied to an evaporator, it can be shown to produce 0.9 lbs of vapor from a pound of water with the remaining 0.1 lbs of water being withdrawn as blowdown containing impurities. The steam vapor formed is useful and pure."[1] In the biopharm industry, if this vapor is taken to a condenser, we have the basis of what is commonly called a pure steam generator with sample cooler - *Figure 1a*. Alternatively, this system could be called a *single effect* evaporator.

"If however, the original pound of steam is supplied to a process as shown in Figure 1b, and the vapor formed in the first evaporator is used as a heat source for a second evaporator operating at a lower pressure than the first, an additional utilization could be made of most of the heat. If both evaporators are fed in parallel with raw water, about 0.85 lbs of pure water would be formed in the first *effect* and about 0.75 lbs would be formed in the second effect. For each pound of steam supplied, about 1.6 lbs of distillate can be produced. When the vapor formed in the first effect is reused as the heating medium in a second effect, this is called a *double effect* evaporator. When applied to three effects, this is called a *triple effect* evaporator (Figure 1c) and the original pound of steam produces about 2.25 lbs of distillate".[1] The actual amount of distillate produced by the steam (given a fixed steam supply) is also a function of the raw water temperature. Conversely, for a fixed output of distillate, the steam consumption will vary somewhat with the raw temperature. The lower the raw water temperature, the higher will be the steam consumption. In practice, feedwater heat exchangers are used to minimize this variation.

In order to maintain temperature differences for heat transfer between the vapor from one effect and the boiling water of the next effect, the pressure of each succeeding evaporator must be lower than its predecessor. Where a number of effects are employed in a multiple effect still, the first effect operating pressure and temperature are typically more than 100 psig and 325°F. The energy input to the first effect is degraded and used in each succeeding effect. The fixed costs of additional effects ultimately dissipate the savings in energy that results from a large number of effects.

The efficiency of a distiller is often expressed in terms of *Economy (E),* which is defined as the mass of distillate produced in pounds (Md) relative to the amount of energy input and can be given by:

E= Md/1000BTU energy input

In the example above, the single effect evaporator has an economy of 0.9, the double effect evaporator has an economy of 1.6, and the triple effect evaporator has an economy of 2.3. A useful tip to remember is that the economy of a multiple effect distiller will always be some number less than the number of effects in the process.[2] It should be noted that the multiple effect process dictates that a certain amount of process cooling water be used for condensing the vapors from the last effect. The amount of cooling water required is a function of several factors including the number of effects on a given unit, the temperature of the cooling water supply, the operating temperature of the plant, and the desired distillate temperature. A portion of the heated cooling water is typically used to feed the ME process itself. However, not all of this cooling water can be used as feedwater, so a large portion

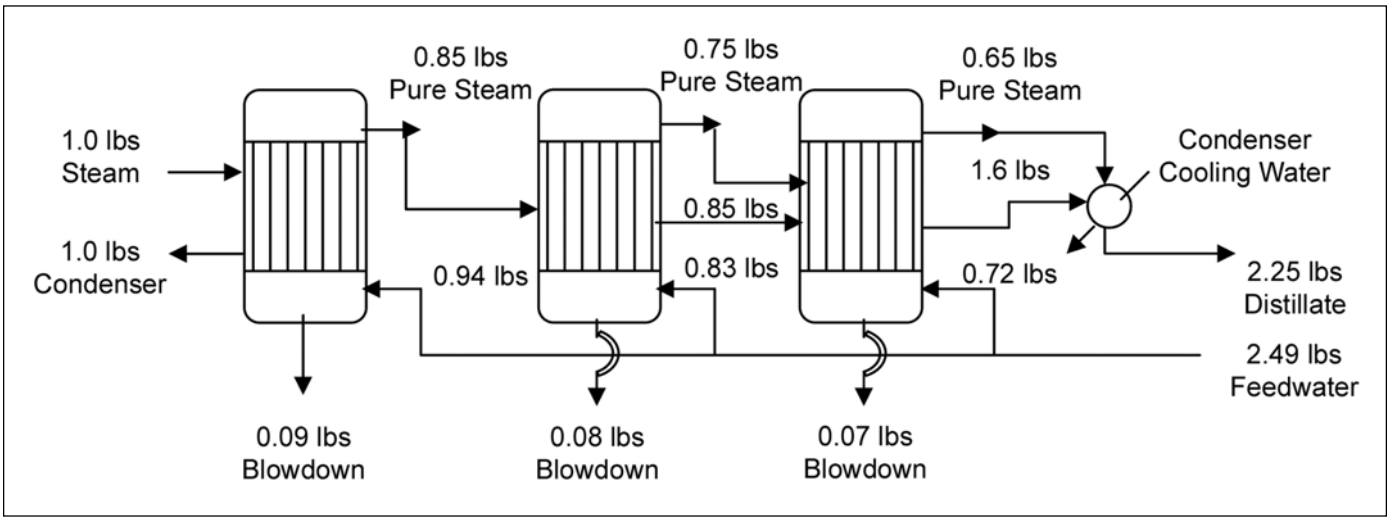

Figure 1c. 1.0 lbs of steam produces 2.25 lbs of distillate in a triple effect separator.

"In theory, it would take approximately 10 effects in a multiple effect plant to match the performance of a vapor compression distiller producing hot WFI."

is typically wasted unless this cooling water is subsequently used as a preheated feed to another process.

Basic VC Theory

The vapor formed within the single effect evaporator (Figure 1a) contains nearly as much heat as is present in the steam supplied to the evaporator. The vapor is condensed with water as a means of heat removal. As noted earlier, this is a waste of both thermal energy and cooling water.

Now consider the basic vapor compression process. If it were not for the fact that the vapor generated is at a lower pressure than the original steam supply, it would be possible to circulate the vapor back to the heating surface and evaporate continuously. A temperature difference must exist between the steam and generated vapors or no heat will be transferred. The vapor from the evaporator can be compressed and in so doing, the temperature of the vapor is raised. The practice of recompressing a vapor to increase its temperature and permit its reuse is called thermocompression or mechanical vapor compression. In the biopharm industry, the latter is used with a mechanical centrifugal compressor. The cost of supplying the necessary amount of compression is relatively small compared to the value of the latent heat in the vapor. The compressed vapor is discharged to the opposite side of the heating surface from which it is generated. In doing so, because a temperature difference now exists across the heating surface, the compressed vapor condenses as WFI giving up its latent heat energy imported through compression to the water on the opposite side of the heating surface. More vapor is generated from the water and the cycle of compression, heat rejection, and evaporation continues. In the vapor compression process, no process cooling water is required to complete the cycle. However, some cooling water is required to remove heat from the compressor although this is an insignificant amount.[3]

Vapor Compression (VC) plants, as used in the biopharm industry, have only a single evaporator. The economy of the VC cycle is primarily a function of compressor efficiency and the amount of heat recovered within the cycle through heat exchange between the outgoing distillate and blowdown streams and the incoming feedwater stream. The steam consumption of the process is reduced as more heat is recovered - *Figures 2a and 2b*. In either case, for a given output of distillate, the compressor energy remains constant.

The economy of a vapor compression distiller producing 180°F WFI is about 7.5. The economy of a vapor compression distiller producing ambient temperature WFI or USP purified water is about 20.

In comparing the two processes, vapor compression is generally considered a more efficient means to produce distilled water. In theory, it would take approximately 10 effects in a multiple effect plant to match the performance of a vapor compression distiller producing hot WFI. Although the measure of economy takes into account all forms of energy used, in practice, the actual price of electricity, steam, and cooling water have a major influence in comparing the operating costs of the two distillers. This is because the vapor compression process derives a portion of its energy requirements from an electrically driven centrifugal compressor as well as steam while the multiple effect process is driven principally by steam.[4]

Energy Consumption and Cost

Tables A and B represent typical energy consumption and cost values for both multiple effect and vapor compression distillers producing 600 gallons per hour of WFI. Energy costs are variable in the vapor compression process depending upon if the water is produced hot or at ambient temperature. Where large amounts of water are produced, the difference in energy costs can be significant. When ambient temperature

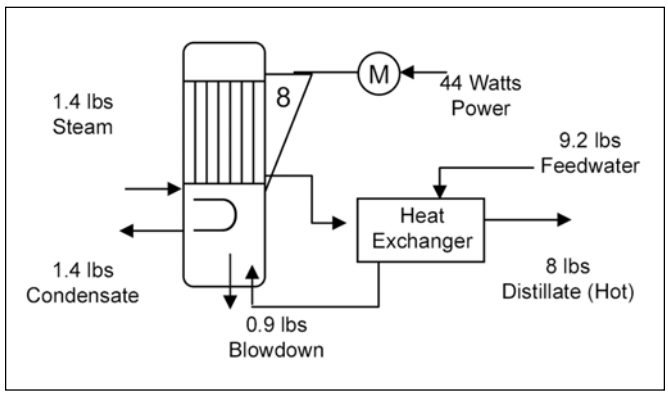

Figure 2a. Hot WFI (180°F) production via vapor compression. 1.4 lbs steam and 44 watts electricity = 8.0 lbs distillate.

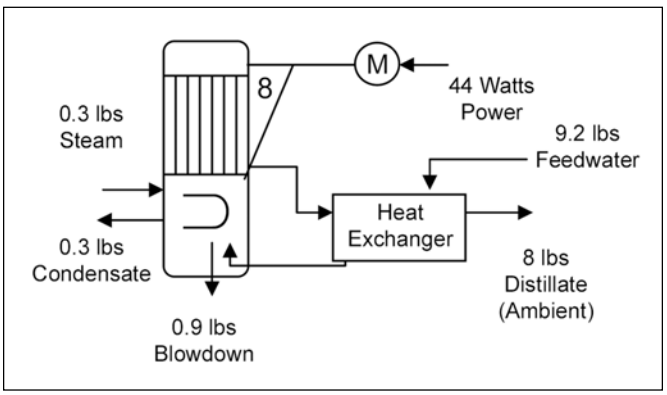

Figure 2b. Ambient production (WFI or USP) via vapor compression. 0.3 lbs steam and 44 watts electricity = 8 .0 lbs distillate.

"The water quality issue can be further explained by examining some of the fundamental principals to achieving a certain quality of product from a distiller."

water is produced, heat is recovered, and the energy cost of the VC process is cut in half.

In the example presented, electricity cost was input at 7 cents per KW hr., steam costs were input at $7.75 per 1000 lbs, and cooling water was considered at $2.00 per 1000 gallons. A shift in the costs for electricity or steam will influence the operational costs of a given distiller. Each distiller should be evaluated based upon prevailing rates for utilities. Your supplier will calculate the energy consumption of a given system when provided with your basic cost data.

Another important consideration is the initial cost of the plant. In the example given, a six effect multiple effect plant was used because the capital expenditure of this size multiple effect unit typically compares with that of a vapor compression plant. Adding effects to the multiple effect plant will reduce its energy consumption, but increase the initial cost. Properly operated and maintained distillers will have a life expectancy greater than 20 years. Some work has been published that indicates the total life cycle costs of a simple VC distiller with softening pretreatment to be comparable to that of membrane and ion exchange based systems.[8]

Feedwater Requirements

One of the major differences between the two processes is in the feedwater quality requirements. The objective of any pretreatment system is to eliminate scale forming constituents from the feedwater as well as minimize the potential for corrosion. The maximum operating temperature of a multiple effect plant is within the first effect and is typically in excess of 325°F. As such, it is most common that the feedwater supplied to this type of plant is DeIonized (DI), Reverse Osmosis (RO) permeate (Figure 3), or a combined RO/EDI product. In addition, some method of dechlorination is always required.

