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ENGINEERING AND OTHER HEALTH HAZARD CONTROLS IN ORAL CONTRACEPTIVE TABLET-MAKING OPERATIONS

REPORT WRITTEN BY:
Mazen Y. Anastas, Ph.D.

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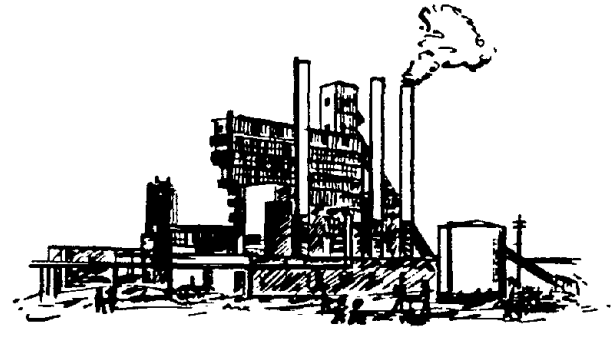

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National Institute for Occupational Safety and Health
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A survey of health hazard controls in oral contraceptive tablet making (SIC-2834) operations was conducted. Four facilities were included in the survey. Engineering controls included using hoods while weighing pure steroids, local and general ventilation, material transfer systems in granulation and tablet forming operations, and using powder feed systems in tablet forming operations. Breathing zone estrogen and progestogen concentrations in granulation operations ranged from 0.15 to 1.04 and from 1.39 to 18.9 micrograms per cubic meter (microg/m3), respectively. Estrogen and progestogen concentrations in tablet forming operations were 0.05 to 0.14 and 0.24 to 7.10microg/m3, respectively. Estrogen and progestogen concentrations in packaging operations were 0.02 to 0.11 and 0.20 to 0.72microg/m3, respectively. All facilities utilized environmental and medical monitoring. Workers in granulation, tablet forming, and packaging operations were protected from exposure to steroids by respirators, coveralls, gloves, and overshoes. All facilities emphasized personal hygiene (frequent showering and changes of protective clothing). Job rotation was practiced at two facilities and good housekeeping was practiced at all facilities. The author notes that all facilities offer intensive training and education programs in health hazards, safety, and personal protective equipment associated with each job title.

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ABSTRACT

As part of an ongoing NIOSH control technology assessment program, a field characterization of the health hazard controls associated with oral contraceptive tablet-making operations was recently completed. Manufacture of combination oral contraceptive tablets containing progestogens and estrogens in ratios between 12 and 50 was focused upon. The manufacturing processes studied usually involved preweighing and batch mixing of active ingredients and excipients, compression of the resulting granulation, and packaging. These operations may be considered typical in the production of tablets in the pharmaceutical industry. Health hazard controls consisting of engineered safeguards, work practices, environmental and medical monitoring of employees, and personal protective equipment were implemented at such operations to reduce exposures to levels acceptable by the companies.

The characterization of the controls included assessment of the engineered safeguards, observation of work practices, and determinations of breathing zone levels of the steroids outside respiratory protective equipment. The engineered safeguards consisted of general and local exhaust ventilation, automated material transfer, enclosure of potential sources of exposure, and isolation of the production facility. Workers are also required to employ good work practices in carrying out their job duties. Such work practices are the results of good training and education programs in the potential health hazards associated with each job, and the requirements for personal protective equipment and personal hygiene.

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INTRODUCTION

The Occupational Safety and Health Act of 1970 (PL 91-596) was enacted to "assure safe and healthful working conditions for men and women." The Act established the National Institute for Occupational Safety and Health (NIOSH), which is now in the Department of Health and Human Services. NIOSH was charged by this Act to conduct research and develop criteria for preventing exposure of workers to harmful chemical and physical agents. In response to this legislative mandate, NIOSH has conducted major programs to document, develop, and disseminate information regarding the recognition, evaluation, and control of such agents.

In 1976, NIOSH instituted a major effort to prevent occupational health problems through the assessment and application of control technology in the workplace. This control technology research program involves assessments in which effective options for the solution to employee exposure problems are evaluated and documented. The major goals of the assessment program are to establish a catalog of solutions by documenting successful applications of control measures, and to foster the more widespread application of these solutions through technology transfer. To date, assessments have been completed on such industrial activities as pesticide manufacturing, solid materials handling, and other chemical process technology.

The pharmaceutical industry manufactures a wide variety of medicinal products. These drugs fall into a number of broad categories according to their use or intended biological effects. Some of the drugs are anti-infective or anti-neoplastic. Others may be cardiovascular, central nervous system, or metabolic agents. Vitamins and nutrients as well as veterinary preparations are two other broad categories. Drugs in the form of tablets represent a significant portion of pharmaceutical dosage forms in all of the categories mentioned above.

In general, the manufacture of tablets involves the preweighing and batch mixing of ingredients to form a granulation, compression of the granulation

into tablets, and packaging. Since it is very important to maintain product uniformity, quality control procedures usually require that assays be performed at each step in the process. These and other considerations mandate the use of batch processing in tablet-making operations.

In the pharmaceutical industry, all of the elements of health hazard control are represented. These are engineering controls (ventilation, automation, etc.), work practices (training and education, and performance audits), environmental and medical monitoring of workers, and personal protective equipment (PPE).

Oral contraceptives (OC) have been selected for study because they represent the largest single use of estrogens, and because they are processed using rather typical pharmaceutical technology. OC tablets contain substances of high biological potency, usually a progestogen such as northindrone or one of its derivatives and an estrogen such as ethynylestradiol or mestranol. In the absence of federal standards for exposure to steroids, hazard controls are implemented by the companies to reduce exposures to levels which they deem acceptable. Consequently, it was felt that systematic characterization of the controls used in OC tablet manufacturing would be beneficial in batch manufacturing processes wherein similar unit operations and active ingredients of similar potency are employed, both within and outside of the OC processing operations.

The unit operation of tableting (or agglomeration) and auxiliary processes is widely used both within and outside the pharmaceutical industry. This operation is used for industrial products including moth balls and other insect repellants, washing compounds, food products, catalysts, fireworks, explosives, water-color paints, dyes, abrasives, plastic preforms, ceramic products, battery components, graphite parts, metal-powder forms, and the like.[1]

This report describes (1) the health hazard controls associated with four OC manufacturing operations, (2) the methodologies employed in the characterization of the engineered safeguards, and (3) the results of

monitoring activities by both NIOSH and the companies which participated in the study.

PROCESS DESCRIPTIONS

PLANT A

Processing

Three workers are involved in the production of granulation. Ingredients for several batches are weighed at one time. The active ingredients (progestogen and estrogen) are weighed in a SterilGARD(R) Class II, Type A hood manufactured by The Baker Company. Excipients are assembled in the excipient dump room, which is directly above the room where the Patterson-Kelly V-blender is located. Each batch of product consists of several hundred pounds of mostly excipients with less than one percent of the active ingredients. The OC tablets produced at this plant each contain 1 mg progestogen and 35 or 50 mcg estrogen. The granulation production scheme is shown in Figure 1.

Some excipients are first milled in the excipient dump room in a Fitzmill (Fitzpatrick Mill). The blender is then charged with excipients through a hopper in the excipient dump room fitted with a rotary feeder at the bottom. The hopper is connected to the blender via a flange fitting. After the excipients are charged, the blender is disconnected from the hopper and its discharge opening closed. Active ingredients contained in paper bags are dumped into a small 20-gallon agitated tank containing granulating liquid. Nitrogen gas is used to force the solution of the actives to the liquid feeding and agglomerate breaking device contained within the blender. The latter rotates about its axis while liquid is being fed. After wet mixing is completed, the material (called wet granulation) in the blender is emptied into stainless steel drums. The material is then transported in the drums to the oven room and manually scooped into the hopper of a Fitzmill, which discharges the wet granulation through a cloth "boot" to a drum. The material is subsequently transferred by manually scooping and spreading into shallow trays lined with paper. The trays are then placed on trucks (or trolleys) which fit into the batch dryers.

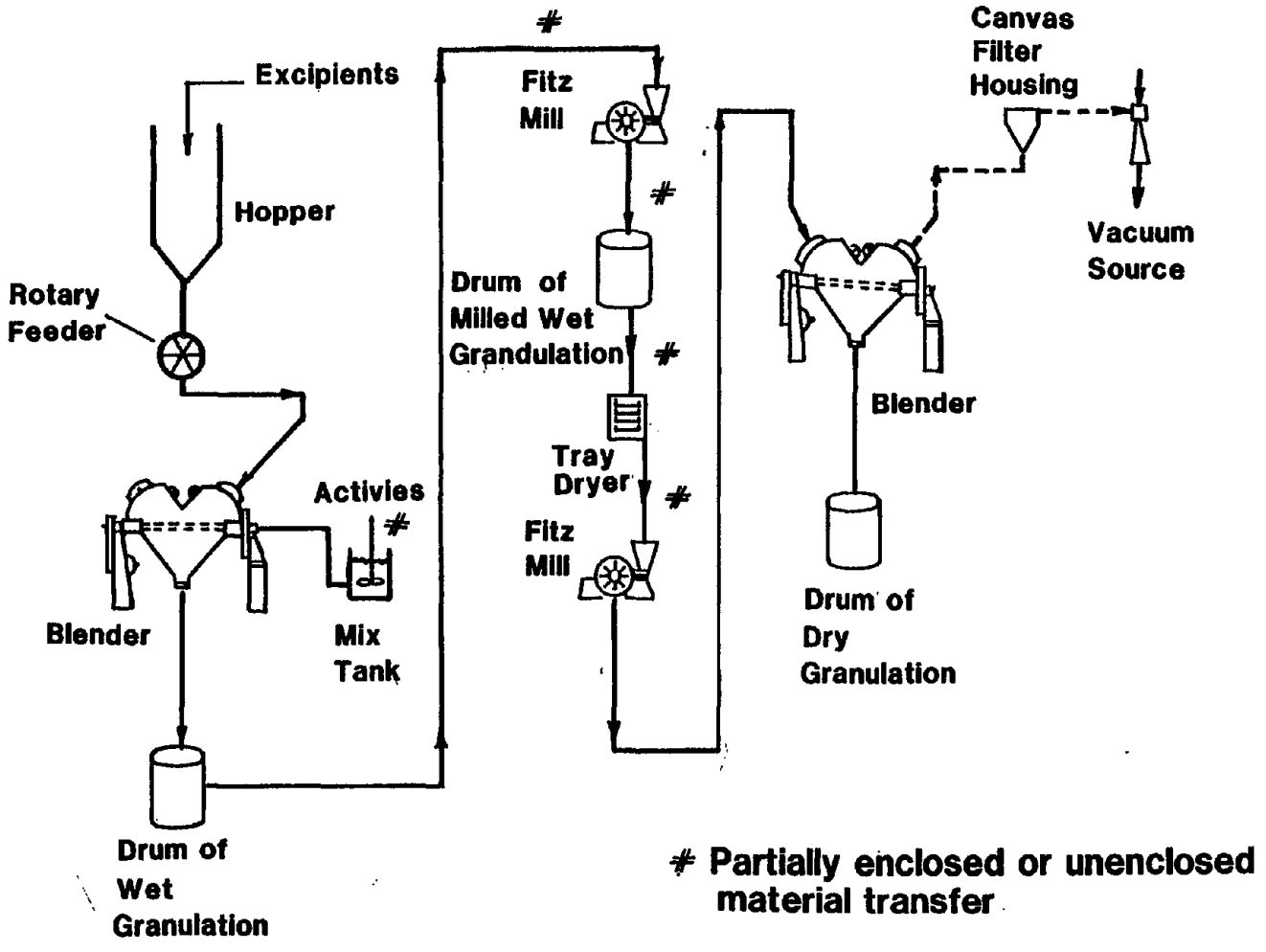

Figure 1. Granulation production scheme at Plant A

The granulation in the tray is allowed to dry overnight then transferred, one tray at a time, to the hopper of the Fitzmill. Lubricant is added at this point. The discharge end of the Fitzmill is connected to the Vac-U-Max(R) vacuum transfer system which transports the granulation to the blender. Vacuum is generated by a pump. A three-way valve is used to connect the filter housing and filter drum to either the return air system or the vacuum pump. When transferring material from the mill, the pump is operating in line with the filter housing and blender. After a certain time of operation in this mode, the filter becomes clogged with powder. The operator at this point turns the three-way valve so that air from the return system flows towards the blender, thus blowing back any material in the filter.

After this transfer is completed, a short blend (few minutes) is performed in the blender. The granulation is then emptied into stainless steel drums and transported to the staging area. Representative samples are taken for quality control analysis prior to releasing for tableting.

Several batches of one product are prepared in the course of one week. Typically, steroid processing is carried out over one 8-hour shift, Monday through Friday. Processing during one shift in the middle of the week involves dry milling and blending of one batch of granulation (which has been left to dry overnight in the ovens), then wet blending of another batch (including wet milling and loading tray dryers), and finally cleanup of equipment and floor in preparation for the same sequence the next day.

Tableting

One worker operates two tableting machines in this area. Model BB2 machines (manufactured by Sharples-Stokes Division of Pennwalt) are used to manufacture oral contraceptive tablets. Granulation is fed to two feed frames of each machine by two hoppers positioned on opposite sides of the rotary head. The principle of operation of rotary tableting machines is described in detail in Reference 2, page 323 and also shown in Figure 2.