Type/Model	Multiple Effect 6ME600	Vapor Compression VC600 GPH Hot/Cold
Product Water WFI [1]	10 gpm	10 gpm
Feedwater [2]	11 gpm	11 gpm
Cooling Water	8 gpm	0
Electricity	3.6 kw[3]	26.5 kw
Steam Supply	1240 lbs/hr @100 psig	650 lbs/hr @40 psig - Hot 180 lbs/hr @40 psig - Cold
Physical Dimensions	160"L x 62"D x 133"H	103"L x 80"D x 117"H
[1] Product Water @190°F [2] Feedwater taken @70°F [3] Power included feed and distillate pump		

Table A. Multiple effect and vapor compression utilities.

Vapor compression plants on the other hand take a relatively low grade of energy in the form of low pressure steam and raise the temperature and pressure of the raw water vapor from slightly above atmospheric pressure such that the plant operates at 215-230°F. As such, it is common practice for VC plants to operate with feedwater only processed by a softener for hardness removal and carbon filtration for dechlorination - *Figure 4*. In some cases, a membrane plant may be used or preferred to remove silica, high alkalinity, or other constituents. There is nothing to preclude the use of RO as a pretreatment step for VC if so desired.

Common Misconceptions

There are a number of misconceptions associated with each process that should be clarified.

1. A common misconception is that the water in a ME plant is repeatedly distilled from one effect to another yielding some benefit to the user. In fact, each effect within a ME plant produces its own output in parallel and the product water from one effect is not redistilled in another. Both vapor compression and multiple effect distillers evaporate a given volume of water only once, converting it to steam and condensing this steam separately.

2. Another misconception is that the combined softener and vapor compression approach is not capable of producing as high a water quality as the RO/ME approach. Both distillation processes generate a water quality meeting the requirements of the US Pharmacopoeia for WFI.[5] RO will certainly reduce the total dissolved solids and endotoxin levels within the feedwater to a still. In some cases, this "belt and suspenders" approach to ensuring water quality

	Multiple Effect 6ME600	Vapor Compression VC600 GPH Hot & Cold Operation
Electricity @ $0.07/kw hr	$1,764/yr	$12,985/yr
Cooling Water @ $2.00/1000 gal	$6,720/yr	$0/yr
Steam Supply @ $7.75/1000 lbs	$67,270/yr	$35,262/yr - Hot $ 9,765/yr - Ambient
Calculated running cost $/yr	$75,754	$48,247 - Hot $22,750 - Ambient
$1000/gal	$18.04	$11.49 - Hot $5.42 - Ambient
Assume 7000 hrs/year operation		

Table B. Operating economics of multiple effect and vapor compression stills.

may be desired or required. However, the RO pretreatment schemes commonly associated with ME installations are not installed to improve water quality, but are required to inhibit scaling and corrosion in the higher temperature effects.

Millions of gallons of WFI are produced using VC absent of a membrane pretreatment step. Typically, these stills are preceded by either softeners or ion exchange.[6] The conductivity of this water is normally 0.2-0.5 microsiemens.[7] VC plants with simple softening have been demonstrated to produce WFI with endotoxin below the detectable limit of 0.005 Eu/ml.

The water quality issue can be further explained by examining some of the fundamental principals to achieving a certain quality of product from a distiller.

Both vapor compression and multiple effect distillers evaporate a given volume of water only once, converting it to steam, and condensing this steam separately. The phase change from liquid to steam is the principal driver in generating high purity water absent of dissolved solids that can influence the water quality as measured by conductivity. Evaporators also use disengagement height and gravity to aid in the separation process. The disengagement space is the distance between the raw water level in the evaporator and the higher level at which the steam vapor crosses to the condensing surface. As the vapor rises up through the disengagement space, the force of gravity removes entrained water droplets which might otherwise affect the quality of the water produced - *Figure 5*.

Both multiple effect and vapor compression evaporators have additional aids to separation at the upper levels of the disengagement space. A variety of designs are available, including demister pads, impingement baffles, centrifugal separators, and others.

Assuming that the designer of the ME or VC still does a good job of incorporating disengagement height and a separation aid to remove dissolved solids from the water that would otherwise contribute to a high conductivity, the other constituents to eliminate that can contribute to a high conductivity are dissolved gasses with an ionic charge such as carbon dioxide and ammonia. Both of these are liberated from the raw water upon heating, when present, and vented through a deaerator or condenser.

3. A distiller's operating temperature is sometimes associated with having an influence over the quality of water it produces. Assuming the distiller is operating within its design parameters, this is not the case. The ME evaporator operates over a temperature range, and while the top temperature in the first effect may reach more than 325°F, the bottom temperature in the last effect typically operates at around 220°F, and each effect produces only a portion of the product. In the vapor compression process, all of the vapor (product) reaches a top temperature of 250°F. As a practical matter, both processes operate well above the generally accepted sanitization standard. The evaporators operate at different temperatures because thermodynamics dictates they do so. The temperature differences between the two processes have no influence on the water quality.

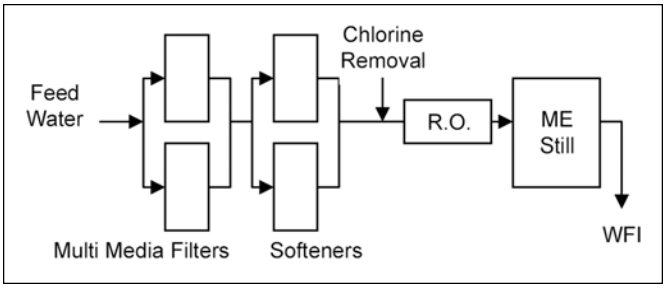

Figure 3. Typical ME pretreatment.

4. Broad statements are sometimes made regarding the maintenance or reliability of one distiller (ME vs VC) versus another. The reliability of a distilling unit can be evaluated numerically as a function of the number and type of components, their operating environment as well as their availability for replacement or repair. Both distillers have a multitude of instruments, valves, controls, gaskets, seals, and like items that contribute to time in the routine preventive maintenance program. The mathematical reliability of either distiller diminishes with the increasing number of these items. Different manufacturers use these items in different quantities depending upon the operating control philosophy. There are some major differences between the ME and VC distillers that should be taken into account when evaluating reliability.

The mechanical compressor is a source of maintenance on the VC process not present on the ME system and the compressor can be a reliability concern if not properly maintained. Evidence is available that indicates with proper preventive maintenance, VC plants do operate very reliably with no unscheduled downtime. Another aspect of a VC distiller that is unique relative to the ME distiller is the evaporator. VC distillers in the biopharm industry employ a single evaporator operating at slightly above atmospheric pressure.

The ME distiller uses multiple evaporators and a separate condenser that are each code stamped vessels operating at a higher temperature and pressure than the VC process. As such, the reliability exposure relative to the number of evaporators and their operating environment is greater on the MEF distiller.

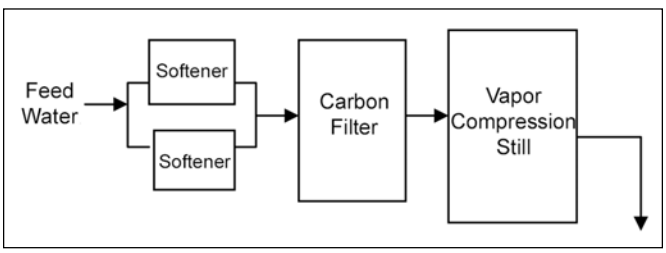

Figure 4. Typical VC pretreatment.

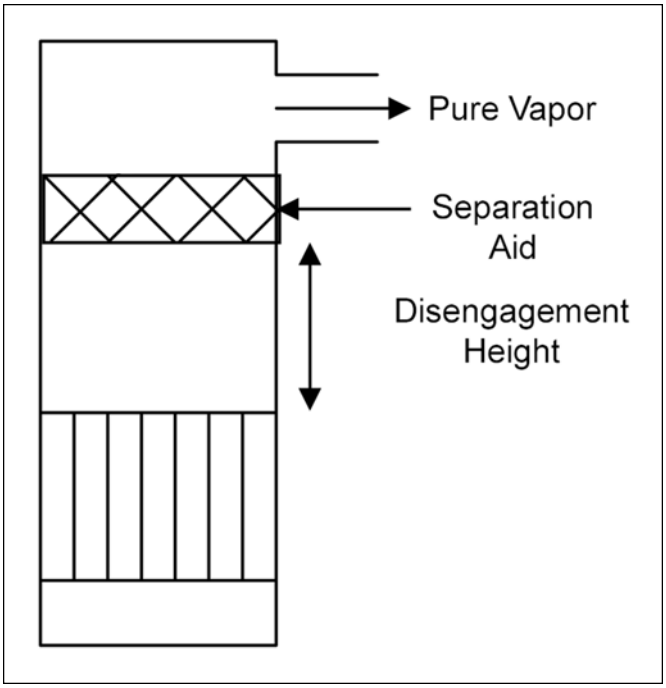

Figure 5. Evaporator fundamentals for achieving water quality.

Both ME and VC distillers are widely used and each has proven to be very reliable. The reliability is directly related to the preventive maintenance and the preventive maintenance effort on both distillers is similar. The maintenance and associated reliability of one distiller versus another is substantially overshadowed by the larger system of pretreatment and distribution upstream and downstream of the distiller. Literature has been previously published that indicates a significantly higher reliability for a still system with simplified pretreatment.[8]

One should evaluate the entire water treatment system and the requirements dictated by a particular system to get a comprehensive view of maintenance and reliability. The water system designs can vary substantially given the type of product water required, the feedwater quality one has to treat, and the type of distiller selected. Often the design options vary so substantially that it is easy to see which offers more reliability and less maintenance.

System Design

System design should start with a determination of the quantity and quality of each type of water to be produced. Where one grade of water quality is to be produced, the design considerations are fairly straight forward for those conversant with the options available. Quite often however, two grades of water quality such as USP purified and WFI are produced. The relative quantities of each may initially guide the designer toward a particular system design concept. Before finalizing a particular design, it is advisable to assess the quality of the raw water feed and determine what feedwater pretreatment processes will be dictated for the design under consideration.

Where large amounts of USP purified water are required and small amounts of WFI are required, it is common to install a RO/EDI system for the production of the USP purified water and a small distiller for the production of the WFI since the quality requirements for each of these grades of water differ - *Figure 6*. The distiller could be either an ME or VC since both will produce equivalent WFI quality water. If the raw water source has high levels of silica or some other constituent such that RO would be required as pretreatment

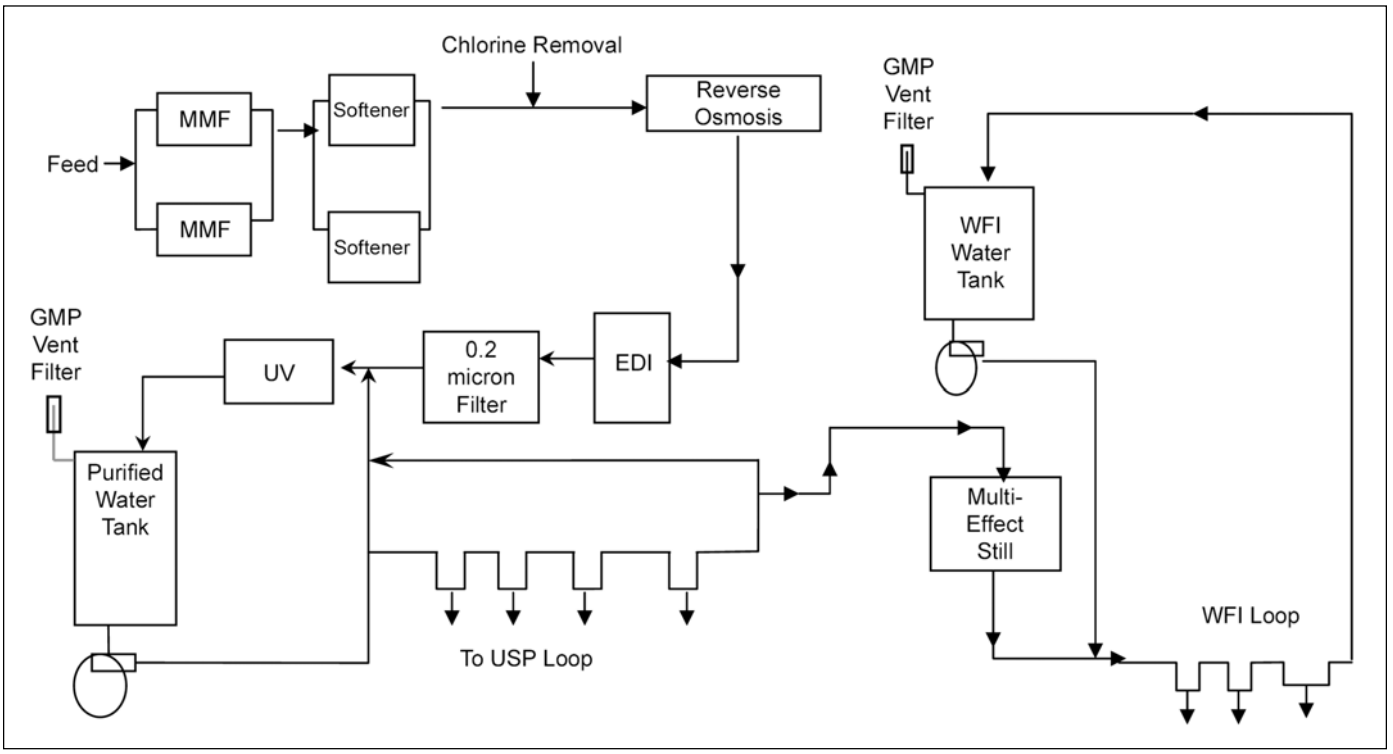

Figure 6. USP purified water system with RO/EDI and ME for the WFI.

to the distiller, it is common to feed the distiller from the USP purified system in place. In this case, and considering a small amount of WFI is required, an ME distiller is often used although the use of VC is not excluded.