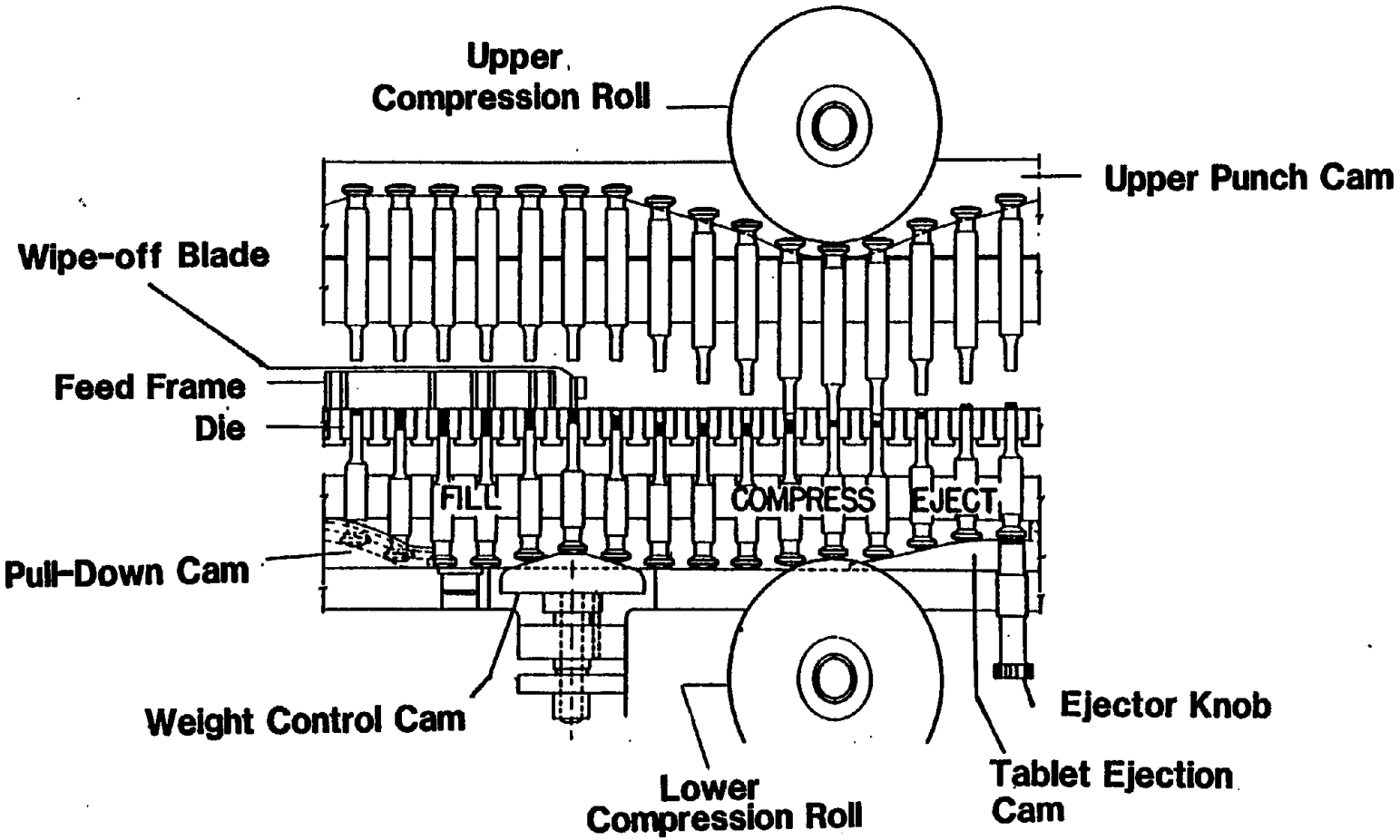

Figure 2. Compression cycle of rotary tablet press

(By Permission, Reference 2)

Briefly, the granulation flows from the hopper to the feed frame which spreads the granulation over a wide area to allow the dies to fill. A cam guides the lower punches to the bottom of their vertical travel allowing the dies to overfill. These lower punches then pass over a weight control cam which reduces the fill in the dies to the desired amount. A wipe-off blade mounted in the feed frame removes excess granulation at the top of each die. The lower punches then travel over the lower compression roll, which causes them to move vertically upward while the upper punches are forced downward by the upper compression roll. This results in the compression of a tablet. After compression is complete, the upper punches travel vertically upward as their heads enter a cam with a recessed groove. Another cam causes the lower punches to move upward through the dies, thus effecting the ejection of the tablets. The tablets strike a sweep-off blade that is anchored to the feed frame and slide down a chute to a conveyor/deduster which empties into a small container lined with plastic film.

The tablet machine operator periodically conducts weight and friability tests and may perform machine adjustments if necessary while the machine is running.

Packaging

Two Hassia machines (Model VAII manufactured by the now defunct Hassia Verpackungsmachinen of West Germany) are used to produce blister packs. The machines are in separate, but adjacent rooms. Before charging the hopper of the machine with tablets, the operator dedusts them with a vacuum device. A schematic representation of the packaging machine is shown in Figure 3. Both OC and placebo tablets are conveyed from their respective hoppers to a brush feeder by two-stage vibratory conveyors. The brush feeder consists of two circular recesses with numerous holes at the bottom. Slowly moving brushes sweep the tablets into the holes which feed the blister-type packs. These packs are formed by the machine whereby a plastic sheet is drawn from a roll and continuously thermoformed into tablet-sized pockets as it passes over a roller. The tablets are then inserted and a cover web (aluminum film) is sealed over the thermoformed plastic sheet.

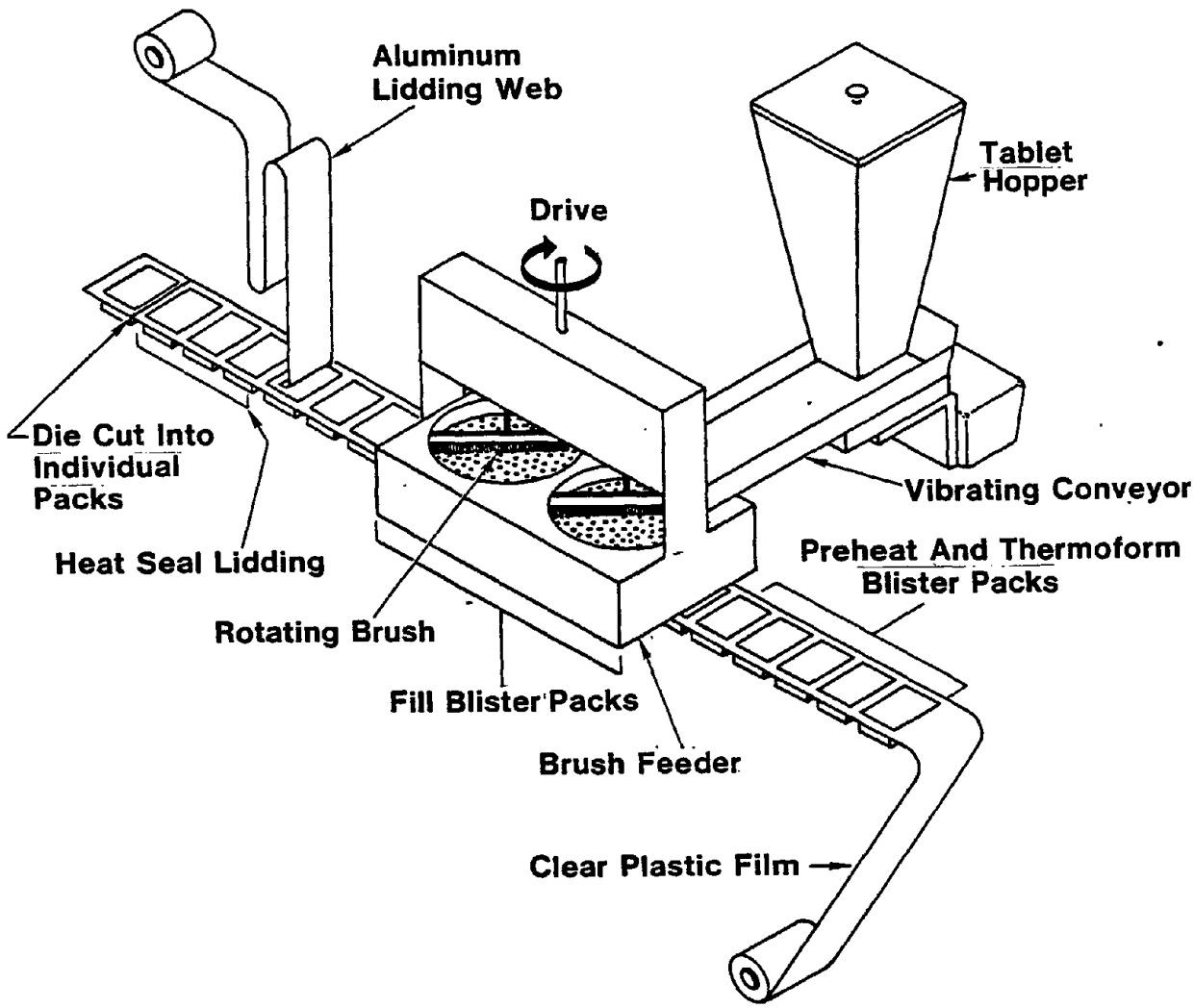

Figure 3. Schematic of packaging line at Plant A

There are three inspectors and an operator assigned to the steroid blistering operation. These employees are supervised by a foreman. The three inspectors rotate positions every 30 minutes. The filler inspector (one person) inspects unsealed blisters for various defects. The filled blister inspector (two persons) perform a second inspection. The blister machine operator dedusts tablets; keeps the filler hoppers supplied; sets up, operates, and adjusts all parts of the machine; supplies the blister material to the machine; maintains records of production; and performs routine, intermediate, and complete cleanups of the equipment and room.

PLANT B

Granulation

A variety of combination OC tablets are manufactured at this plant. During the NIOSH visit, products containing 0.5 to 1.0 mg progestogen and 35 to 50 mcg estrogen were manufactured.

Active ingredients for many batches are weighed out in the preweigh room. One worker weighs the batches using an electronic balance located in a hood. The material for each batch is placed in a container lined with a clear plastic bag.

Excipients are preweighed into fiber drums at a location outside the steroid manufacturing facility and are brought to the material staging room.

A process flow sheet of granulation production operations is shown in Figure 4. Excipients in the material staging room are transferred from drums to a V-blender by use of a Vac-U-Max(R) system (Vac-U-Max Corporation). The progestogen is added to the V-blender directly. The estrogen is dissolved in a preweighed quantity of granulating liquid in a small mixing tank. The plastic bag that contained the estrogen is rinsed with granulating liquid. A positive displacement pump is used to transfer the solution of active to the V-blender.

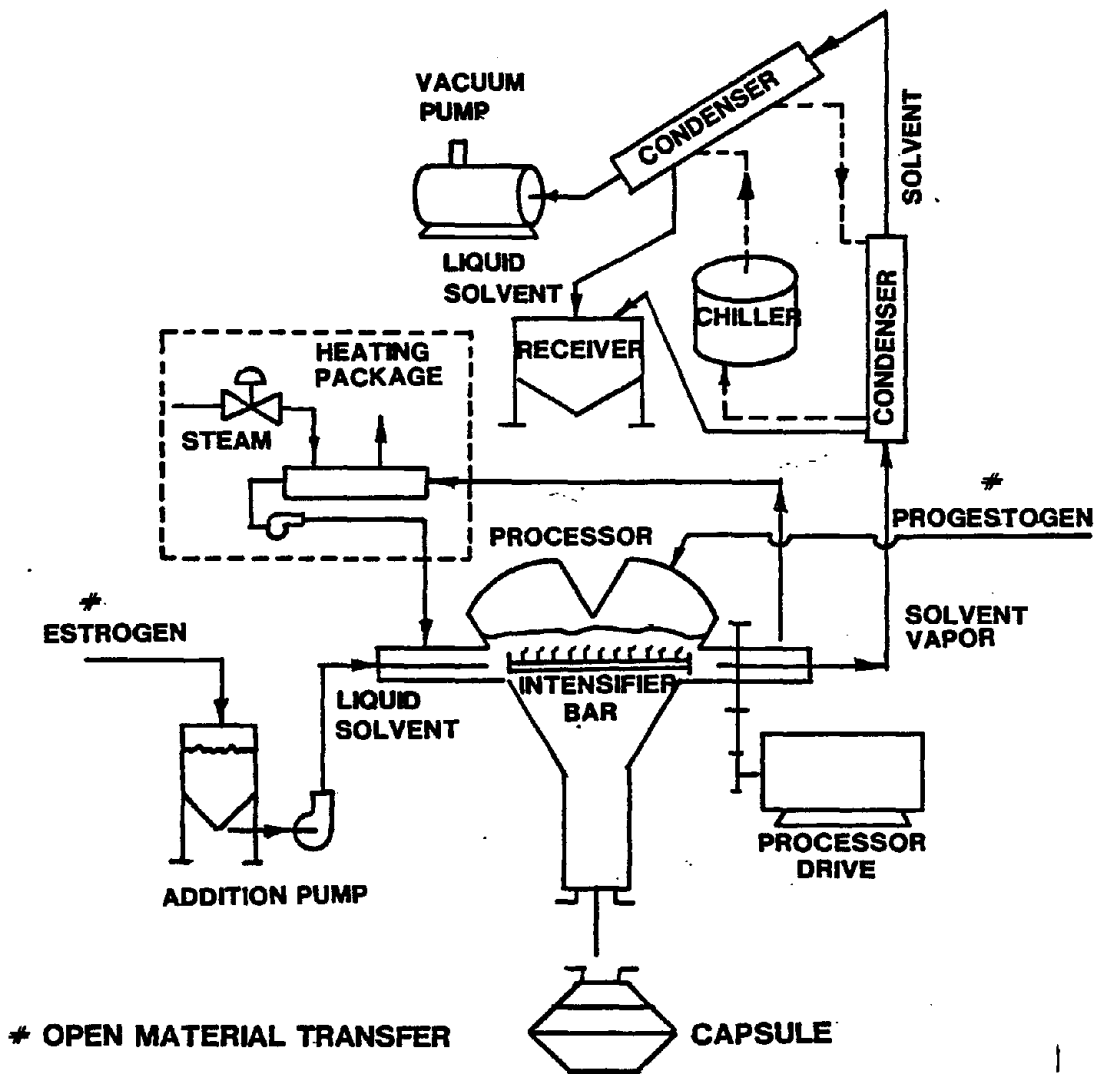

Figure 4. Granulation production scheme at Plant B

The solution of estrogen is dispersed through other ingredients by pumping under pressure through the "intensifier bar" of the V-blender while the latter is rotating. The liquids in the wet granulation are removed by passing steam-heated fluid through the V-blender jacket. The vapor produced is withdrawn by vacuum (pump) and is condensed in two condensers in series. Chilled water is passed through the condenser jackets. The worker uses a "thief" to sample granulation from both sides of the blender when drying is complete. A loss-on-drying test is performed on these samples. After it has been determined that drying is complete, a "capsule" is rolled underneath the blender to receive all of its contents. The capsule is attached to the V-blender before the dump valve is opened, making it essentially a closed system.

One worker operates the system during the shift. However, help from one or two additional workers is required at the beginning, when transferring excipients and actives to appropriate pieces of equipment, and at the end when emptying the V-blender contents into the capsule. In the latter instance, a worker on top of the blender uses a tool to push residual granulation into the capsule.

Tableting

The tableting operation is performed in a room dedicated for this purpose. One worker operates the tableting machine and performs quality control testing which includes the periodic monitoring of tablet weight and friability.

The tableting machine used at Plant B is a Manesty rotapress MK IIA sold in the U.S. by Thomas Engineering, Hoffman Estates, Illinois. Granulation is fed to the rotary press from a capsule that is inverted over the feed chute which terminates into a flange at floor level in the mezzanine. Granulation in the chute is fed to the two machine hoppers by a screw conveyor, which turns only when the level of powder in the hoppers is low. An optical level detector is installed in the hoppers. A force-flow feeder accomplishes feeding of the dies and scraping of excess powder. From this point on, the machine is

similar in operation to other rotary machines whose principle of operation is shown in Figure 2.

Packaging

The OC tablets obtained from the tableting operation at Plant B are packaged, along with placebo tablets, in blister packs. The machinery which produces the packs is proprietary.

The packaging room is divided into two parts. The first part (filling) is physically separated and environmentally isolated from the second by a wall with two doors, one on each side of the conveyor. The latter passes through a window to the second part of the room (called packaging).

One line tender and three packers operate equipment and perform various quality control functions in the room where pack filling occurs. The line tender's duties include (1) making adjustments on process control equipment, (2) helping the packers in troubleshooting line problems, and (3) making sure that the hoppers are filled. Two packers are always at the second belt conveyor inspecting the individual packs. The ones which are defective (missing or broken tablets) are removed from the conveyor and discarded into a cardboard box. The third packer stands in front of the tablet feed chutes and inspects the columns of tablets for defective ones. These are removed by vacuum applied through a small probe attached to a flexible hose. The three line packers switch duties periodically during the shift.

The pack-filling operation is followed by other packaging operations such as additional quality control, addition of literature to the pack, and packing the small packs into larger boxes for shipping.

PLANT C

Processing

Oral contraceptive tablets manufactured at Plant C contain 1 to 2 mg progestogen and 35 to 100 mcg estrogen. Excipients and active ingredients are weighed in separate hoods in the preweigh room. Again, ingredients for several batches are weighed out at one time.

Excipients and active ingredients contained in fiber drums are transported to the processing area. The method used to produce granulation is schematically shown in Figure 5. Two workers are needed to dump the excipients into a hopper located above and connected to the blender. The actives are added to a small mixing tank containing granulating liquid.

The solution of actives is pumped to the intensifier bars of the blender and mixed into the excipients. This mixing process takes place for a period of about one-half hour. When mixing is complete, the wet granulation is emptied into bowls which fit into the fluid bed dryer. These bowls have wire mesh screen bottoms which allow the passage of heated air after the bowls are inserted into the dryer bottom. A bag collector covers the mouth of the bowl and prevents the carryover of fines from the bowl.[2]

When drying is complete, the dryer bowl is wheeled to a ventilated semi-enclosure in the milling room. A vacuum transfer system is used to transfer the dry granulation from the bowl to a double-cone blender through a tornado mill. After a short blend (few minutes), the dry, milled granulation is emptied into fiber drums lined with transparent plastic bags. Quality control samples are obtained from the drums by laboratory technicians before the drums are closed and temporarily stored.

One worker (processing technician) can perform the necessary tasks in the area where granulation is prepared.

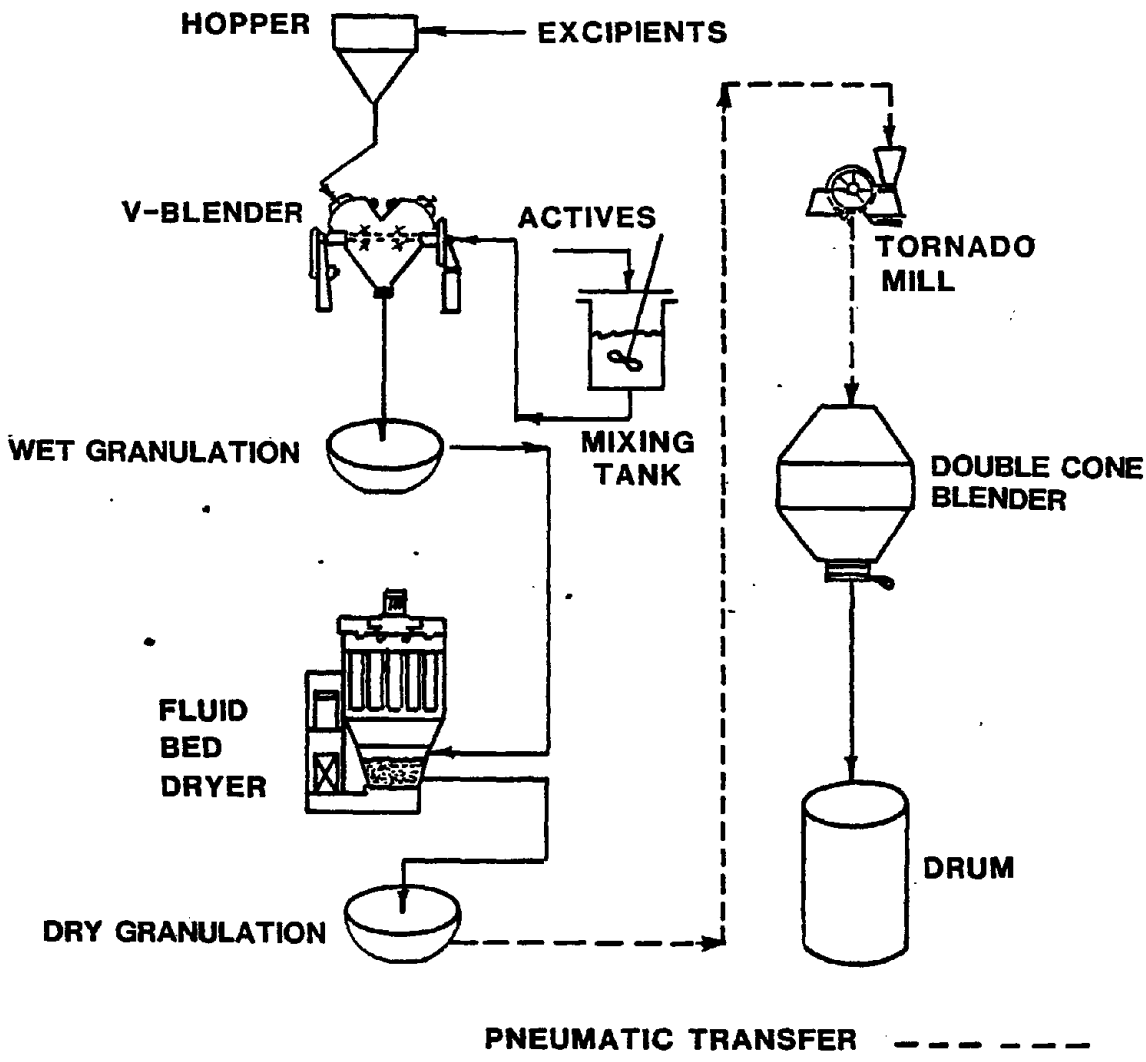

Figure 5. Granulation production scheme at Plant C

Tableting

A number of tableting machines individually housed in separate cubicles are used to compress approved granulation into tablets. These are Model Mark IIa Machines manufactured by Manesty. A Vac-U-Max pneumatic transfer system (to be described later) is used to transfer granulation from fiber drums to an intermediate hopper, which in turn feeds the two machine hoppers via a "Y-assembly." The two hoppers provide powder to two force-flow feeders identical to those in the Plant B tableting machine. The principle of operation of the rotary double-sided machine is also the same.

One worker usually can operate more than one machine. Job duties include obtaining samples for instantaneous determinations of tablet weight, performing adjustments while the machine is running, and replacing empty containers of granulation with full ones. Friability and hardness tests are performed on tablets by quality assurance technicians in a separate laboratory.

Packaging

The compressed tablets containing active ingredients are packaged in blister packs after being approved by Quality Control. The principle of operation of the blister pack feed system is illustrated in Figure 6. Dedusted tablets are scooped into the hopper. A spiral conveyor slowly moves the tablets upward to a vibratory table. The vibratory motion has the effect of moving tablets in a circular path around the table. Nine coiled springs, oblong in cross section, are attached to the vibrating table at one end and to a blister pack feeding block at the other. When the tablets reach the point where the coiled springs are attached to the vibrating table, some of them drop into the coiled springs. The rest fall to the bottom and are picked up by the spiral conveyor again and recycled. A similar feed system is used to introduce placebo tablets to the blister packs. However, only three coiled springs are attached to the vibrating table.

Each pack contains 21 tablets with active ingredients and 7 placebo tablets arranged in columns 7 tablets long. An individual pack thus contains 3

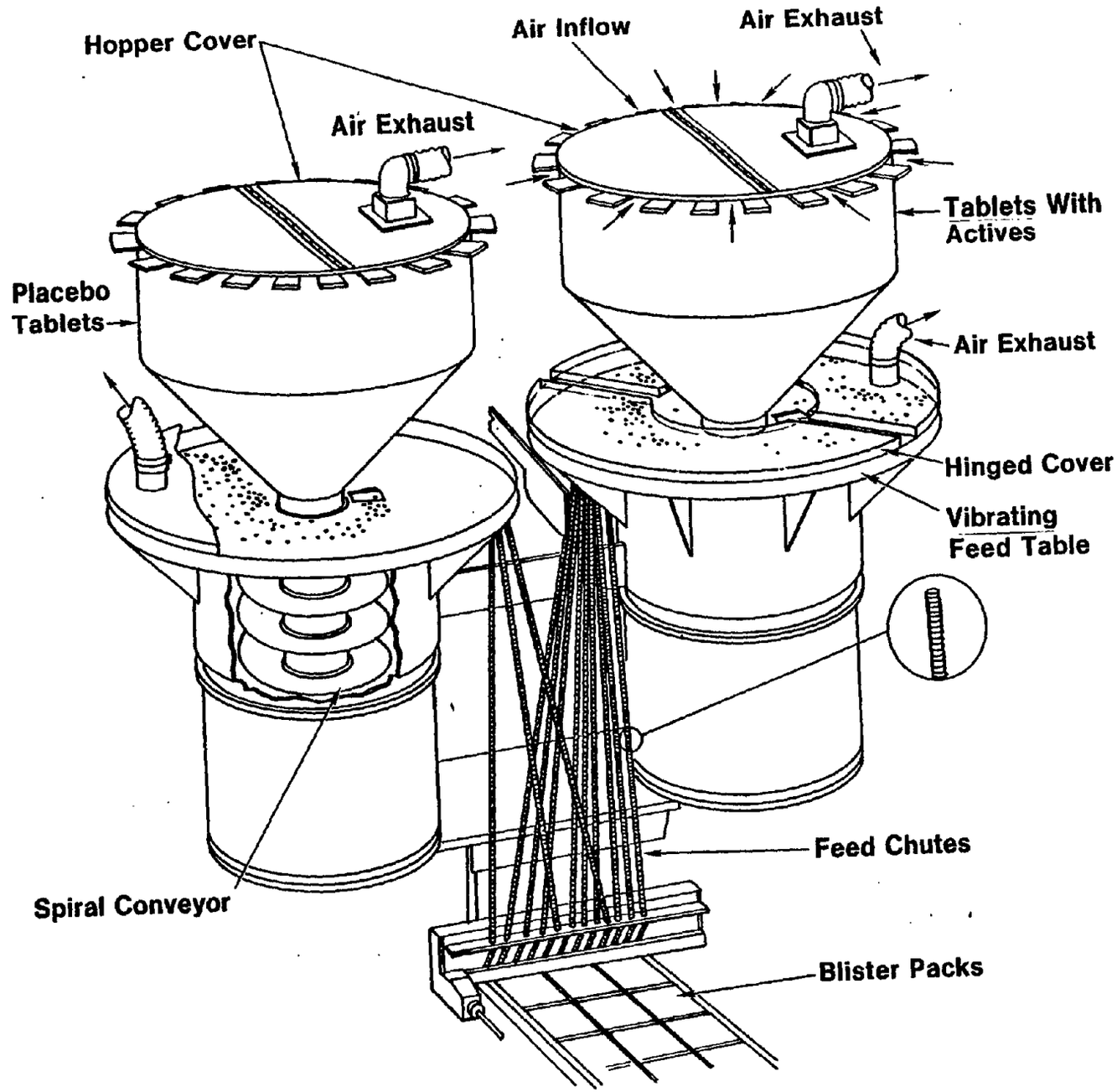

Figure 6. Schematic of packaging line feed system at Plant C

columns of tablets with actives and 1 column of placebo tablets. The tablet feed systems are designed to fill three blister packs simultaneously one row at a time (9 tablets with actives and 3 placebo tablets).

Three workers operate each packaging line. One of the workers attends to front end operations which include the filling of the hoppers with tablets, performing minor adjustments of line controls, and turning the line off and on as necessary. The other two workers inspect the blister packs to make sure that they do not contain broken or missing tablets.

PLANT D

It was not possible for NIOSH to conduct a detailed survey at this facility. However, company officials provided some information on the engineering controls (mainly local exhaust systems in processing and tableting), work practices, and results of employee monitoring activities performed by company officials. Most of this information will be incorporated in this report to enhance its usefulness.

Processing

A typical OC tablet manufactured at Plant D contains 1.5 mg progestogen and 30 mcg estrogen. These active ingredients are preweighed within the confines of a hood located in the granulation production facility. The granulation production scheme through drying is similar to Plant C. The blender is first charged with excipients and one of the active ingredients. The estrogen is dissolved in a granulating liquid and gradually dispersed through the excipients. The wet granulation in the blender is emptied into fluid bed dryer bowls and dried. After drying is complete, the bowl is then removed from the dryer and the top covered with a funnel, which attaches to the feed throat of a tornado mill. The mill discharges into an enclosed hopper, which in turn discharges into the V-blender. After a short blend, the dry granulation is emptied into tote bins.

Monitoring data provided by the company imply that three workers (two operators and one supervisor) are involved in the production of granulation during each shift.

Tableting

Granulation approved by Quality Control is compressed into tablets using a double-sided rotary machine. The dies are fed by two hoppers which in turn are fed by gravity from the tote bins through an airtight adapter. Tablets exiting both sides of the machine are dedusted and fall into fiber drums lined with clear plastic bags.