As systems grow larger, (more than 200 GPH), the advantages of operating VC may weigh more heavily. Overall utilities are typically reduced unless an ME plant employs a large number of effects. Feedwater for the VC can often be taken from the dechlorinated and softened water supply allowing the size of the RO/EDI system to be reduced.

As the percentage of WFI production increases, it is becoming more common to produce all of the water to the higher grade via the vapor compression. This is especially the case if a simplified dechlorination and softening pretreatment scheme can be used - *Figure 4*. This eliminates the need to produce, store, distribute, maintain, and validate two separate grades of water - *Figure 6*. Note that quite often the RO/EDI systems employed for the production of USP purified water are hot water sanitizable. These systems are more complex, but have the intended benefit of controlled bio-growth within the system. In some cases, the water produced from the RO/EDI systems is reheated for hot storage.

Summary

The most appropriate design of a given water system is not always readily apparent and is sometimes found through an iterative process. It is best to have a complete understanding of all of the processes employed in producing a given quality of water. These processes often "stack up" and feed off of one another as a necessity, but sometimes the necessity is not actually there.

The obvious benefit of distilling all of the water is the higher quality of product. The less obvious, but equally beneficial, feature is that the water can be produced via distillation and distributed either hot or at ambient temperature on demand with the associated benefits to operating efficiency of the VC cycle.

The raw water quality that one has to start with can have a major influence on the type of system employed. If RO is not required as a feedwater pretreatment step, the system may be greatly simplified. An early determination of the different water qualities and quantities to be produced in the future can have a large impact on the final design output. When a significant percentage of the water required is WFI quality, it may be justified to produce all of the water to the WFI standard. This is especially the case where hot water USP systems would otherwise be employed. The choice of process should be evaluated on a case-by-case basis. Relevant factors for consideration typically include the methods of pretreatment given the feedwater quality, the ratios of various water qualities to be produced, capital and operational expenditures, system validation, facility layout, as well as control and maintenance of the system.

References

1. Kern, Donald Q., *Process Heat Transfer,* McGraw-Hill Book Company, New York, 1950, p. 394.

2. Perry, Robert H. and Don Green, *Perry's Chemical Engineering Handbook, Sixth Edition*, McGraw Hill Book Company, New York, 1984, p11-37.

3. Hughes, C.H. and Pottharst, J.E., III, 30 Years in Vapor Compression, 4th International Symposium on Freshwater From the Sea, Vol lI, 1973, p 341-346.

4. Gsell, G.V., Multiple Effect & Vapor Compression Processes Compared, MECO Pharmaceutical Water Training Seminar, Oct. 2000, Section 7.

5. Disi, S. and Owens, Brian, ISPE Baseline® Pharmaceutical Engineering Guide, Final Treatment Options: Water for Injection (WFI) USP Water for Injection Systems Comparison, July, 1997, Vol 4, Chapter 6, p. 73.

6. MECO Reference List, Biopharm Vapor Compression Distillation with Softening Pretreatment, 2003.

7. Spano, J., Service Trip Report VC Installation and Startup, March 2003.

8. Jackman, D.L. and Sneed, L.C., Using Stills for USP Purified Water Production, Ultrapure Water Expo East, April 2-4, 1990.

About the Author

George Gsell has a BS in mechanical engineering from Tulane University and an MS in desalination technology from Glasgow University. He is currently a Principal and President of MECO, an engineering design and manufacturing firm specializing in water purification plants to the biopharm industry. He has been with MECO for 20 years in various positions of engineering and management. He has been directly involved in the turnkey design and construction of numerous biopharmaceutical water systems utilizing a variety of technologies. Gsell has a patent and patent pending on apparatus for producing USP and WFI purified water. He is a member of ISPE and has been a speaker at ISPE seminars. He is also a member of the Louisiana Engineering Society. MECO was recently named "2003 Innovator of the Year" by New Orleans City Business Magazine for their contribution to the field of water purification. He can be contacted by tel: 1-504/599-4137 or email: ggsell@meco.com.

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This article describes the measurement of Carr Indices for a powder flow evaluation that can help predict potential flow problems of new formulations prior to clinical supplies manufacturing.

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Use of Carr Index for Determination of Machinability of Phase I Formulations

by Sunil "Neil" Shah and Mike Killeen

Introduction

A number of pharmaceutical companies have initiated efforts to shorten the product development cycle. The goal of this effort is to reach the first dose in human in 12 months or less after declaration of a lead compound. This goal reduces development activities in the formulation group and subsequently poses a number of challenges during clinical supplies manufacturing. Additionally, the requirements for Phase I clinical supplies have drastically increased from a couple of thousand units to 10,000 units or more. The reason for such an increase is to quickly initiate Phase II studies if the compound is well tolerated in single and multiple dose tolerance studies. Formulation development studies are often done in small-scale equipment due to limited drug supply and shortened timelines. Selected formulations are not evaluated using automated machines and usually processes are not optimized. Recently, a number of capsule formulations developed internally using a semi-automatic capsule machine posed flow-problems during clinical supplies manufacturing using a single dosator automatic capsule-filling machine. These flow-problems caused unexpected clinical supplies manufacturing difficulties from substantial fill weight variations to variable capsule plug hardness. While the weight variations led to poor content uniformity, the hardness variation resulted in dissolution issues. In addition, these difficulties were time consuming, required frequent machine adjustments, resulted in poor product quality and low yield, and in some cases delayed very expensive clinical trials.

The flow of a powder is an important parameter that greatly influences a solid's integration into a tablet or capsule formulation. It greatly affects the manufacturing performance because good powder flow is critical for capsule and tablet operations to ensure mixing and acceptable weight uniformity. R.L. Carr[1,2] based on his extensive work with 2,800 dry materials, identified particle shape, size, porosity, cohesion, surface area, bulk density, and fluidity as the properties affecting the flow. The flowability is the movement of the powder from static to dynamic state. The floodability, on the other hand, is the intrinsic ability of the powder to discharge from a hopper. Based on his work, Carr defined the flow index

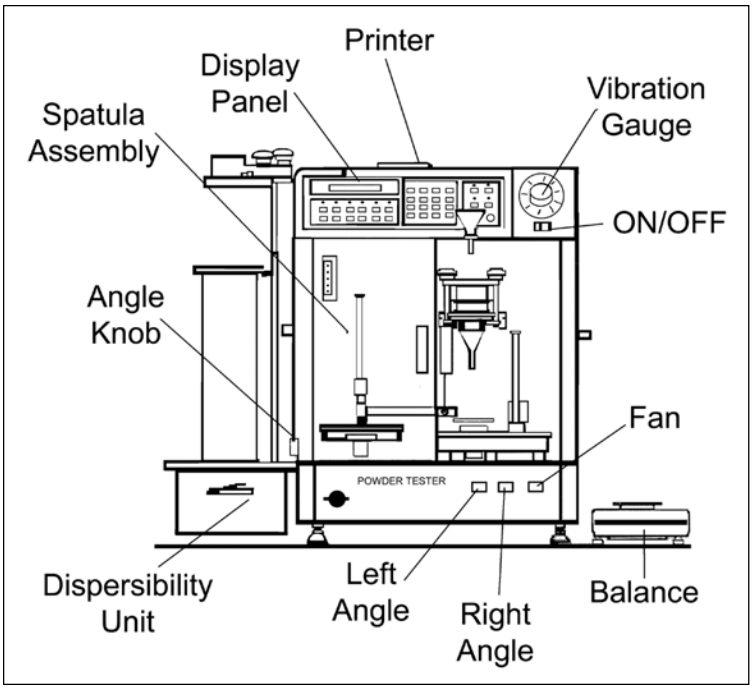


Figure 1. Schematic diagram of powder tester.

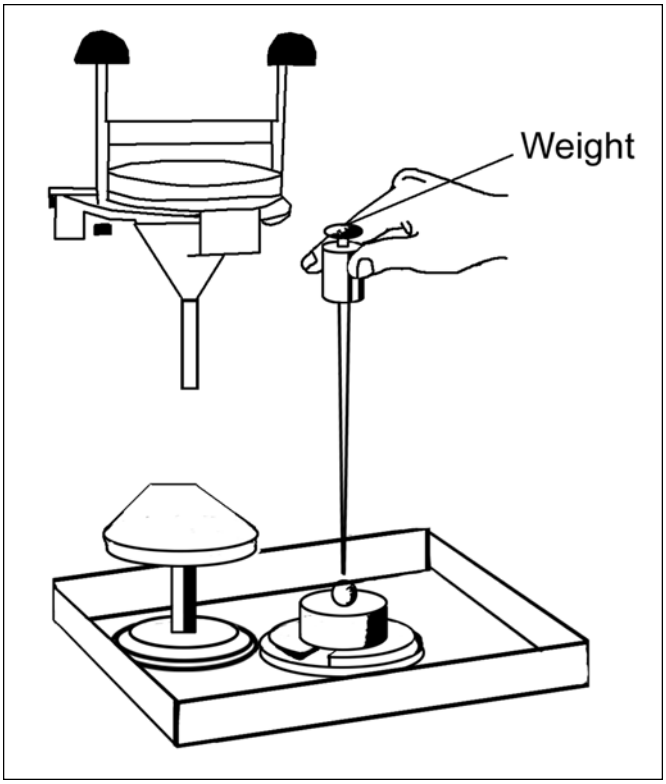


Figure 2. Schematic diagram for angle of fall measurement.

that is characterized by angle of repose, compressibility, angle of spatula, and cohesion. The flood index is characterized by flow index, angle of fall, angle of difference, and dispersibility. The flowable powders exhibit consistent and steady flow through a small orifice while floodable powders exhibit discontinuous, gushing, and uncontrolled flow. Carr developed a method for evaluating flowability with the establishment of a powder characteristic tester. This multi-purpose unit provides nine mechanical measurements that characterize the flowability and floodability behavior of powders with applications in both chemical and pharmaceutical engineering. The objective of this work was to evaluate the use of the powder tester in clinical manufacturing and possibly use information to predict/identify potential flow problems for new formulations. The flowability of seven commonly used excipients and four formulated products was tested to assess powder flow properties.