At least two workers are involved in the tableting operation - an operator and a group leader. The job duties of the two apparently overlap a great deal.

Packaging

The filling and inspection of blister packs is performed by Machine Operators. Machine service workers set up and maintain the packaging machines. A foreperson supervises the activities of both jobs.

PROCEDURES FOR CHARACTERIZATION OF CONTROLS

The health hazard controls of interest were: (1) engineering controls, including isolation, ventilation, and automation; (2) work practices which result in lower exposures; (3) monitoring of workers' exposures and their health for detecting and correcting problems as they occur; and (4) personal protective equipment that is effective in further reducing exposures to levels that are considered acceptable by each company.

The health hazard controls in effect at Plants A, B, and C were characterized during 5-day surveys conducted by NIOSH. Activities during the surveys included air sampling to measure steroid levels outside respiratory and other personal protective equipment, observation of work practices, and assessment of the engineering controls.

Monitoring of workers' "breathing zone" levels of steroids outside of respiratory protective equipment was conducted by the NIOSH survey team at Plants A and C for workers in granulation and tableting. Similar historical data obtained by company industrial hygienists were provided by Plants A, B, C, and D. The NIOSH team also collected area samples in the granulation, tableting, and packaging rooms in Plants A, B, and C. Such data characterize the engineering containment component of the control system.

Samples obtained by NIOSH were at an air rate of 3 lpm through a 37 mm Teflon filter Millipore FALP 37000 mounted in a cassette. The filters were desorbed with acetonitrile and the extracts were analyzed by high performance liquid chromatography (HPLC). Similar sampling methods were employed by the participating companies. However, some companies employ radioimmunoassay for analysis. The analytical techniques are described in Appendix A.

Work practices were observed while the workers performed their job duties and operated process equipment, and while they donned or removed protective clothing and respiratory protective equipment.

Since ventilation is an important control at all sites visited, measurements were made to obtain information on the principles of operation and characteristics of the ventilation systems used. The objectives of the measurements where general ventilation was employed were to obtain first-hand information on: (1) the techniques used to isolate the steroid facilities from surrounding areas by maintaining a negative pressure within the facilities, (2) the volumetric rates of ventilation of each area within the steroid facilities, and (3) the distribution of the airflow within each area.

Local exhaust hoods were extensively used to control dust at the sources of emission. Of interest to NIOSH were the capture characteristics of such hoods at points which were judged to be critical to the hoods' effectiveness. Airflows were estimated by taking face velocity measurements.

Most of the velocity measurements were made using a Kurz Model 441 anemometer. Other flow measurements were made using a FlowHood(R) (Shortridge Instruments) Model CFM-83. A magnehelic pressure gauge was used to measure differences in pressure between various locations.

Also of interest to NIOSH were the principles of operation of various process equipment and equipment used for dust control. This information was obtained from the facility operator or the equipment vendor.

ENGINEERING CONTROLS

GENERAL REMARKS

In this chapter, a discussion of the engineered safeguards will be given for each significant control in each step of the manufacturing processes studied; namely, preweighing of ingredients, production of granulation, tableting, and packaging. To the extent possible, the mechanism and sources of dust generation together with the applicable control measures will be discussed.

PREWEIGHING OF INGREDIENTS

Local Exhaust Systems

Active ingredients are preweighed in a SterilGARD(R) hood (The Baker Company) at Plant A. The principle of operation of the hood is shown in Figure 7. Air passes through a HEPA supply filter that is 99.97 percent efficient in removal of particles with an average diameter of 0.3 um before entering the work of the hood area. The filtered air travels vertically through the cabinet at an average velocity of 100 ft/min (fpm). Air exits from the work area via two exhaust grilles which extend across the entire width of the cabinet in the rear and in front of the work surface. This air travels back to the motor-filter units through three return air plena located behind the two side walls and the rear wall. Air from one side wall and half of the rear wall plena moves to each of two motor-filter units. All return plena and the two motor-filter units housings are under negative pressure. Upon leaving the motor-filter unit housing, the air enters a positive-pressure zone that is surrounded by the negative-pressure plena. Approximately 90 percent of the air in the positive-pressure area passes through the HEPA supply filter to the work area. The remainder, 0.4 room volumes per minute (RVPM), passes through a HEPA exhaust filter. A volume of room air equal to that exhausted is taken into the cabinet at the front opening. This air does not penetrate the work area, but passes into the exhaust grille at the front of the work surface and into the return air plenum.

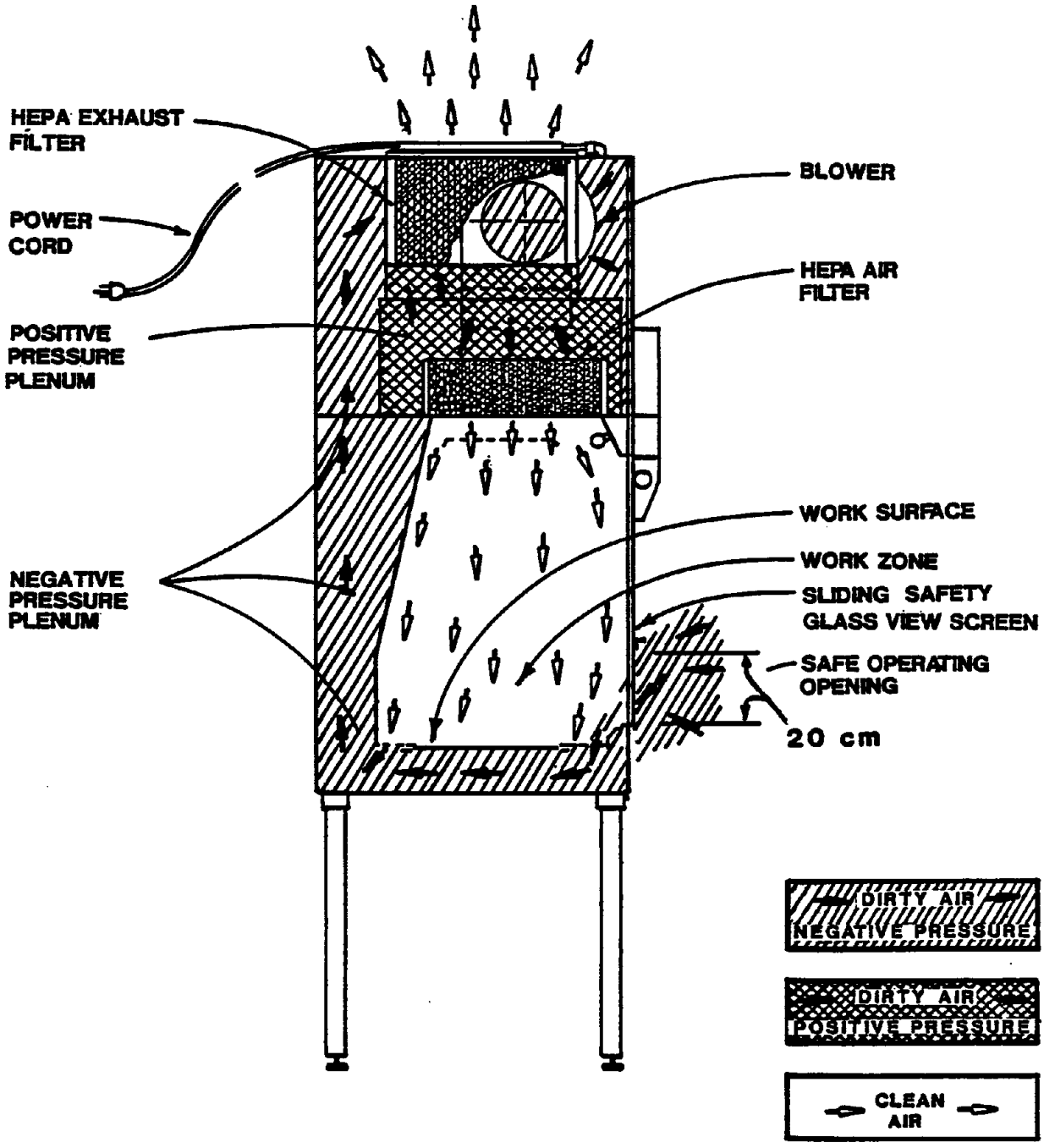

Figure 7. SterilGARD® hood in use at Plant A

The cabinet is equipped with a movable front-view window of 0.64 cm thick safety plate glass that can be raised to a maximal height of 60.9 cm to permit entrance of large items. However, when the hood is in use, the window may be raised only 20 cm.[3]

At Plant B, active ingredients are preweighed in the preweigh room within the confines of a Type A hood also manufactured by The Baker Company. The design airflow through this hood is 575 cfm. NIOSH measurements indicated a flow of 620 cfm through the hood. The exhausted air is ducted to the dust collector, an American Air Filter, FABR, pulse unit, which has a rated particulate filtration efficiency of 99.9 percent at 1 um. The capture characteristics of the hood are such that an air velocity of 100 fpm is obtained at the front end of the balance, where dust may be generated in transferring ingredients from one container to another.

At Plant C, both active ingredients and excipients are preweighed in two separate hoods in a room dedicated for this purpose. The hood used to preweigh actives has a control velocity of 52 fpm obtained at the point where pure active ingredients are likely to be dropped into a receiving container from a scoop. Since the container of actives is likely to be placed deeper into the hood (right hand side), a higher control velocity would be obtained in that vicinity.

At Plant C, excipients are preweighed in a booth. An overall control velocity of 81 fpm is achieved across the face of the booth. Additionally, there is a semi-circular flanged slot hood in front of which excipients are weighed into fiber drums. The geometry of this hood is such that the slot is just above the top of the drum. Control velocities ranging between 50 and 140 fpm, were measured at the critical points.

At Plant D, face velocities of about 100 fpm were reported in the hood where actives are preweighed. Because of the geometry of the hood, such face velocities would result in control velocities that are slightly higher than 100 fpm around the weighing activities.

General Ventilation

Ventilation air is supplied to provide dilution of contaminants, to satisfy part or all of the requirements of local exhaust systems, or both. The air is provided by air handling systems which will be discussed later.

In the preweigh room at Plant A, air supplied at the rate of 1.4 RVPM at one end and exhausted at the rate of 1.3 RVPM at the other end producing a laminar flow. An additional 0.2 RVPM is continuously exhausted through the SterilGARD(R) hood. Therefore, a negative pressure relative to surroundings is maintained in this room. The supply (return) and exhaust plena are shown in Figure 8, which is a schematic representation of the preweigh room. Distribution of the supplied air across the face of the plenum is achieved by covering it with sheet steel perforated with 1/4-inch holes.

At Plant B, air is supplied at a rate of 0.15 RVPM and completely exhausted through the preweigh hood at a rate of 0.19 RVPM. Again, a negative pressure relative to surroundings is maintained in this room. To maintain this negative pressure when either of the two access doors is opened, switches attached to the doors cause motorized dampers, which control air supply, to close.

At Plant C, 1.19 RVPM is supplied and 1.37 RVPM is exhausted through the two hoods (actives and excipients). Negative pressure with respect to surroundings is maintained.

GRANULATION

Sources of Dust Generation

In the production of granulation, dust containing the active ingredients may be generated from a number of sources. These include: (1) material transfer operations such as dumping the contents of the blender into drums or other containers, (2) milling of the dry granulation, and (3) charging the blender and/or the mixing tank with active ingredients.

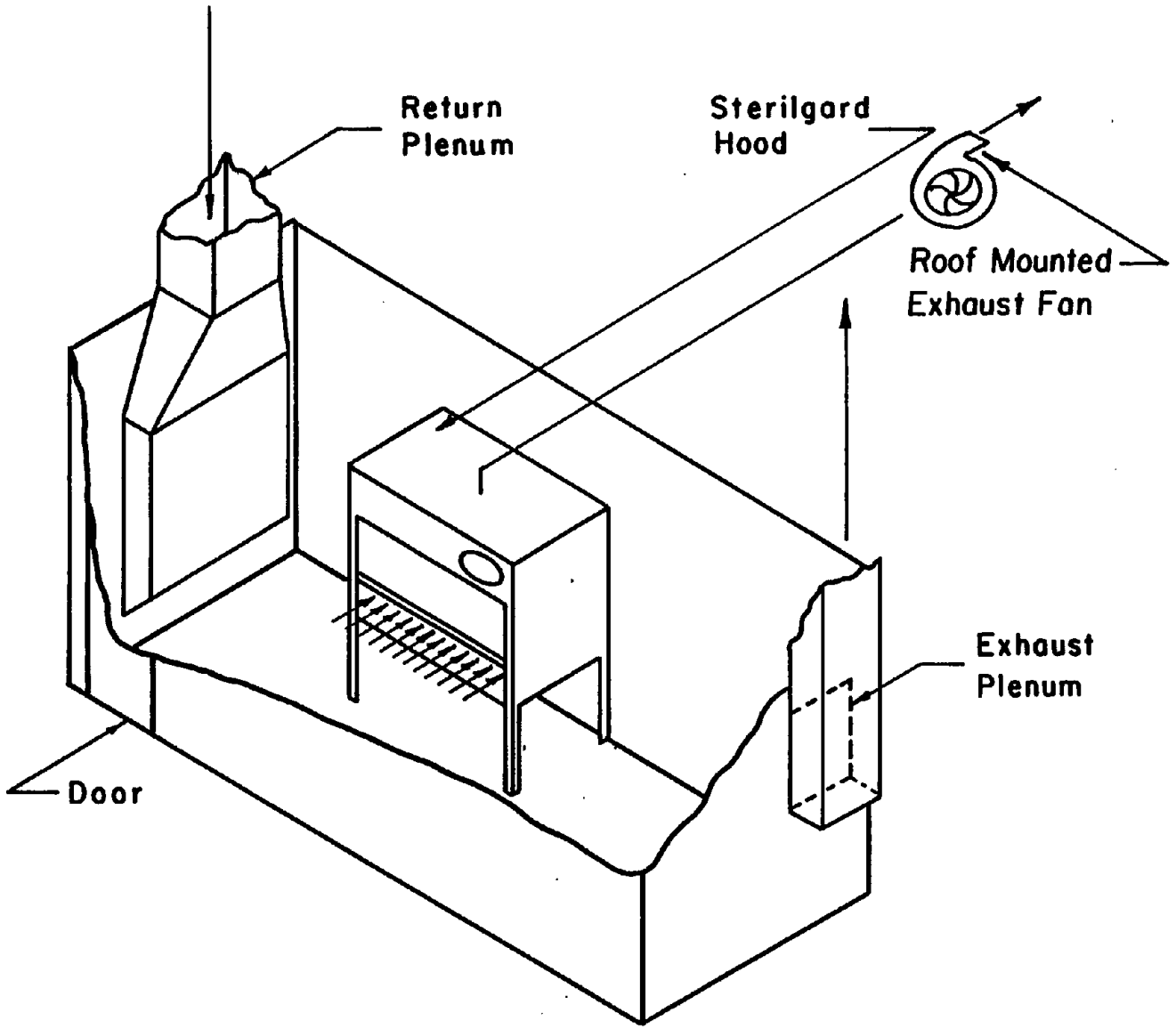

Figure 8. Weigh room and ventilation controls at Plant A

Controlled Access to Processing Area

Access to the area where granulation is produced is always through some type of air lock in which, ideally, the worker removes street clothing and dons personal protective clothing upon ingress to the area. Upon egress from the area, the worker decontaminates outside surfaces of protective clothing and showers before putting on street clothing.