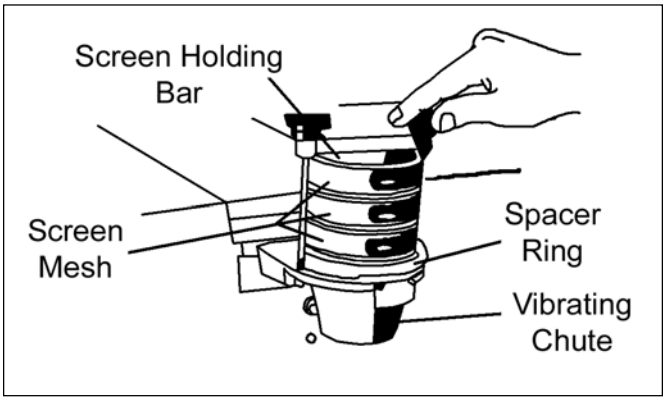


Figure 3. Schematic diagram for cohesion measurement.

Materials

Seven commonly used excipients—lactose, talc, magnesium stearate, cornstarch, and three grades of microcrystalline cellulose—were obtained for flowability and floodability testing. Lactose monohydrate fast-flow NF, corn starch NF, Magnesium stearate NF, and talc USP were used in this study. Formulations A, B, and C were prepared using a wet granulation method and Formulation D was prepared using a dry blend method.

Methods

The schematic diagram of the powder tester is shown in Figure 1. Each test was selected by pushing the desired measurement on the display panel of the powder tester.

Angle of Repose

The angle of repose was measured by allowing powder to fall through a mesh screen and a glass funnel for 180 seconds onto a horizontal platform. Vibration was adjusted by rotating the vibration dial in a clockwise direction to facilitate flow through the funnel. Angle of repose is the angle between the horizontal platform and a heap of powder dropped from a constant elevation.

Angle of Fall

The angle of fall was measured after a small steel weight was dropped from a constant height three times as shown in Figure 2. It is a smaller angle formed after shocking the powder after the angle of repose measurement.

Angle of Difference

The angle of difference was calculated by subtracting the angle of fall from the angle of repose.

Aerated Density and Packed Density

The aerated density was measured by allowing powder to fill an empty bulk density cup. The difference in weight before and after the cup is filled gave the aerated (loose) bulk density. The powder tester has an automatic tapping device that counted 180 taps for each sample of powder. A cup extension piece is placed over the previously filled cup and

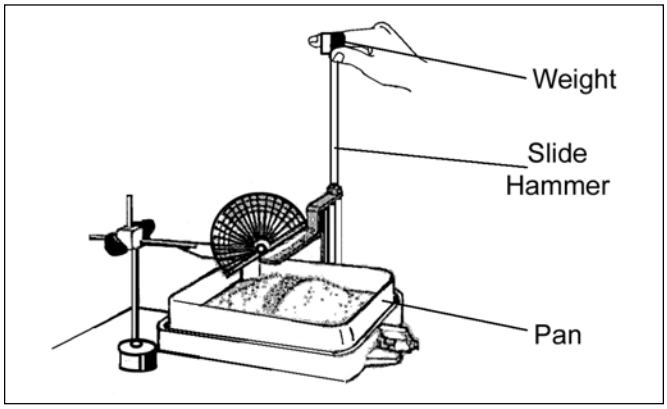


Figure 4. Schematic diagram for angle of spatula measurement.

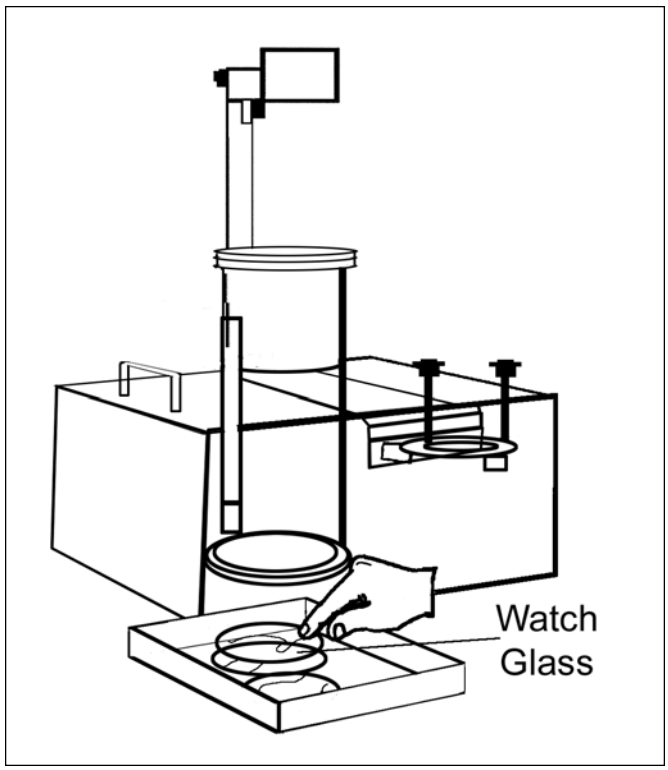


Figure 5. Schematic diagram for dispersibility measurement.

after completion of 180 taps; the cup was leveled to a flat surface and weighed. The difference in weight before and after tapping was the packed density.

Compressibility

The compressibility was calculated by taking the difference between the aerated and packed densities, dividing by the packed density, and multiplying by 100 to obtain a percentage.

Cohesion

The cohesion calculated the amount of powder that retains on three individual mesh screens, after a 2 gm sample is placed on the top screen as shown in Figure 3. To facilitate the powder to disperse through the top (coarse), center, and bottom (finer) screens; vibration was applied. The vibration gauge was rotated in a clockwise direction until amplitude of 1 m/m was reached. Based on previous density results, the tester obtained a specific time (approximately 90 seconds) for each sample to disperse through the three layers of screens.

Angle of Spatula

The angle of spatula was measured by inserting a blade into a pan of powder and then lifting the blade up above loaded with powder as shown in Figure 4. The left angle switch was used to measure the angle obtained. A stainless steel weight from a constant height was raised and allowed to drop once. The smaller angle was measured. The average of the two angles is the angle of spatula.

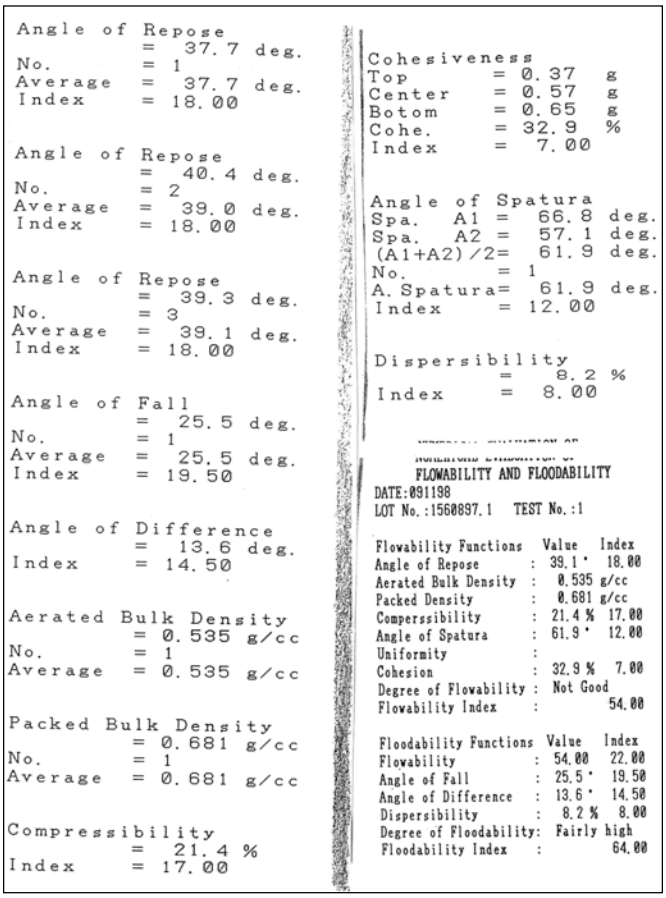
Dispersibility

The dispersibility was measured by allowing a 10 g sample of powder to disperse through a 4" cylinder and displace onto a 4" watch glass as shown in Figure 5. The amount of powder retained on the watch glass influenced how floodable a powder was.

Nine tests were performed on each sample in triplicate, and a mean value was recorded. Environmental factors were constant for all powders that gave each sample equal opportunity to be influenced by moisture and humidity conditions. Each measurement value has a corresponding index score that depicts a powder's flow and flood behavior. A sample printout from the tester is shown in Figure 6.

Results and Discussion

The results of the experimentation of the seven excipients are summarized in Tables A and B. For each parameter, mean and Standard Deviation (SD) of triplicate measurements are listed. Using the mean value, a corresponding index value was obtained from the printouts (see Figure 6 for a sample printout). The index value also can be obtained from tables in the Operating Instructions manual.[3] The index value for each parameter also is listed in Tables A and B. The sum of the indices for repose angle, spatula angle, cohesion, and compressibility equals to the flow index. Dispersibility, angle of fall, angle of difference, and flow indices values are added to obtain the flood index. Each measurement has a maximum



```
Angle of Repose
          =  37.7 deg.
No.       =  1
Average   =  37.7 deg.
Index     =  18.00

Angle of Repose
          =  40.4 deg.
No.       =  2
Average   =  39.0 deg.
Index     =  18.00

Angle of Repose
          =  39.3 deg.
No.       =  3
Average   =  39.1 deg.
Index     =  18.00

Angle of Fall
          =  25.5 deg.
No.       =  1
Average   =  25.5 deg.
Index     =  19.50

Angle of Difference
          =  13.6 deg.
Index     =  14.50

Aerated Bulk Density
          =  0.535 g/cc
No.       =  1
Average   =  0.535 g/cc

Packed Bulk Density
          =  0.681 g/cc
No.       =  1
Average   =  0.681 g/cc

Compressibility
          =  21.4 %
Index     =  17.00
```

```
Cohesiveness
Top       =  0.37   g
Center    =  0.57   g
Botom     =  0.65   g
Cohe.     =  32.9   %
Index     =  7.00

Angle of Spatura
Spa.  A1  =  66.8 deg.
Spa.  A2  =  57.1 deg.
(A1+A2)/2=  61.9 deg.
No.       =  1
A.Spatura=  61.9 deg.
Index     =  12.00

Dispersibility
          =  8.2 %
Index     =  8.00

FLOWABILITY AND FLOODABILITY
DATE:091198
LOT No.:1560897.1   TEST No.:1

Flowability Functions  Value    Index
Angle of Repose     :  39.1°    18.00
Aerated Bulk Density :  0.535 g/cc
Packed Density      :  0.681 g/cc
Compersibility      :  21.4 %   17.00
Angle of Spatura    :  61.9°    12.00
Uniformity          :
Cohesion            :  32.9 %   7.00
Degree of Flowability : Not Good
Flowability Index   :           54.00

Floodability Functions  Value   Index
Flowability         :  54.00    22.00
Angle of Fall       :  25.5°    19.50
Angle of Difference :  13.6°    14.50
Dispersibility      :  8.2 %    8.00
Degree of Floodability: Fairly high
Floodability Index  :           64.00
```

Figure 6. A sample printout from the powder tester.

Excipient	Angle of Repose		Compressibility		Angle of Spatula		Cohesion		Flow Index
	Degrees*	Index	Percent*	Index	Degrees*	Index	Percent*	Index	
Lactose	28.9° ± 2.36	24	17% ± 1.83	18	34.8° ± 2.48	21	5.7% ± 0.64	15	78
PH-101**	45.6° ± 1.56	14.5	31% ± 0.70	10	63.5° ± 2.57	12	0.2% ± 0.76	15	51.5
PH-102**	41.9° ± 0.50	16	22% ± 0.21	14	57.8° ± 1.96	16	8.5% ± 0.46	14.5	60.5
PH-200**	36.5° ± 2.00	18	17% ± 0.90	18	45.7° ± 0.15	17	17.7% ± 2.55	12	65
Corn Starch	54.9° ± 0.20	10	38% ± 1.55	5	74.8° ± 1.30	10	17.8% ± 2.89	12	37
Talc	57.4° ± 0.85	7	43% ± 1.53	2	63.3° ± 0.80	12	25.3% ± 3.32	12	33
Mg Stearate	49.3° ± 0.50	12	51% ± 1.04	0	61.7° ± 1.00	12	9.0% ± 1.60	14.5	38.5

**Microcrystalline cellulose
*Mean and SD (Standard Deviation) of triplicate measurements

Table A. Flowability of excipients.

Excipient	Flow	Angle of Fall		Angle of Difference		Dispersibility		Flood Index
	Carr Index	Degrees*	Index	Degrees*	Index	Percent*	Index	
Lactose	25	21.0° ± 1.21	22	7.9° ± 0.46	8	16.8% ± 1.63	12	67
PH-101**	21	43.1° ± 1.25	12	2.5° ± 0.62	3	23.6% ± 2.75	16	52
PH-102**	25	34.7° ± 1.67	16	7.2° ± 0.51	6	9.5% ± 1.48	10	57
PH-200**	25	31.2° ± 0.85	17	5.3° ± 0.49	3	23.6% ± 0.82	16	61
Corn Starch	12	52.1° ± 0.30	16	2.8° ± 0.10	3	57.3% ± 0.72	25	56
Talc	10	53.8° ± 1.30	16	3.6° ± 0.43	3	40.0% ± 0.64	21	50
Mg Stearate	15	47.3° ± 0.45	12	2.0° ± 0.06	3	55.8% ± 4.62	25	55

**Microcrystalline cellulose
*Mean and SD of triplicate measurements

Table B. Floodability of excipients.

index value of 25. For a majority of the tests, as the value of the property increases, the index score decreases, eventually reaching zero for the poorest material. For example, as the angle of repose enlarges the repose index subsequently declines.

Lactose

Lactose monohydrate NF is a white free-flowing powder consisting mainly of spherical aggregates of microcrystals. Due to the spherical nature of these aggregates, fast-flow lactose is highly fluid, nonhygroscopic, and very compressible.[4] According to the results, the angle of repose is 28.9° that confirms that it is a free-flowing powder. When a powder compresses, the gas voids between particles are reduced and the powder tends to become a solid mass. A powder or granulation with more void spaces will have a greater chance of flowing freely than a densely packed, low porosity powder.[1,2] Powders with compressibility percentages greater than 20% are not free- flowing because they have a tendency to create bridges in the hopper. Lactose monohydrate is 17.0% compressible with an index equal to 18, which suggests that it does have good compressibility. The cohesion index of 15 indicates that it has a normal tendency to agglomerate. The angle of internal friction measured by the angle of spatula also gives lactose an index of 21 that supports its very good flowability behavior.

The dispersibility of lactose is 16.8%. Dispersibility is a measure of how a material flushes or falls from a hopper, and too large or too small a value interrupts a powder's flow. A low dispersibility value can offer suggestions for eliminating bridge formation to ensure a smooth discharge from a hopper. On the contrary, a high dispersiblity index powder should follow special precautions to minimize the flushing phenomenon.

Talc, Magnesium Stearate, Corn Starch

Talc (400) or hydrous magnesium silicate is a white crystalline precipitate of magnesium ammonium phosphate. Due to its fine particle size, this powder exhibits poor flow that is demonstrated by a large angle of repose of 57.4°. It can be assumed those finer particles (< 100 mesh or < 150 µm) create mixing problems because surface areas are very great and lead to strong electrostatic force.[1,2] The average bulk density of talc is 0.406 g/cm^3 and it has a high compressibility value of 43.2%. This high compressibility percent is an indication that talc is more likely to build up in a hopper or storage bin than a powder with a lower compressibility percent, such as Avicel. Talc has a greater tendency to form fine particle agglomeration than any of the other excipients, and therefore has the highest value of cohesion, 25.3%. These parameters support the notion that talc is highly slippery and hygroscopic.[4] This helps distinguish it from lactose or Avicel PH-200, two free-flowing powders.

A commonly used glidant to help improve flow, talc decreases interparticulate friction.[4] With a compressibility index of only 2, talc is a highly cohesive fluid powder. Its high dispersibility of 40.0% (index of 21) and large angle of spatula of 63.3° (index of 12) also support the fact that talc is not a free-flowing powder.

"Compressibility is an important parameter that helps distinguish degrees of good powder flow. According to the Carr index, a higher value of compressibility usually indicates lower flowability indices, representing better flowing powders."

Magnesium stearate and cornstarch are two commonly used excipients that demonstrate poor flow and very high floodability values. Their angle of repose values clearly represent rough particle surfaces because a large angle indicates high frictional force in loose powders. The angle of repose measurement for magnesium stearate is 49.3° and 54.9° for cornstarch. Both excipients also demonstrate high compressibility values, magnesium stearate at 51 and cornstarch at 38, giving them a high risk for developing bridges. Angle of spatula measurements confirm that both have poor flow because they both exhibit large angles of internal friction; magnesium stearate presents an angle of 61.7° and corn starch holds a value of 74.8°, the highest value of all seven excipients. Both also demonstrate the maximum possible value for dispersibility, indices of 25.

Cornstarch is commonly used as a binder and diluent. Moisture, electrostatic charges, particle size and shape and chemical nature (i.e., presence of unsaturated valencies, ionic or hydrogen bonds on surface) are the main causes of holding a powder together. Therefore, from our results it is apparent that talc and cornstarch have strong forces that promote agglomeration and consequently inhibit flow.

Microcrystalline Cellulose

Microcrystalline Cellulose (MCC), a commonly used direct compression tableting agent, was evaluated using three Avicel grades: PH-101, PH-102, and PH-200. MCC PH-101, the original product, shows a distinct difference in flow from PH-200, which is composed of larger particle size ball- like agglomerates. During handling, static charge was observed in all three grades, yet PH-101 and 102 had more apparent static attraction than PH-200. This force of friction on the protective coat of a surface particle explains why PH-101 and 102 have poor flow.[5]

The testing indicated a downward decline in flow capability among three grades of MCC from PH-200 to PH-101. Each performed measurement that characterizes flowability (repose angle, compressibility, spatula angle, and cohesion) shows a distinct trend in values. For example, PH-200 has the highest repose index of 18 (36.5°), followed by PH-102's index of 16 (41.9°), and then PH-101's low repose index of 14.5 (45.6°). This regression supports the theory that as particle size increases, flow potential also enhances.

Microcrystalline cellulose's strong hydrogen bonds and low bulk density help characterize its high compressibility value.[1,2] There is a comparative trend in the compressibility percentages of MCC: PH-101 is 31%, PH-102 is 22.0%, and PH-200 is 17% compressible with indices of 10, 14, and 18, respectively. The downward decline of compressibility can be accounted for because of the broad particle size range of the three grades of Avicel. A common generalization is that as particle size increases, angle of repose decreases and powder flow improves. Avicel supports this, and the values for Carr's flow index and particle size (micron) are: 51.5 and 50 for grade 101; 60.5 and 100 for grade 102; and 65 and 200 for grade 200. Thus Avicel grade 200 demonstrates better flow properties than grades 101 and 102, and this can be substantiated by its higher particle size.

Product	Angle of Repose		Compressibility		Angle of Spatula		Cohesion		Flow Index
	Degrees*	Index	Percent*	Index	Degrees*	Index	Percent*	Index	
Formulation A	47.0° ± 0.75	12	16.9% ± 0.46	18	45.3° ± 2.60	17.5	32% ± 5.92	7	54.5
Formulation B	48.9° ± 1.81	12	48.9% ± 0.56	0	71.6° ± 1.00	12	49% ± 2.85	7	31
Formulation C	33.5° ± 3.55	21	2.8% ± 0.49	25	27.8° ± 1.35	24	59% ± 3.82	2	72
Formulation D	52.4° ± 1.10	12	49.0% ± 0.95	0	64.1° ± 0.80	12	41% ± 2.96	7	31
*Mean and SD of triplicate measurements									

Table C. Flow data of formulated products powder blends/granulations.

Product	Flow	Angle of Fall		Angle Difference		Dispersibility		Flood Index
	Carr Index	Degrees*	Index	Degrees*	Index	Percent*	Index	
Formulation A	16	46.5° ± 0.25	12	2.4° ± 0.58	3	23.9% ± 1.27	16	47
Formulation B	22.5	46.5° ± 2.14	12	0.5° ± 1.32	3	7.8% ± 2.07	8	45.5
Formulation C	25	33.1° ± 3.82	16	0.4° ± 0.36	3	6.7% ± 0.21	6	50.3
Formulation D	16	40.3° ± 4.42	15	12.1° ± 3.59	12	34.3% ± 1.4	19.5	62.5
*Mean and SD of triplicate measurements								

Table D. Flood data of formulated products powder blends/granulations.

Excipient	Pt.Size (microns)	Aerated Density* (g/cm^3)	Packed Density* (g/cm^3)	Compressibility* Percent	Cohesion* Percent
Lactose	100	0.555 ± 0.00	0.669 ± 0.00	17.0% ± 1.83	5.7% ± 0.64
Talc	10	0.294 ± 0.00	0.518 ± 0.01	43.2% ± 1.53	24.5% ± 3.32
Mg Stearate	5	0.099 ± 0.00	0.203 ± 0.00	51.2% ± 1.04	7.4% ± 1.60
PH-101**	50	0.313 ± 0.00	0.451 ± 0.01	31.0% ± 0.70	0.2% ± 0.76
PH-102**	100	0.353 ± 0.00	0.453 ± 0.00	22.0% ± 0.21	8.5% ± 0.46
PH-200**	200	0.364 ± 0.00	0.437 ± 0.00	17.0% ± 0.90	17.7% ± 2.55
Corn Starch	5	0.519 ± 0.01	0.829 ± 0.00	37.3% ± 1.55	17.8% ± 2.89
*Mean and SD of triplicate measurements					

Table E. Particle size, density, compressibility, and cohesion values of excipients.

Formulated Products Powder Blends/ Granulations

Good powder flow results in capsules and tablets with consistent weight. For tablets, consistent weight can provide consistent hardness and dissolution. The powder properties of Formulations A - D powder blends and granulations were tested on the powder tester to determine which formulated product has the best flow. Results are summarized below in Tables C and D.

From the results depicted in Tables C and D, it is apparent that Formulation C with a flow index of 72.0 has the best flowability among the four products. A small angle of repose of 33.5° and a low compressibility value of 2.8% both result in high indices of 21 and 25. The Formulation C is made up of active, magnesium stearate NF, flavor, Confectioner's Sugar, and talc. In contrast, Formulation D powder blend exhibits poorer flow with a total index of only 31. The Formulation D is composed of: active, Confectioner's Sugar USP, Lactose NF, Talc USP, and Magnesium stearate NF. Its cohesion value of 41%, 64.1° angle of spatula, and compressibility of 49% also demonstrate non-free-flowing characteristics. Both formulations have two distinct manufacturing processes. Formulation C is prepared by a wet granulation method. Formulation D capsule powder blend, on the other hand, is prepared by a dry mixing method. The flow indices show a wide difference in flow potential as represented in Table C.

Formulation A's angle of repose (47.0°) and small compressibility (16.9%) suggest it has normal flow. In contrast, Formulation B has a compressibility value of 48.9% and compressibility index of 0.0, demonstrating poor flow. It may, therefore, create bridges in the hopper. Formulation A contains three actives, microcrystalline cellulose NF, cornstarch NF, carboxymethyl starch, hydroxypropyl cellulose NF, zinc stearate as well as some other additives. Formulation B, similar to Formulation D, also has a higher angle of spatula (75.7°), which suggests a high value of internal friction, preventing good flow. Both products have different formulas, which may influence each flow index. Formulation B granulation is composed of active, magnesium trisilicate, Aspartamine, magnesium stearate NF as well as some other additives.