At Plant A, access to the area where granulation is produced is controlled as shown in Figure 9. Workers proceed from the office to the air lock. An alarm sounds when both doors of the air lock are open simultaneously. Workers enter the change room, remove their street clothing, and don protective clothing. They then enter the degown room where they don respirators before entering the processing area. Upon returning from the process area, they degown (or remove protective clothing) under the laminar flow hood in the ceiling. They then proceed to the shower room, where they are required to take a shower before putting on their street clothes in the change room.

Air is exhausted from the air lock at about 1.0 RVPM (estimated). Air is supplied to the change room at a rate of 0.25 RVPM. Air is exhausted from the shower room at a rate of 0.15 RVPM. The ventilation scheme in the degown room is a company design which simulates an "air shower" to remove dust from outside surfaces of protective clothing and respirators. Air at the rate of 1.0 RVPM is supplied at one end of the room from a plenum. Air is exhausted at the other end of the room (4.0 RVPM). This exhaust air is divided into two parts. One part (2.4 RVPM) is returned to the cooling/air-conditioning system, while the other part (1.6 RVPM) is recirculated to the laminar flow hood in the ceiling. This hood is fitted with a fan and a HEPA filter and distributes clean air over a 10-square-foot area at the rate of 100 fpm. An identical controlled access to tableting is employed at Plant A.

Access to all processing areas (granulation, tableting, and preweighing) at Plant B is through the locker rooms. The men's locker is diagrammed in Figure 10. The worker removes his street clothes in the locker room and dons personal protective equipment which is picked up from the "wet suit" room.

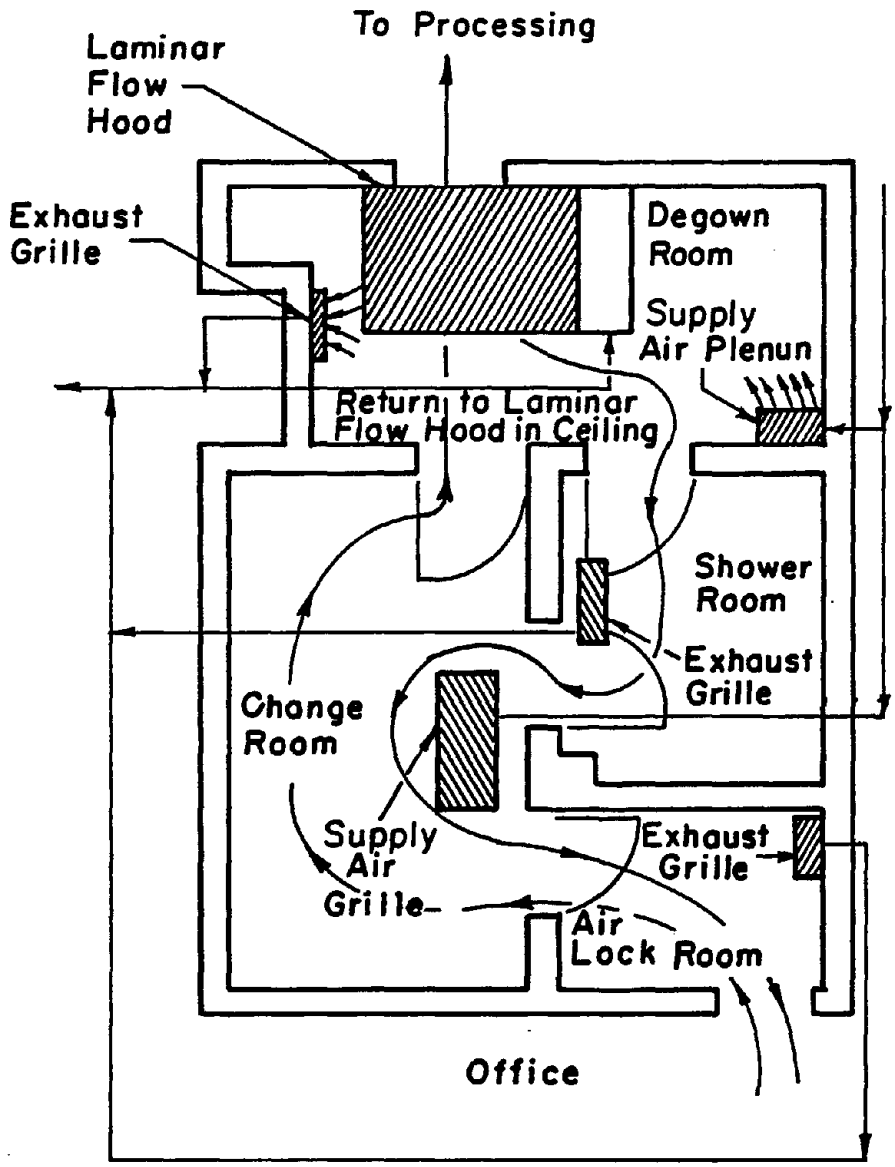

Figure 9. Controlled access to processing area at Plant A

	AIR SUPPLIED CFM	AIR EXHAUSTED CFM
Suit Wash	55	55
Air Blast	50	50
Wet Suit	100	250
* Shower	100	100
* Toilet	150	150
Locker Room	750	500

* 250 cfm are transfer air to toilet and shower

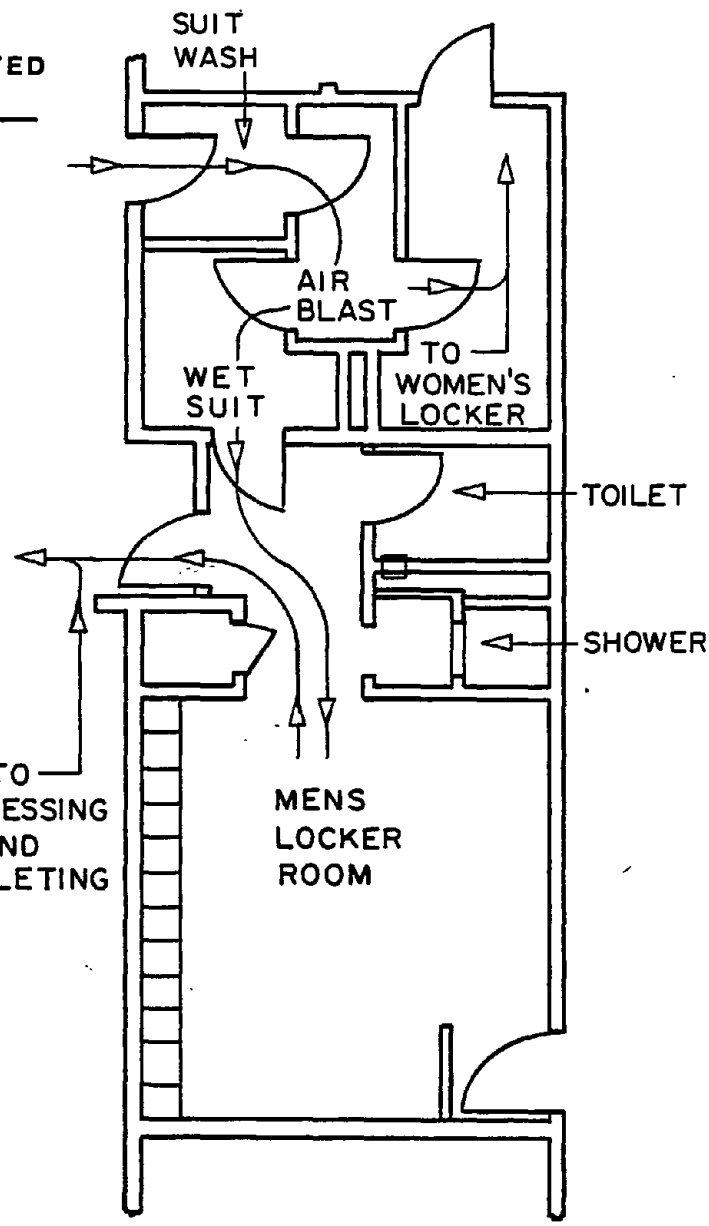

Figure 10. Controlled access to granulation and tableting at Plant B

The worker then enters processing from the entry door shown in the diagram. The worker returns through another door leading to the suit wash, where jets of water remove particulate from the outside surfaces of the suit. The worker proceeds through the air blast to the "wet suit" room where he takes the vinyl suit off and hangs it to dry in an appropriate location. The design ventilation airflows and air distribution scheme are also shown.

At Plant C, access to the area where granulation is produced is through an air shower. When the worker needs to exit the processing area, he or she proceeds to the first door of the air shower. Opening the door activates the air nozzles and jets of air impinge upon outside surfaces of protective equipment and clothing. Air is exhausted from the air shower enclosure through a grating in the floor. While the air nozzles are activated, the second door (that which leads to the process area) will not open for a predetermined period controlled by a timer. When the workers enter the process area and open the second door, the air nozzles are also activated.

Local Exhaust Systems

At Plant A, excipients are charged into the blender through a hopper located in the excipient dump room, which is directly above the blender room. An airtight connection is made between blender and hopper through a pipe connection which is flanged at the lower end to facilitate attachment to the discharge end of the blender. A rotary feeder is installed at the hopper bottom as an aid in the charging operation. A circular hood attached to one of the four sides of the hopper is intended to control dust emissions. Active ingredients at Plant A are added to small tank containing granulation liquid. Local exhaust in the form of a circular unflanged hood is employed to capture dust which may become suspended while charging the tank with actives.

At Plant C, the blender is charged with excipients through the ventilated hopper shown in Figure 11. Air is exhausted by six slots that are intended to control dust emissions while dumping the materials from fiber drums or bags. The capture characteristics of this local exhaust system are greatly influenced by the size and shape of the container being emptied into the

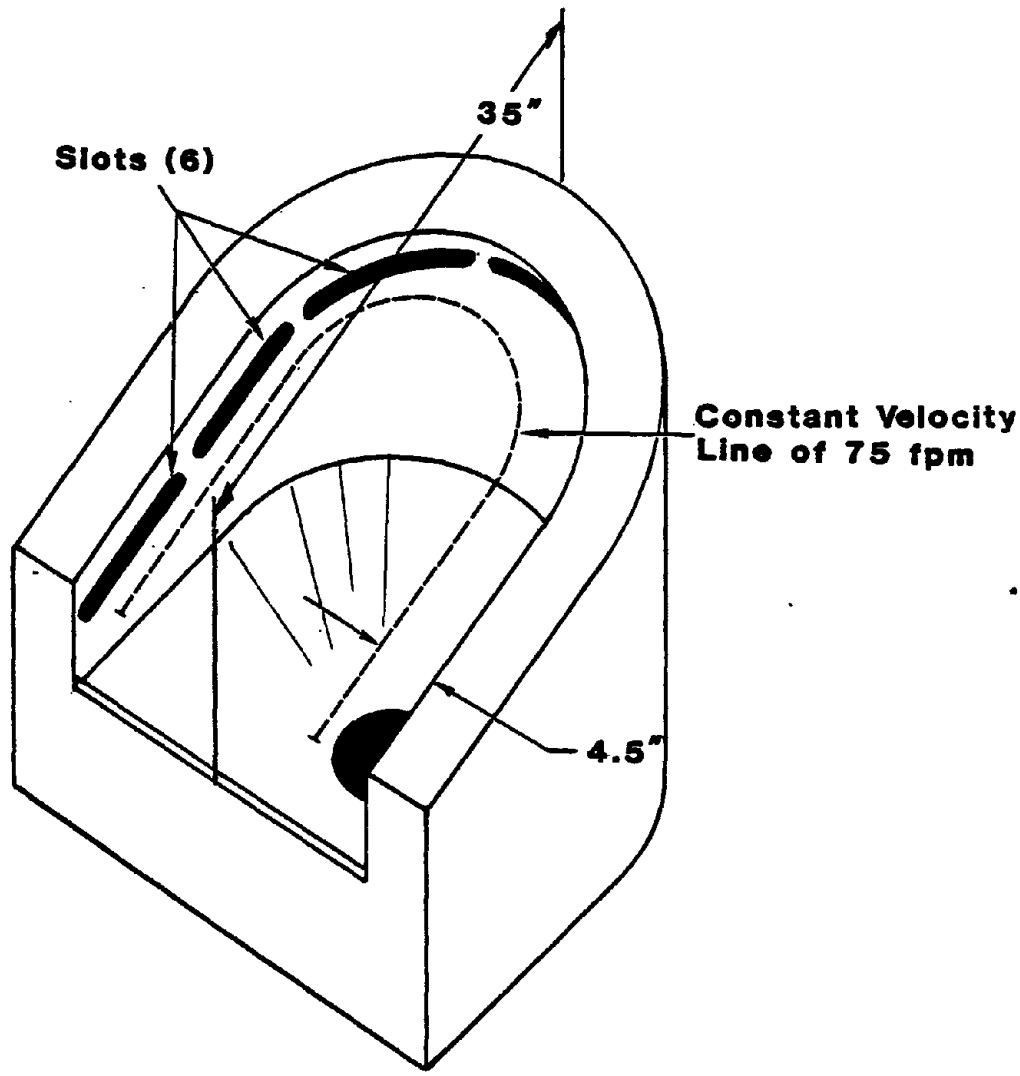

Figure 11. Charging hopper for excipients at Plant C

hopper. The individual slots may be visualized as flanged slot hoods with aspect ratios of about 0.06. From a knowledge of the flow in each slot, the constant velocity lines may be constructed as explained in Reference 4. The 75 fpm line was estimated to be 4.5 inches from the periphery. The actual control velocity field is altered favorably by the presence of a fiber drum in the space between the slots while dumping its contents. The presence of the drum causes the control envelope to expand to cover a larger space.