Compressibility is an important parameter that helps distinguish degrees of good powder flow. According to the Carr index, a higher value of compressibility usually indicates lower flowability indices, representing better flowing powders. Formulation C only is 2.0% compressible with an index of 25, in comparison to Formulation B and Formulation D which both have indices of 0.0. This data suggests that the latter two products have larger differences in their aerated and packed densities and therefore larger compressibility percentages and poorer flow. Large differences in densities can lead to powder segregation, larger compressibility values, and lower indices. For example, magnesium stearate has the highest compressibility percent, 51.2%, with its aerated and packed densities being 0.099 and 0.203g/cm^3, respectively. This large difference in densities will hinder its flow.

Usually, generalizations should not be made as to what property correlates with what other property. Carr's flow and flood indices are based on nine parameters that collectively characterize a powder's flow potential. It is likely though, that higher bulk density powders such as lactose and Avicel PH-200 flow well because they tend to stay as separate units of matter. Low particle size, and low aerated and packed densities powders, such as talc and magnesium stearate, usually have a smaller particle size and some surface moisture, which inhibit good flow. Particle size, aerated and tapped densities, compressibility, and cohesion values of all seven excipients are shown in Table E.

There is an inverse relationship between a dischargeable diameter and the flowability index. When a powder is released from the hopper, a higher numerical evaluation of its flowability index can suggest that a smaller critical discharge diameter be used. This can prevent bridging or the stoppage of flow as a result of particles which have formed a rigid structure within the powder bulk. Therefore, prior knowledge of a powder's good flow properties and indices can serve as a useful guide for planning the assembly process.

Conclusions

At the early stages of development, each lot of active drug, excipient, and formulated blend should be characterized for physical properties as completely as possible. Powder flow must be included in this evaluation. Although this may be a difficult task, these nine parameters give a collective decision and a reliable indication of a powder's potential to flow and flood. Carr's indices give a numerical reference to these nine parameters that should guide the development of a solid formulation.

Flowability of a powder has very important consequences that could facilitate or hinder the performance of manufacturing a solid dosage form. Many drugs require several excipients for filling, binding or disintegrant processes, and prior knowledge of a powder's flowability and floodability index can be very beneficial. A smooth downward flow minimizes air pocket formation. Powders with a higher Carr's flow index will have minimal fine powders that limit surface contact, which can ease the lubrication process. Flowable powders also are characteristic of even tablet hardness; therefore, good flow can ensure a low variation in average weight coefficient. Flow information can give a formulator insight and direction in choosing a formulation method, excipient selection and auxiliary equipment (e.g., auger feeder, force feeder) requirement. Meaningful data can sort out causes of unexpected formulation or manufacturing difficulties.

Based on this study, Phase I formulations with the Carr flow index value of <60 will have poor machinability. Reformulation or use of auxiliary mechanisms, e.g., auger feeder, force feeder, will be required to facilitate the flow and improve machinability.

References

1. Carr, Ralph, "Classifying Flow Properties of Solids," *Chemical Engineering,* January 1965, pp. 21-27.

2. Carr, Ralph, "Classifying Flow Properties of Solids," *Chemical Engineering,* February 1965, pp. 7-10.

3. "Powder Characteristics Tester - Operating Instructions," Hosokawa Micron Division, Summit, NJ.

4. Handbook of Pharmaceutical Excipients, Second Edition. Edited by Ainley Wade and Paul J. Weller. American Pharmaceutical Association. Washington, 1994.

5. Doelker, E., Massuelle, D., Veuillez, F., and Humbert-Droz, P., "Morphological, Packing, Flow and Tabletting Properties of New Avicel Types," *Drug Development and Industrial Pharmacy,* 21 (6), 1995, pp. 643-661.

6. "Hosokawa Micron Powder Characteristics Tester," Hosokawa Micron Division, Summit, NJ.

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Fabrication and Study of Simple and Robust Microfluidic Devices

by Ryan Hill, Jeffrey Millman, and Orlin D. Velev

Microfluidic devices on a chip promise to revolutionize many areas of analytical chemicstry, chemical engineering, pharmaceuticals, and biotechnology.

This article was the winning undergraduate poster in the Student Poster of the Year Contest held at the 2002 ISPE Annual Meeting in Orlando.

Background

The microscale synthesis, processing, and analysis of chemical and biological samples require manipulation of microscopic volumes of liquids, which can be done with chips with microchannels and microreactors. Lab-on-a-Chip devices promise significant benefit to bioarrays, parallel drug synthesis, and drug delivery.[1] They could revolutionize drug analysis and synthesis in the same way that integrated chips have revolutionized the electronics industry.[2] Microsystems, in the guise of microarray-based systems, have already revolutionized genomics.[3] For pharmaceutical and healthcare companies, microchemical systems have already had a large impact on combinatorial synthesis, small molecule screening, and systems for nucleic acid synthesis and detection.[4] The worldwide market for these systems is expected to be about $1 billion early in the next century.[2] A number of companies are now pursuing the commercialization of microfluidic devices.[1]

Microfluidic systems have very diverse chemical and pharmaceutical applications. There are five main areas of current research activity in microfluidics: analytical systems for DNA sequencing, high-throughput drug screening systems, analytical systems used for detection of biological and chemical weapons, devices for point-of-care clinical analyses, and microreactor systems that permit large-scale toxic compound synthesis.[2] High temperature, catalytic, enzyme/substrate, and light induced reactions also can be carried out at a small scale. In addition to chemical and biological analysis, microfabricated systems are expected to have significant advantages in chemical synthesis, kinetics studies, and process development.[4]

With large numbers of experiments becoming the trend in biotechnology, the equipment used for analysis will naturally become smaller.[1] The most obvious advantage of decreasing the equipment size is the smaller space needed for laboratory equipment. Many functions can be carried out on a small benchtop. Microfluidic chips have excellent temperature distribution control. High heat and mass transfer rates are possible in the small dimensions of microfluidic systems. Therefore, higher yields can be achieved compared to conventional reactors.[4] Also, new reaction pathways could be pursued that are too difficult in conventional microscopic equipment.[4]

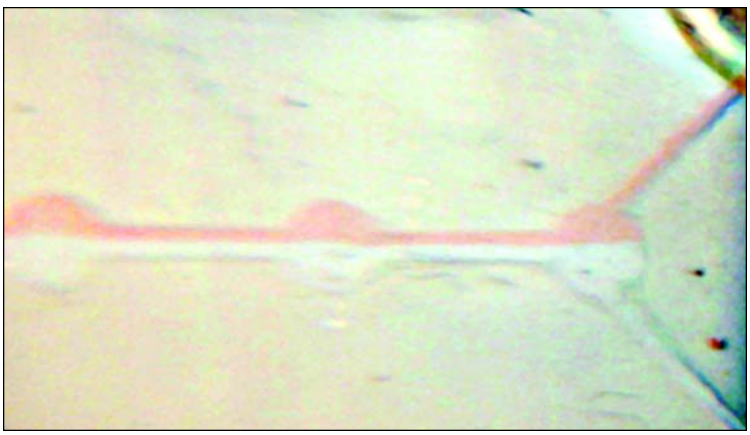

Figure 1. Experimental image of laminar flow in a microchannel with minimal mixing between the two adjacent liquids.

The reduced process volumes needed in microfluidic systems also have considerable advantages in terms of cost and safety. Experimentation at the conventional laboratory scale is limited by high costs of reagents and safety concerns. The small volumes of microreactors could effectively eliminate such problems.[4] These microfluidic systems also have low manufacturing,

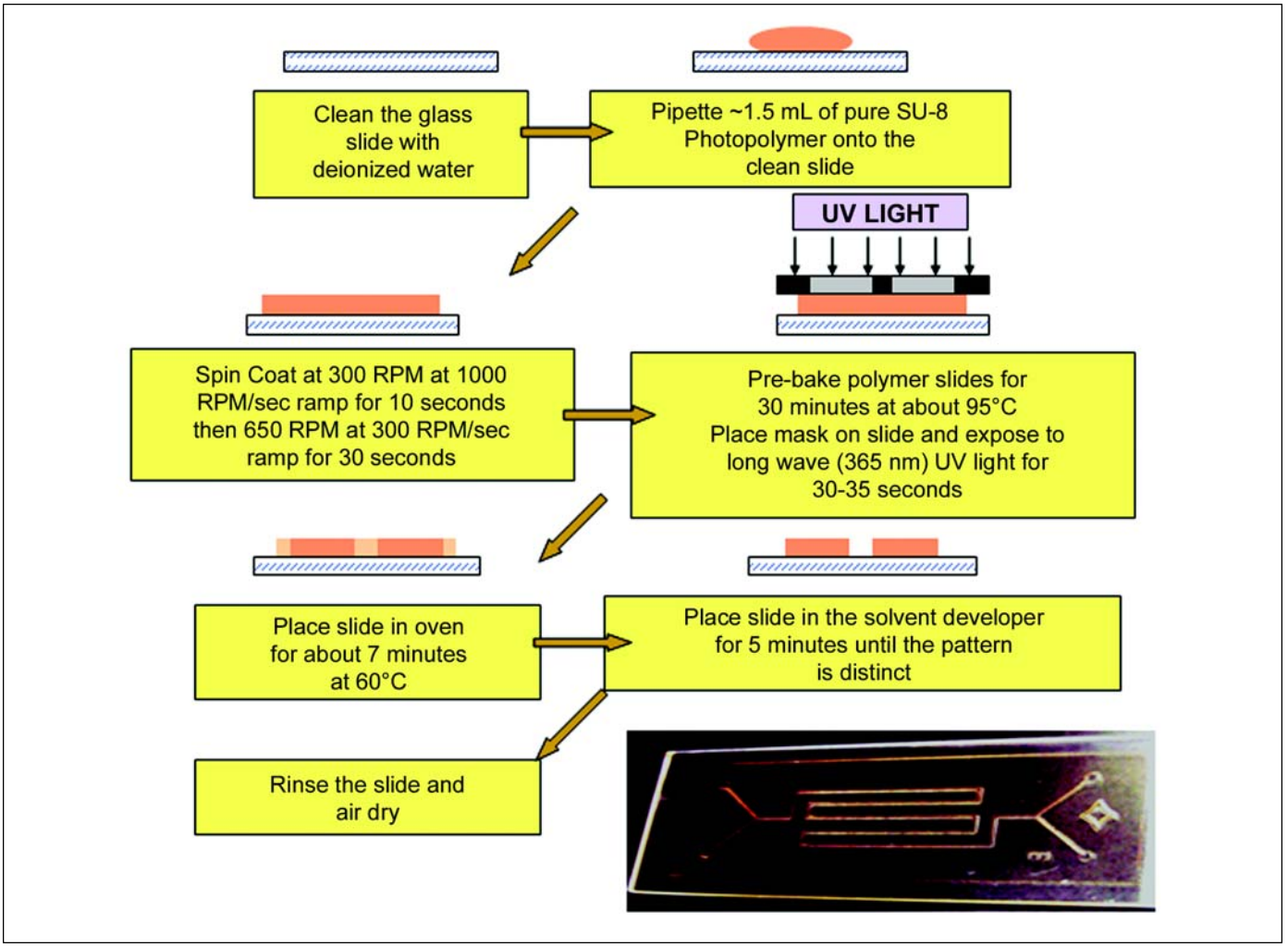

Figure 2. Schematics of the microchannel fabrication process.

operating, and maintenance costs along with low power consumption.[2] Smaller process volumes are also much safer when dealing with toxic, hazardous, or highly reactive chemicals. If a microreactor fails, the small quantity of chemicals released could be easily contained.[4] Other advantages include automation, reduced waste streams, increased precision and accuracy, and disposability.[2]

Research Objectives

This microfluidics research project had the following three main objectives:

- to develop simple and robust hands-on technology for laboratory fabrication of microfluidic devices
- to observe and characterize fluid flow within microfluidic channels
- to introduce the results in undergraduate student education and help prepare specialists in this emerging technology

In order to advance the research and development of lab-on-a-chip technologies, colleges and universities must strive to develop innovative ways to prepare upcoming specialists in microfluidics. Hands-on learning is a very effective tool for teaching students about new technology. Students will be able to observe and characterize the fabricated microfluidic device and see the immediate results of their work.