Active ingredients are dissolved in a granulation liquid contained in a small covered and agitated tank. Ventilation controls have been applied at two locations in the tank's cover as shown in Figure 12. At the point at where the actives are added to the tank, measurements by NIOSH indicate that a capture velocity between 150 and 200 fpm is obtained midway between the two slot hoods when the cover is open. To prevent the dispersion of granulation liquid vapors into the work area, the vapor space in the mixing tank is also ventilated as shown in the drawing.

When wet or dry granulation is discharged from the blender into drums at Plant A, dust emissions are controlled by the scheme shown in Figure 13. A drum enclosure with vacuum connections is placed over the drum. The blender flange is lowered by a pneumatically-driven mechanism and presses against a gasketed mating surface located on top of the drum enclosure. Material flow from the blender takes place through a gate valve. The level of material in the steel drum is periodically checked by elevating the blender flange. The total exhaust rate applied to the drum enclosure was estimated at 50 cfm. An improvement in the control would result if the granulation were discharged to a container with sufficient volume to hold the entire batch as is practiced at Plant B. Space limitations and constraints imposed by the operations of drying and milling preclude implementation of such a modification.

At Plant C, the wet granulation is discharged from the blender into the fluid bed dryer bowl under the local exhaust hood shown in Figure 14. Based on the total airflow and the geometry, capture velocities between 75 and 150 fpm were estimated. The lower figure would correspond to the capture velocity at the outer rim of the bowl. A similar local exhaust system is used to control dust

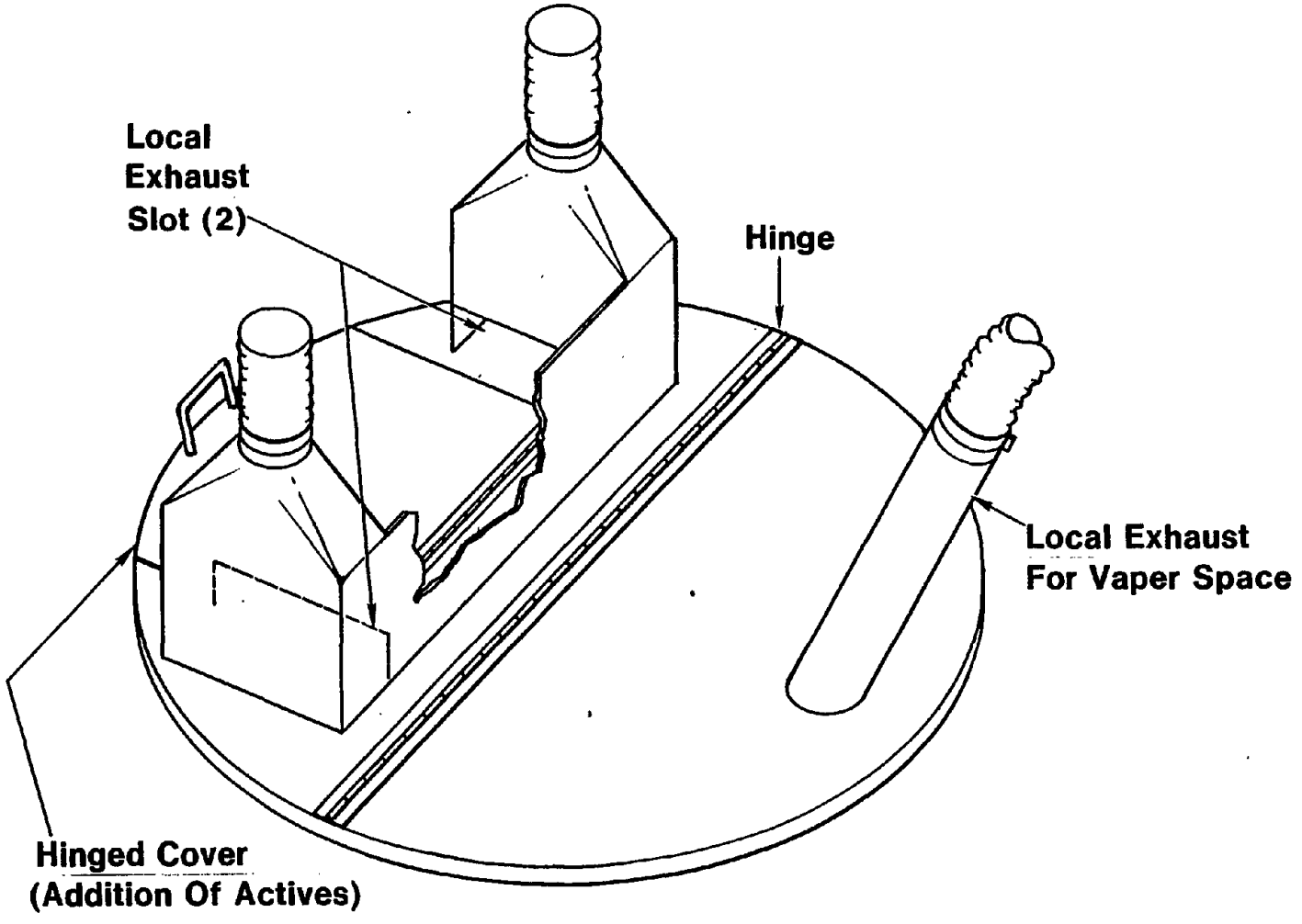

Figure 12. Ventilation of mixing tank at Plant C

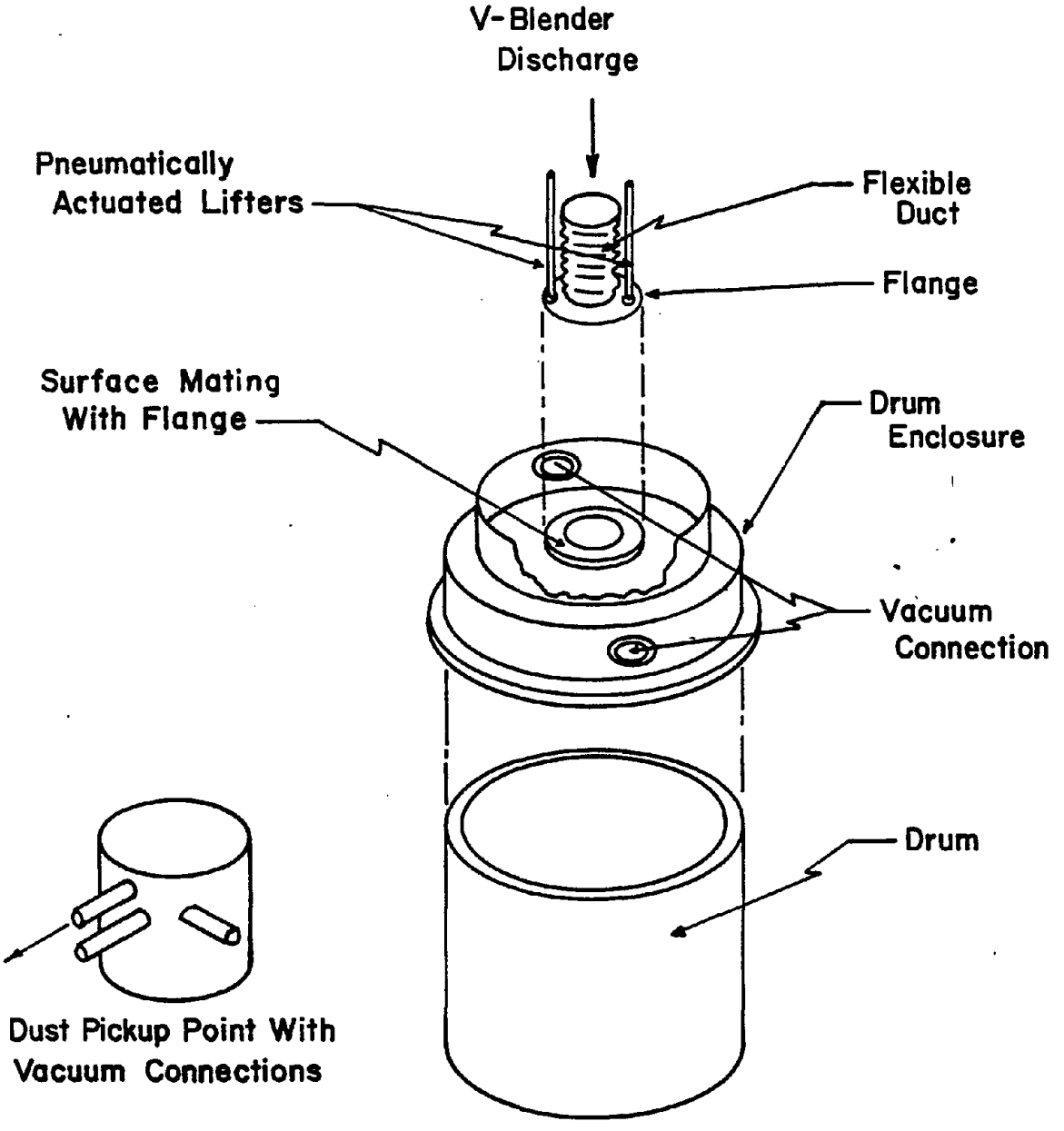

Figure 13. Dust controls associated with V-blender discharge. at Plant A

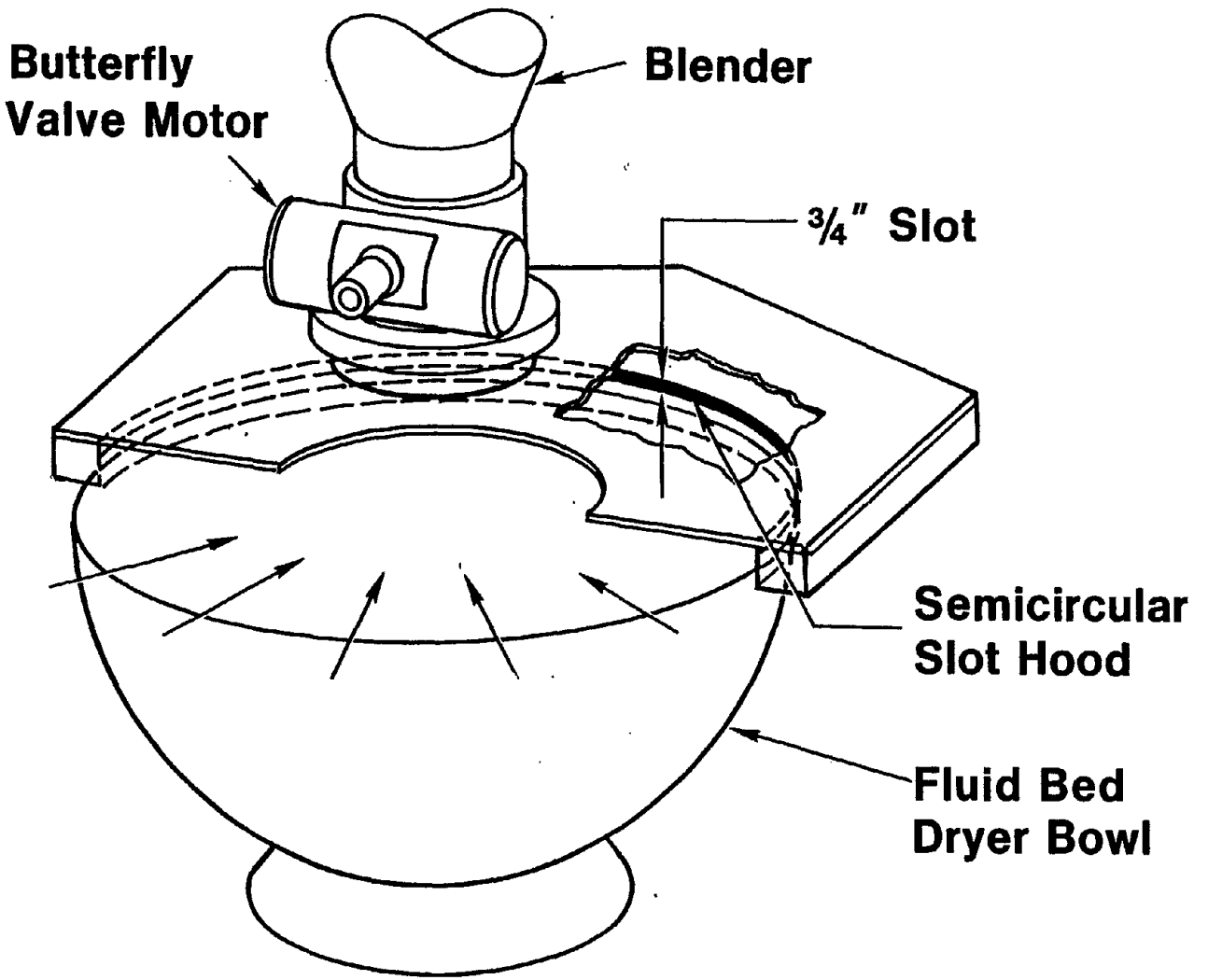

Figure 14. Local exhaust for dumping wet granulation from blender at Plant C

emissions when the dryer bowl is disengaged from the fluid bed dryer after drying is complete.

As mentioned earlier, dry granulation is transferred by vacuum from the dryer bowls to the double-cone blender via a tornado mill at Plant C. Emissions from the dryer bowl while material is being transferred are controlled by the local exhaust system shown in Figure 15. The measured control velocities at two critical locations (shown in the figure) control dust emissions while the wand of the vacuum transfer system (to be discussed later) is moved within the bowl during the transfer operation. Measurements conducted by NIOSH indicate a control velocity of about 150 fpm at the outer rim of the bowl.

At Plant D, dry granulation in fluid bed dryer bowls is milled in a tornado mill which discharges directly into a blender for a final blend. As may be seen in Figure 16, the top of the dryer bowl is covered and the bottom is attached to a funnel which discharges into the mill. The mill discharges into a hopper which in turn empties into the blender through a connection. The hopper is enclosed and the enclosure is ventilated at the rate of 100 cfm as reported by the company.

Material Transfer Systems

In all of the plants studied (A, B, and C), vacuum transfer systems designed and manufactured by Vac-U-Max(R) are employed in transferring excipients or dry granulation from individual containers to other process equipment. These transfer points are pointed out in the process flow diagrams for granulation presented earlier.

It should be pointed out at the outset that the Plant B granulation process has fewer transfer points than the other processes. Steroids may become dispersed in the processing area at Plant B when the progestogen is manually dumped into the blender, when the estrogen is introduced to the mixing tank, when the worker periodically obtains a sample of granulation during drying, and when residual granulation is manually removed from the interior surfaces of the blender when granulation is complete. When the drying part of the

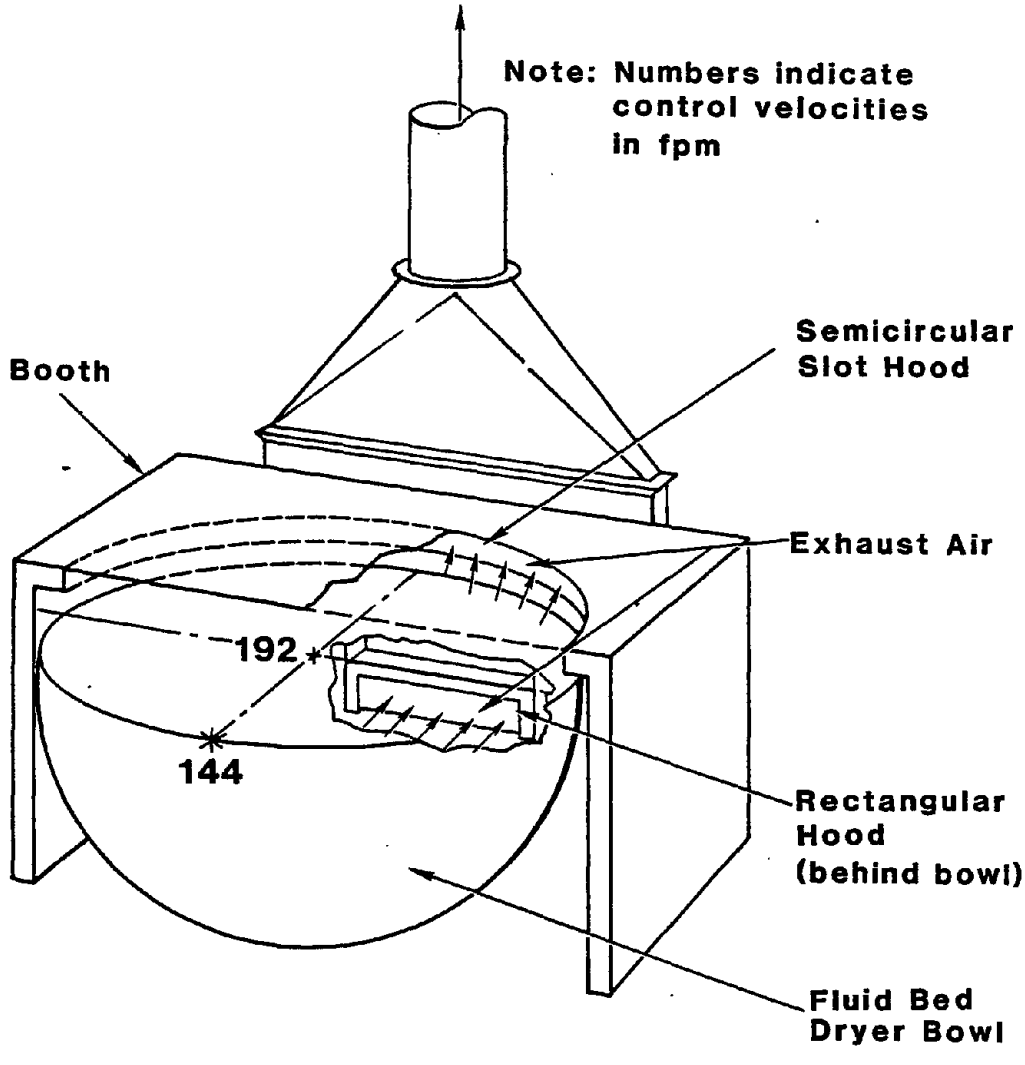

Figure 15. Local exhaust system used when transferring granulation from dryer bowl to mill at Plant C

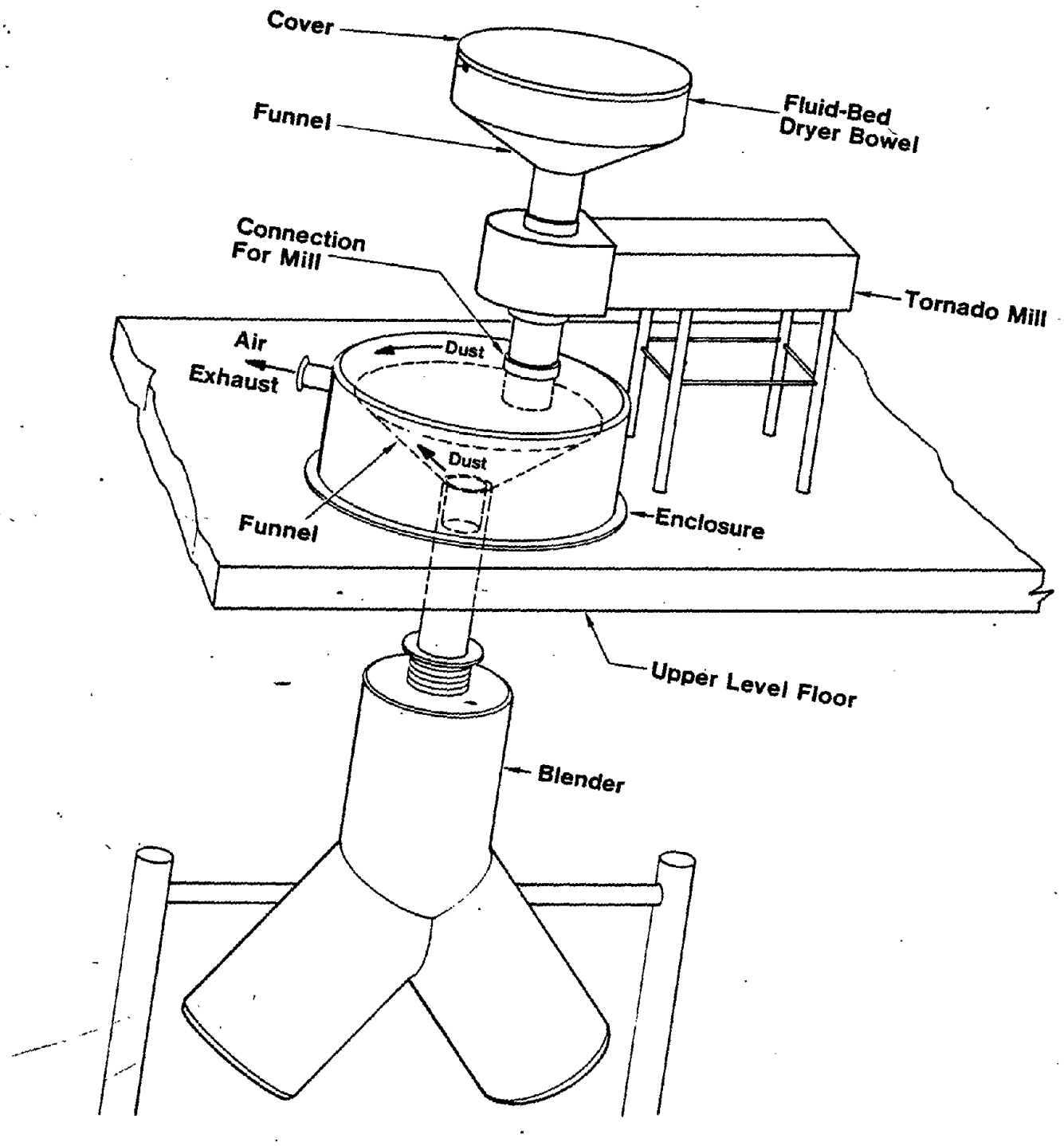

Figure 16. Ventilation controls employed in milling of granulation at Plant D

cycle is completed, the entire batch of granulation is dumped into a large container called a "capsule" through a flange connection between it and the blender. This is a recent development at Plant B. Previously, the granulation was emptied into the capsule under local exhaust without having an airtight connection between the capsule and the blender.

At Plant A, the granulation is milled in a Fitzpatrick(R) mill after drying in a tray dryer. The granulation is manually scooped from the trays into the hopper of the mill. The mill discharge is connected to a Vac-U-Max(R) vacuum transfer system which transfers the dry granulation to the blender for a subsequent short blend. The principle of operation of the transfer system is shown in Figure 17. Vacuum is generated by a pump. A three-way valve is used to connect the filter housing and filter drum to either the return air system or the vacuum pump. When transferring material from the mill, the pump is operating in-line with the filter housing and blender. After a certain time of operation in this mode, the filter becomes clogged with powder. The operator at this point turns the three-way valve so that air from the return system flows towards the blender, thus blowing back any material in the filter.

A similar system is used at Plant B to transfer excipients from fiber drums to the blender. The scheme used there is shown in Figure 18. Vacuum is developed by the vacuum pump and powder mixed with air moves through the lines to the blender. The small amount of powder that does not settle in the blender is intercepted by the canvas filter. As more powder deposits on the filter, it becomes plugged - thus inhibiting airflow. In this case, "blowback" of the filter is necessary. This is accomplished automatically by closing the pinch valve and turning the three-way valve such that outside air flows toward the filter housing. The flow is induced by the vacuum which existed during the first part of the cycle. The sequence (blowback and material flow) is controlled by a timer. To protect the vacuum pump from being deadheaded during blowback, the safety valve opens when a preset vacuum level is reached in the suction side of the pump.

Dried granulation in fluid bed dryer bowls is milled in a tornado mill at Plant C. The vacuum transfer system used for transferring the granulation