The most widely used technology for industrial fabrication of microfluidic devices is photolithography. This is a complex and costly process that can not be easily implemented in a student laboratory. This project focuses on producing microfluidic devices simply and inexpensively. With an effective method, the students can quickly and easily design and fabricate a microfluidic device. Once the device is made, the student can then conduct an analysis of fluid flow on the microscale and observe the effects of the design. This project is intended to accelerate research in this area by shortening the time between the idea and the experimental device.[2] It also can be used in the development of new and inexpensive techniques for the production of commercial prototypes. As microfluidic devices begin to become commercialized, there is no standard for simple microfluidic components such as pumps, valves, and mixers. Therefore, it is important to focus on simple fabrication methods for rapid prototyping that reduce cost and delays.[1]

Once the device is made, experiments can be done to characterize the parameters of the fluid flow inside small channels. Fluid flow characterization is basic in understanding microfluidic technology. Mixing is another fundamental process step in many biological and chemical lab-on-a-chip processes.

Flow in Microfluidic Channels

Scaling down from a macroscopic pipe to a microscopic channel can ensure significant changes in fluid flow and processes. The type of flow present can be calculated using the dimensionless Reynolds number (Re). The Reynolds number can be written as the ratio of the kinetic energy of a volume of liquid to the energy dissipated by that volume in the shear caused by interactions with its solid boundaries.[1]

$$Re = \frac{\rho V D}{\mu}$$

Re = Reynolds number
ρ = density (1 g/mL, 62.43 lb_m/ft^3 for water)
V = average liquid velocity (mm/s, in/s)
D = channel diameter (mm, in)
μ = liquid viscosity (993×10^{-6} Ns/m^2 at 20°C, 7.6×10^{-4} lb_m/ft sec for water)

If Re < 2100 the flow in the microchannels will be laminar
If 2100 < Re < 2300 the flow is in the transition region
If Re > 2300 the flow will be in turbulent region

Microfluidic devices are small enough so that flows inside them behave differently than the large-scale flows that are familiar to most industrial engineers.[1] Fluids flowing in channels with dimensions on the order of 50µm and at readily achievable flow speeds are characterized by a low Reynolds number.[1] Laminar flow of around 1 or lower is commonly encountered in microfluidic channels.[1] Laminar flow has a parabolic velocity profile whereas turbulent flow has a more flat profile except for at the walls. It is characterized by parallel streamlines and no radial turbulence (see our experimental image shown in Figure 1).

Fluid pumping in microfluidic systems is accomplished using either pressure, or for water and other ionic solvents, by electroosmotic flows driven by electric fields.[1] Electroosmosis is a macroscopic phenomenon that results from an electrical double layer formed by ions in the fluid and by surface electrical charges immobilized on the capillary walls. When an electric field is applied, the bulk solution moves toward one of the electrodes of the device.[2]

Microfluidic Channel Fabrication

Several methods exist for microfluidic channel fabrication. Presently, the typical microchip is made from silicon, glass, quartz, or plastic that has etched or molded chambers and channels.[2] It is then sealed with a plate to contain samples and reagents.[2] Microfabrication of glass lab-on-a-chip systems already forms the foundation for many devices for biological research.[4] However, polymer-based chips offer the potential of being mass produced inexpensively.[2] Commercial manufacturers of microfluidic devices see many benefits in employing polymers that include reduced cost and simplified manufacturing procedures, particularly when compared to glass and silicon.[5] Channels in the polymer chips can be fabricated by using techniques such as hot embossing, injection molding, and laser ablation.[2] Though these techniques are rapidly expanding, they require expensive equipment and can be complicated.[4]

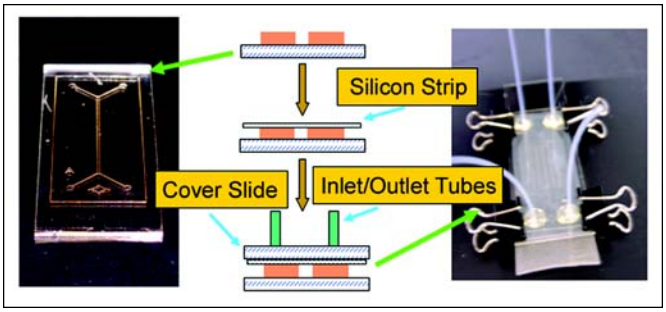

Figure 3. Schematics of the microfluidic device assembly.

Our process is shown in Figure 2. It is based on simple photolithography that requires inexpensive equipment. The channels of the devices are etched into SU-8 photoactive polymer. The SU-8 photoresist is commonly used in micromachining and for microelectronic applications.[6] The use of the SU-8 photoplastic allows the fabrication of monolithic, auto-assembled channels for microfluidic applications.[7] Some of the desirable properties of SU-8 include high aspect ratio imaging, near UV processing (350-400 nm), film thicknesses from 1 to >200µm (single spin coat), and superb chemical and temperature resistance.[6] It is transparent and is well suited for near vertical side walls in very thick films.[6] SU-8 is also inexpensive and may be used as a photoplastic for permanent use.[7]

The design of the microfluidic channels is done by PC computer using a basic CAD program. The design of the channel pattern is made into simple masks by printing on a transparency with an ink jet printer. The smoothness of the channel edge is dependent on the resolution of the printer. All designs for this project consisted of four inlet/outlet ports, two on each opposing side. With this design there can be two inlets/two outlets, three inlets/one outlet, etc. The devices were produced on a 3x1 inch glass slide.

Once the masks have been printed, the fabrication process can begin. There were seven basic steps for creating microchannels:

1. pipette SU-8 onto a clean glass slide
2. spin coat
3. soft bake
4. place mask on slide and expose
5. hard bake
6. develop
7. rinse and dry

It is important to thoroughly clean the glass slide before deposition of the photoresist. About 1/4 inch of the slides were

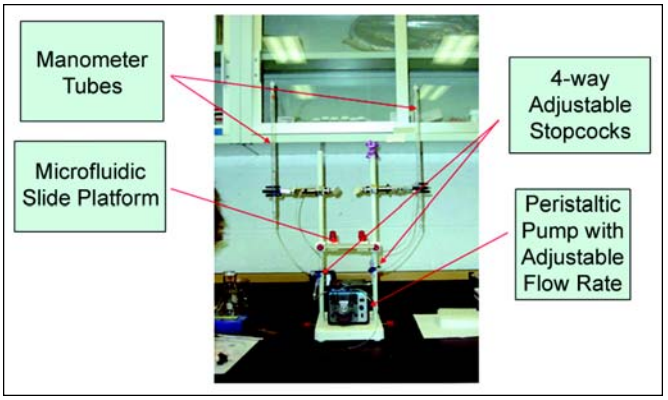

Figure 4. Schematic of the microfluidic setup.

cut off with a glass cutter so that they would lay flat on top of the UV source. Hydrophobizing the glass surface helps with adhesion, but is not necessarily required. We used a 1.5 mL disposable plastic pipette, the narrow tip of which was cut off for easier deposition of the viscous photoresist. The photoresist must be deposited carefully to avoid air bubble entrapment in the film. After deposition, the photoresist is spread toward the edges of the slide with the pipette.

Several formulations of the SU-8 and SU-8 developer, PM acetate solvent, were compared. Initially, formulations of 50/50 and 70/30 SU-8/solvent were used. These formulations produced very thin films of around 20 µm thickness at the end of the process. Eventually, pure SU-8 25 was used to create film thicknesses of 60-70 µm.

Spin coating distributes the photopolymer evenly over the glass slide for a flat, even film. It was done in two steps. The first step was up to 300 RPM with a ramp of 1000 RPM/sec for 10 seconds. The second step was tested at 500, 600, and 700 RPM at a ramp of 300 RPM/sec for 60 seconds. It was found that 600 and 700 RPM had the smoother photoresist surface. The duration of the second step was decreased to 30 seconds as the full 60 seconds was not needed to further level out the photopolymer. Further spin coating trials showed that the best setting for the second step was around 650 RPM.

The photopolymer deposition was followed by a soft bake. It serves the purpose of evaporating the solvent and relaxing the polymer molecules so they can be in an optimal conformation for crosslinking.[7] According to previous research, the

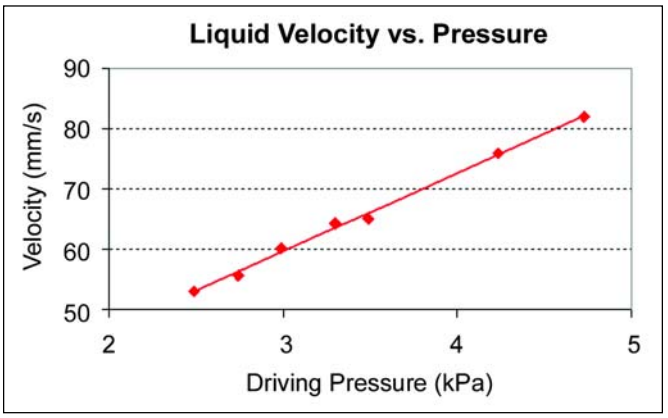

Figure 5. Pressure-Flow characterization of a microfluidic channel.

prebake (soft bake) time is the most important factor to high quality resolution.[8] Adequate prebake time must be allowed so that the retained solvent level is low and there is reduced risk of exposed resist loss, swelling, and adhesion failure.[9] The soft bake cycle used was 30 min at 95°C (203°F).[9]

UV light exposure through the mask is another critical step. Underexposing will cause the polymer to rinse away in the developing stage. Overexposing will cause poorly formed channels. As the photoresist structure gets thicker, the effect of developing time on the photoresist quality increases.[8] After several trials, we found that 30 to 35 seconds exposure produced the best channels with a 60-70µm film thickness. The exposure was followed by acid-initiated, thermally driven epoxy cross-linking during the post exposure bake step (hard bake).[6] The hard bake was done for ca. seven minutes at 60°C (140°F). During polymerization, the photoresist undergoes shrinkage of ca. 7.5% due to the crosslinking of the molecules.[7] After the hard bake, the surface of the polymerized section is lower than the nonpolymerized one.[7]

After the hard bake, the slide should be allowed to cool to room temperature before developing. The development of the photoresist was done at room temperature using the solvent PM acetate.[7] The slide was immersed in solvent with medium to intense agitation for five to seven minutes.[9] The procedure was repeated until there was no more white stain on the slide.[9] The plates with the newly formed microchannels were rinsed with a pipette of fresh solvent to wash away any dissolved polymer and then air-dried.

Device Assembly

One of the major challenges of this project was to develop a simple and fast technique for sealing the channels. The device was covered with another glass slide on top, sandwiching the polymer layer. Various sealing procedures were tried. First, rubber sealant was used, but it was not effective at sealing the channels. Next, SU-8 solution was distributed around the edges, exposed, and baked. It seeped into the device too far eventually blocking the channels. Epoxy glue worked the best if it was well distributed, but it had a tendency to seep close to the channels.

Instead of using liquid adhesion methods, it was proposed that flexible silicon rubber strips are used to cover the channels and effectively seal them - *Figure 3*. The advantage of silicon rubber is that the bonding is a reversible, room temperature process and a small amount of pressure will create an adequate seal.[10] This allows the devices to be peeled open, cleaned, and reused.[10] Adequate sealing can be checked by visual inspection.

Both the glass cover slide and the silicon strips needed four holes of about 1 mm diameter to allow fluid in and out of the channels. The holes were drilled into the glass slide with a precision drill. A hole-punch was used for the silicon strip holes. The input and output tubes were made of 1 mm outer diameter Teflon®. Epoxy glue was used for immobilizing and sealing the Teflon tubes to the glass cover slide. In order to provide adequate pressure to hold the layers together, ordinary paper clips were used. Small silicon strips were placed

between the areas of contact between the clips and the glass slides to prevent breakage.

The tests showed that the silicon strips were effective in sealing the channels. However, higher pressure and higher flow rates caused slight leaks. Two silicon strips were used to solve this problem. One strip is placed on the polymer layer and completely covers it. The other strip is trimmed to only cover the areas were channels exist. This reduces the area that pressure is applied and therefore puts greater pressure over the top of the channels to prevent leakage. With the holes lined up, the two slides are pressed together so that the silicon strips meet and seal. This method was done under the assumption that silicon rubber will bond better and more easily to itself than another material. It also allows higher pressure to be applied because the silicon layer is twice as thick and is more compressible. Using two layers of silicon instead of one proved to be a working and repeatable procedure that completely sealed the microfluidic channels.

Microfluidics Setup

A microfluidics setup was designed in order to support the devices while in use, with the aims of simple operation, easy observation, and quick exchange of the devices for analysis. - *Figure 4*. The components of the setup included peristaltic pumps, device platform, manometer tubes, two four-way stopcocks, and inlet/outlet tubes.

The speed of the peristaltic pump can be varied and the flow can be reversed to pull liquid out of the microfluidic device. The chip platform is a slab of plastic with holes that accommodate the inlet/outlet tubes in the device. As the device rests on the platform, the tubes are oriented downward. The manometer tubes serve as a way to quantify the pressure in the channels. They also serve as buffers to smooth out the flow from the peristaltic pump when the stopcocks are fully open. The stopcocks can close off the streams to allow only the pump pressurized liquid to flow through the device, only the manometer column liquid pressure to flow through, the pump to flow into the manometer tubes, or all three tubes to be open and connected.

Pressure-Flux Measurements

The next step, after proving that the devices and the set-up are functional, was to perform experiments to characterize the flow within the channels. The first trials compared the height of the liquid level in the manometer tubes to the velocity of the fluid flowing through the channel. The height of the water inside the manometer tube can be converted into pressure using the following equation:

$$\Delta P = \rho g h$$

ΔP = pressure at the input (kPa, psi)
ρ = density (1 g/mL, 62.43 lb_m/ft^3 for water)
g = gravitational constant (9.8 m/s^2, 32.2 ft/s^2)
h = height of liquid level in manometer tubes (in, cm)

The type of design that was used had two inlets and one outlet so that the flow rate could easily be measured by collecting the outlet flow in a small beaker. The tubes were filled to different heights ranging from 10 to 19 inches (25.4cm to 48.3cm) above the microfluidic platform. Using a stopwatch, the amount of fluid (water) was timed and then weighed to determine the flow rate.

The graph in Figure 5 shows a linear relationship between head pressure and fluid velocity for water. To calculate the velocity from the flow rate, measurements of the dimensions

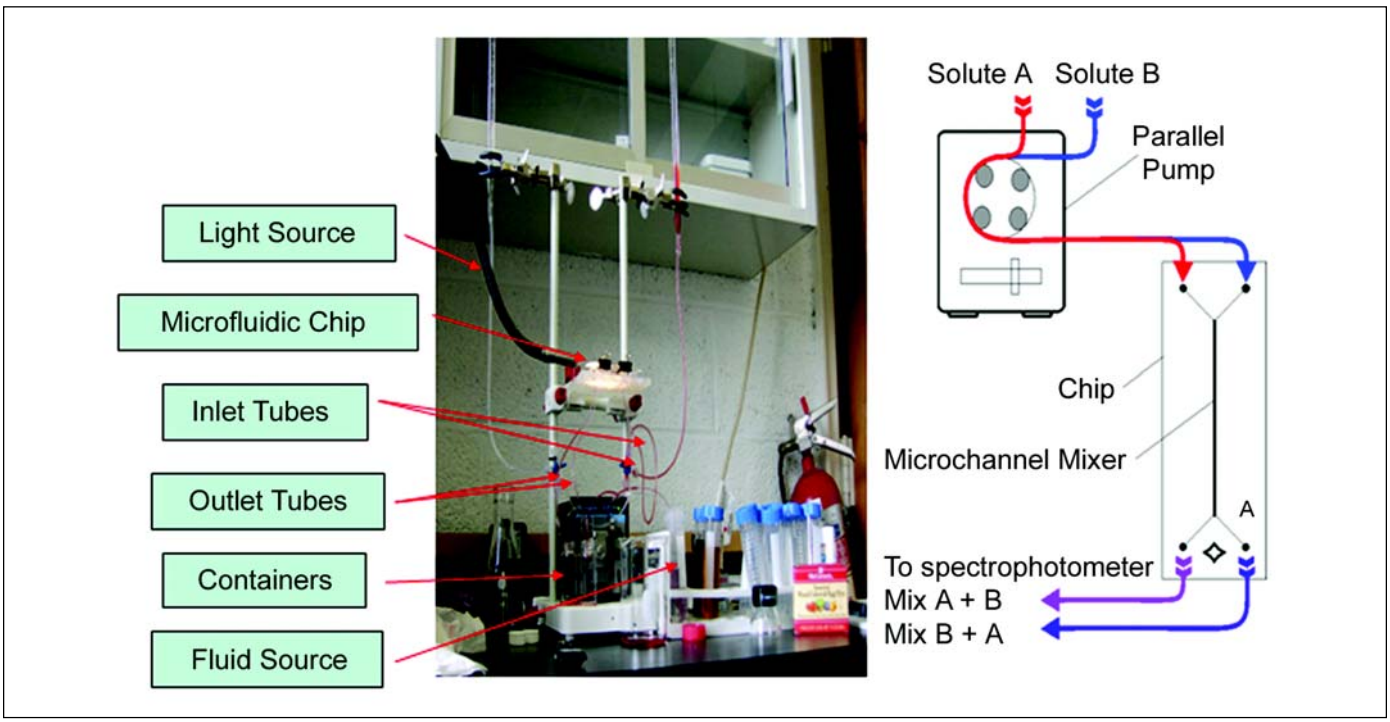

Figure 6. Schematics of the setup for testing and characterizing of the microfluidic devices.

of the cross-sectional area of the channel must be taken. The cross-section of the channel is a critical factor in manufacturing because it determines the production output per time.[2] Using a confocal microscope, the channels were measured to have a height of about 65µm and a width of about 400µm. Multiplying these values gives a cross-sectional area of about .026 mm^2. The velocity can then be calculated using the following equation:

$$V = \frac{Q}{A}$$

V = average liquid velocity (mm/s, in/s)
Q = volumetric flow rate (mm^3/s, in^3/s)
A = cross sectional area (mm^2, in^2)

The liquid height in the manometer tubes had to be at least 10 inches (25.4cm) of water to have sufficient head to push the liquid through. This equates to a pressure of at least 2.5 kPa (.36 psi). A design challenge for engineers would be to balance the gains made in heat and mass transfer in the channels of smaller dimensions against the increases in pressure drop.[4] Ultimately, the design of a microfluidic unit is a tradeoff between mixing speed, pressure drop, volume flow, feasibility of microfabrication, and integration with chemical detection devices.[4]

Mixing Considerations

Since the flow in microfluidic channels is laminar, there is no radial turbulence to facilitate mixing of two adjacent streams. In these small dimensions, mixing only occurs through diffusion, which is a relatively slow process.[10] In the laminar flows, adjacent streams of fluids with different chemical composition remain distinct except for diffusive mixing at their interface.[1] This characteristic becomes both a challenge and an advantage for liquid-phase reaction systems.[4] The slow mixing of co-flowing streams offers additional opportunities for phase transfer reactions and separation devices, and can be exploited in novel fabrication schemes.[4] It is possible to utilize laminar flow to deliver reagents to the surface of a cell with subcellular accuracy.[1]

There are several ways to increase the amount of mixing when it is desired. The walls of the channels around the streams can be laminated to increase the contact area and reduce diffusion lengths.[4] Two fluids could be brought into contact and then the resulting stream separated perpendicularly to the mixing interface. Then they can be brought back together which results in the doubling of the fluid interface and halving of the diffusion length.[4] Rapid mixing can then be accomplished by repeating the cycle. Another approach is to have the side flows squeeze (hydrodynamically focus) the inlet flow into a thin stream, which would result in rapid diffusive mixing.[4]

Using the two inlet - two outlet microfluidic channel design, a mixing trial was conducted to characterize the degree of mixing within the channel - *Figure 6*. Using one stream of colored water and another stream of clear water, the two streams come together in the device then separate. It was shown that the two liquids flow concurrently with a very low level of lateral mixing - *Figure 1*. Using a spectrophotometer, the concentration of the color stream was measured as a reference point. The exit streams were collected separately and measured at varying flow rates. The samples were diluted enough to be within the readable range of the spectrophotometer used.

A mixing factor was calculated for the different flow rates that were used in the experiment. It measures the degree of mixing in a given microfluidic system.[11]

$$F_{mix} = \frac{D_c T}{L^2}$$

F_{mix} = mixing factor
D_c = diffusion coefficient ($1x10^{-9}$ m^2/s, $1.1x10^{-8}$ ft^2/s for water)
T = contact time(s)
L = central distance between streamlines (0.2 mm, .008 in)

If $F_{mix} > 0.1$, substantial mixing
If $F_{mix} << 0.1$, no mixing

The mixing factor values calculated were << .1 indicating that very little mixing occurred. This was verified from the mixing experiment that showed less than 8% mixing and corresponds to the expected diffusion-only mixing mechanism.

Concluding Remarks

The experiments proved that simple laboratory scale technology can be used for the fabrication of functional devices for microfluidics testing and education. The techniques could easily be mastered by undergraduate researchers. When completed, this experimental methodology will be transferred to the undergraduate chemical engineering laboratory. More complex experiments will be developed over time, eventually leading to projects in the capstone design core sequence where the students design new microfluidic loops, fabricate them quickly by photopolymerization, and then characterize the performance of the new chips that they have created. The modular structure of the devices will allow departments other than Chemical Engineering to use the contents of these modules as a part of the courses and projects they offer.

References

1. Whitesides G., Stroock A., "Flexible Methods for Microfluidics," *Physics Today,* Vol. 54, No. 6, 2001, pp. 42-48.

2. Freemantle, M., "Downsizing Chemistry," *Chemical and Engineering News,* Vol. 77, No. 8, 1999, pp. 27-36.

3. Sanders G. and Manz A., "Chip-based Microsystems for Genomic and Proteomic Analysis," *Trends in Analytical Chemistry,* Vol. 19, No. 6, 2000, pp. 364-378.

4. Jensen, K., "Microreaction Engineering - Is Small Better,?" *Chemical Engineering Science,* Vol. 56, No. 2, 2001, pp. 293-303.

5. Becker H., Locascio L., "Polymer Microfluidic Devices," *Talanta,* Vol. 56, No. 2, 2002, pp. 267-287.

6. Microchem - http://www.microchem.com/.

7. Gurein L., Bossel M., Demierre M., et. al., "Simple and Low Cost Fabrication of Embedded Microchannels by Using a New Thick-Film Photoplastic," *Transducers '97,* 1997 International Conference on Solid-State Sensors and Actuators, Chicago, June 16-19, 1997, pp. 1419-1422.

8. Zhang J., Tan K., Hong G., et. al., "Polymerization Optimization of SU-8 Photoresist and its Applications in Microfluidic Systems and MEMS," *Journal of Micromechanics and Microengineering,* Vol. 11, No. 1, 2001, pp. 20-26.

9. SU-8: A Thick Photo-Resist for MEMS - http://aveclafaux.freeservers.com/SU-8.html/.

10. Bousse L., Cohen C., Nikiforov T., et. al., "Electrokinetically Controlled Microfluidic Analysis Systems," *Annual Review of Biophysics and Biomolecular Structure,* Vol. 29, 2000, pp. 155-181.

11. Koch M., Evans A., and Brunnschweiler A., *Microfluidic Technology and Applications,* Baldock, England: Research Studies Press Ltd., 2000.

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