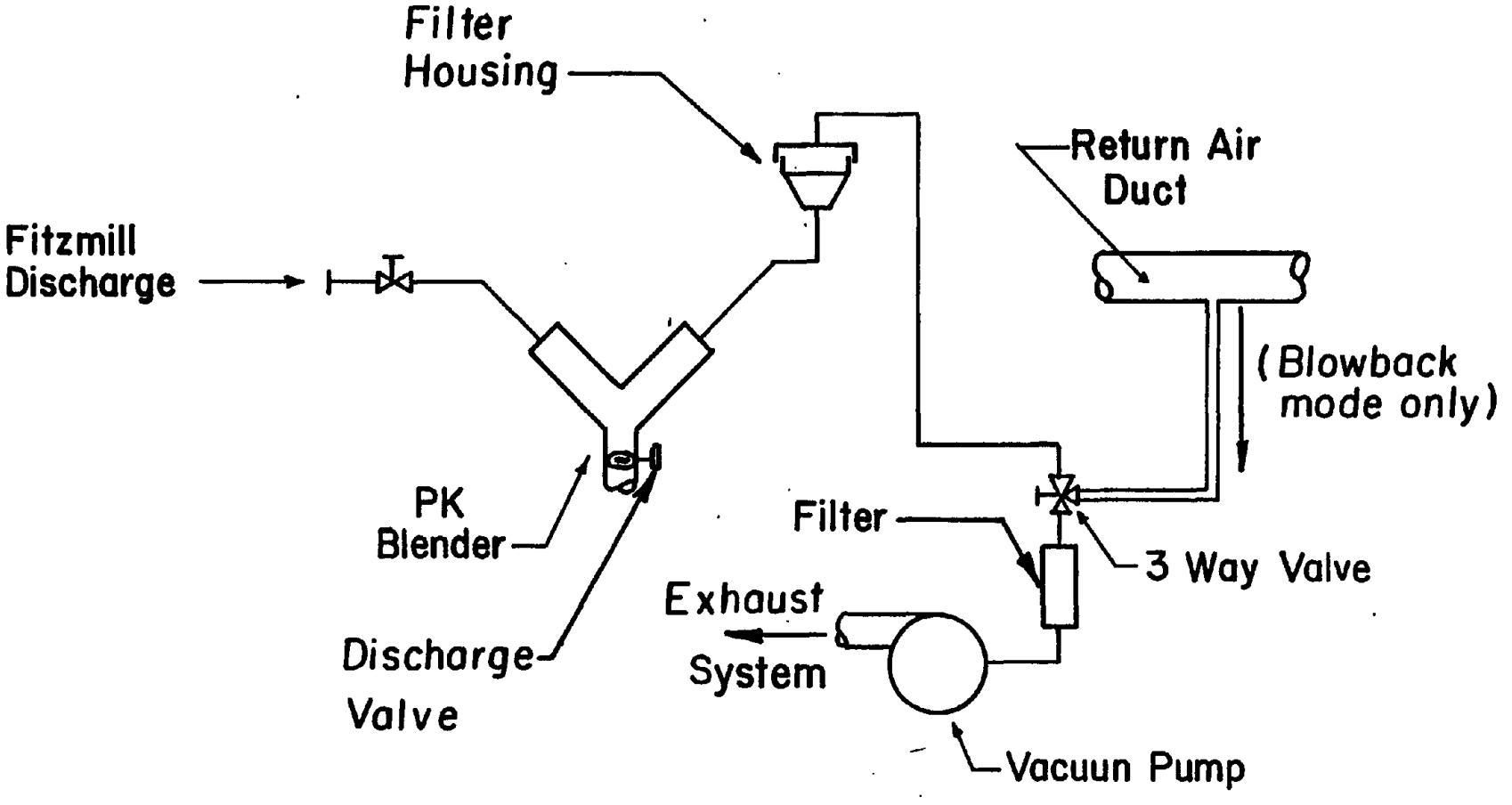

Figure 17. Vacuum transfer system at Plant A

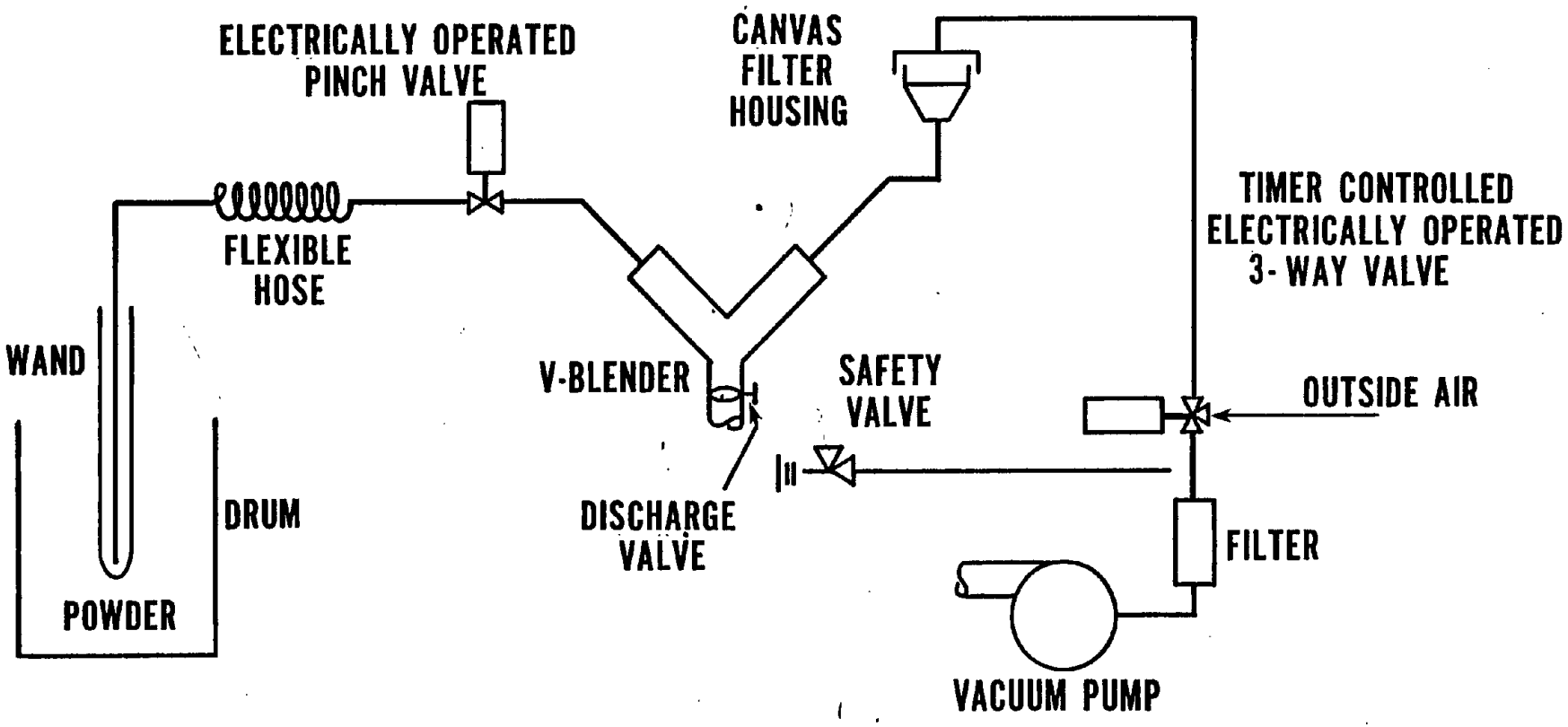

Figure 18. Excipient vacuum transfer system at Plant B

from the bowl to the mill and then to the double-cone blender for a final blend is shown in Figure 19. The worker wheels the bowl, places it into the ventilated semi-enclosure that was discussed earlier, inserts the wand into the powder, and turns the vacuum system on. Powder (in air) flows from the bowl to the hopper and accumulates there until the hopper is full. A filter in the top of the hopper removes powder from the air. The vacuum causes the "V" valve to close so that no powder is discharged from the hopper while it is being filled. This valve is constructed from neoprene or silicone and attached to the bottom of the hopper by a hose clamp. When the weight of the material in the hopper (as detected by a scale-type system) reaches a certain point, material flow stops and the "V" valve opens to discharge powder into the throat of the mill. The rate of material flow (by gravity) is controlled by raising or lowering the height of the "V" valve relative to the slope of the throat of the mill.

The mill discharges into a vacuum receiver connected to the mill housing by a cloth skirt. Powder in the receiver is continuously transferred by a second vacuum pump to the double-cone blender for a final short blend.

The finished granulation is emptied into fiber drums under local exhaust, using the drum filling scheme shown in Figure 20. The drum is placed on the platform which is raised upward pneumatically until the drum is totally covered by the coverplate. An airtight seal between the drum and the coverplate is obtained. The discharge valve of the double-cone blender is fully opened and granulation flows into the drum until the level reaches the extension. Powder flow stops and the blender valve is closed.

General Ventilation

Air is supplied to various processing areas through grilles or plena to either satisfy the requirements of local exhaust systems as at Plant C, or to dilute contaminants in the work environment as at Plants A and B. In the latter case the air is, at least partially, exhausted through appropriately located exhaust grilles. To ensure that process areas are isolated, air is exhausted

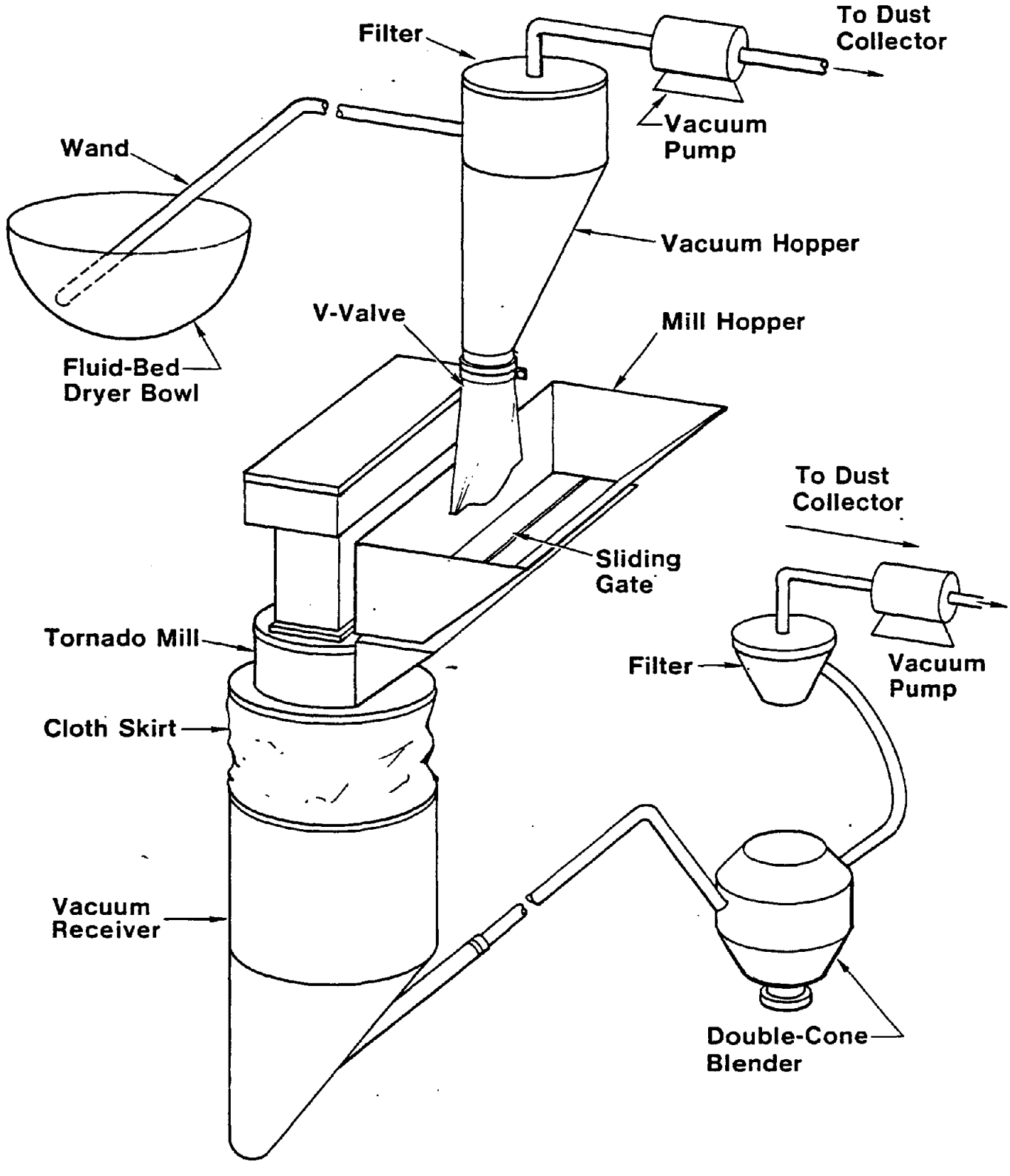

Figure 19. Vacuum transfer system in milling at Plant C

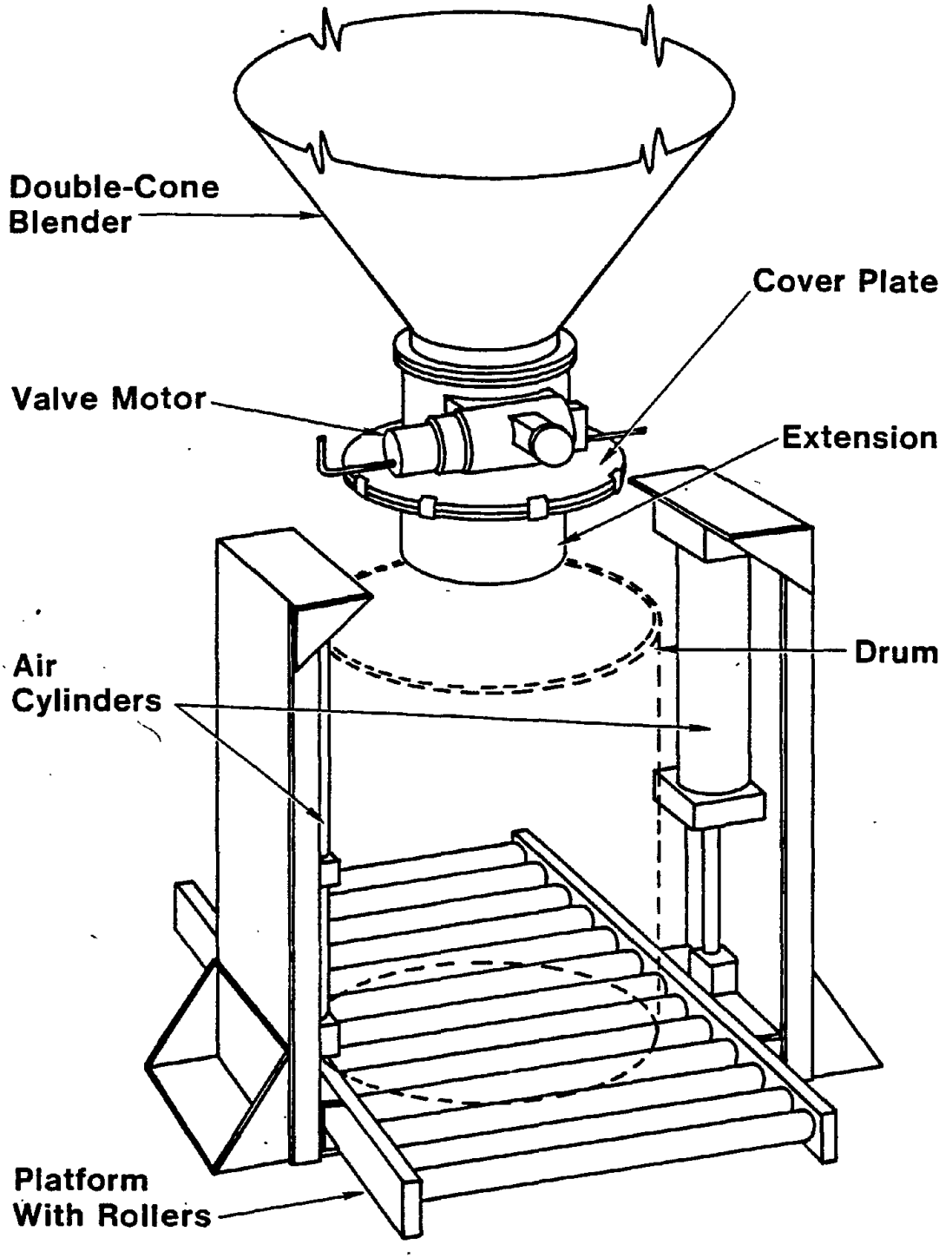

Figure 20. Drum filling system at Plant C

at a greater rate than it is supplied. In the following paragraphs, a number of general ventilation schemes will be discussed.

In the oven room at Plant A, air from two plena is supplied at the rate of 1.3 RVPM. Air is withdrawn from the room in the exhaust plenum and from the crawl space behind the ovens at the rate of 1.6 RVPM. The oven room and ventilation controls are shown in Figure 21. Makeup air for the ovens is obtained from the outside. It is filtered and preheated. Air discharged from the ovens contains granulating liquid vapors and is totally filtered and exhausted to the outside through a high riser.

At Plant B, general dilution ventilation is employed in the room where the blender is located as shown in Figure 22. The supply and exhaust grilles are at ceiling level. The supply grilles are designed to deliver the supply air to within a few feet of floor level. Air at the rate of 0.03 RVPM is exhausted to the dust collector and 0.068 RVPM is exhausted to the air handling system through the grille in the ceiling. Air is supplied at the rate of 0.083 RVPH through the two supply grilles in the ceiling. The motorized damper shuts off the air supply when either the double door leading to the hallway or the one leading to the room where approved granulation is stored or both are opened. Switches, located at these doors, activate the motorized damper. Shutting off the air supply when the doors are opened has the effect of preserving positive air infiltration into the room where the blender is located.

Air Handling Systems

At Plant A, about 40 percent of the exhausted air (which includes clean air from surrounding areas) is HEPA-filtered before being emitted to the atmosphere. The balance is returned to the air-conditioning/cooling unit which serves the oven room, blender room, weigh room, and the staging area. This unit consists of HEPA filters, cooling and heating coils, a humidifier, and a damper for the control of pressure drop across the filters. None of the air exhausted from the oven room is returned to the A/C cooling unit when granulating liquid vapor is present in the air (when handling wet granulation).

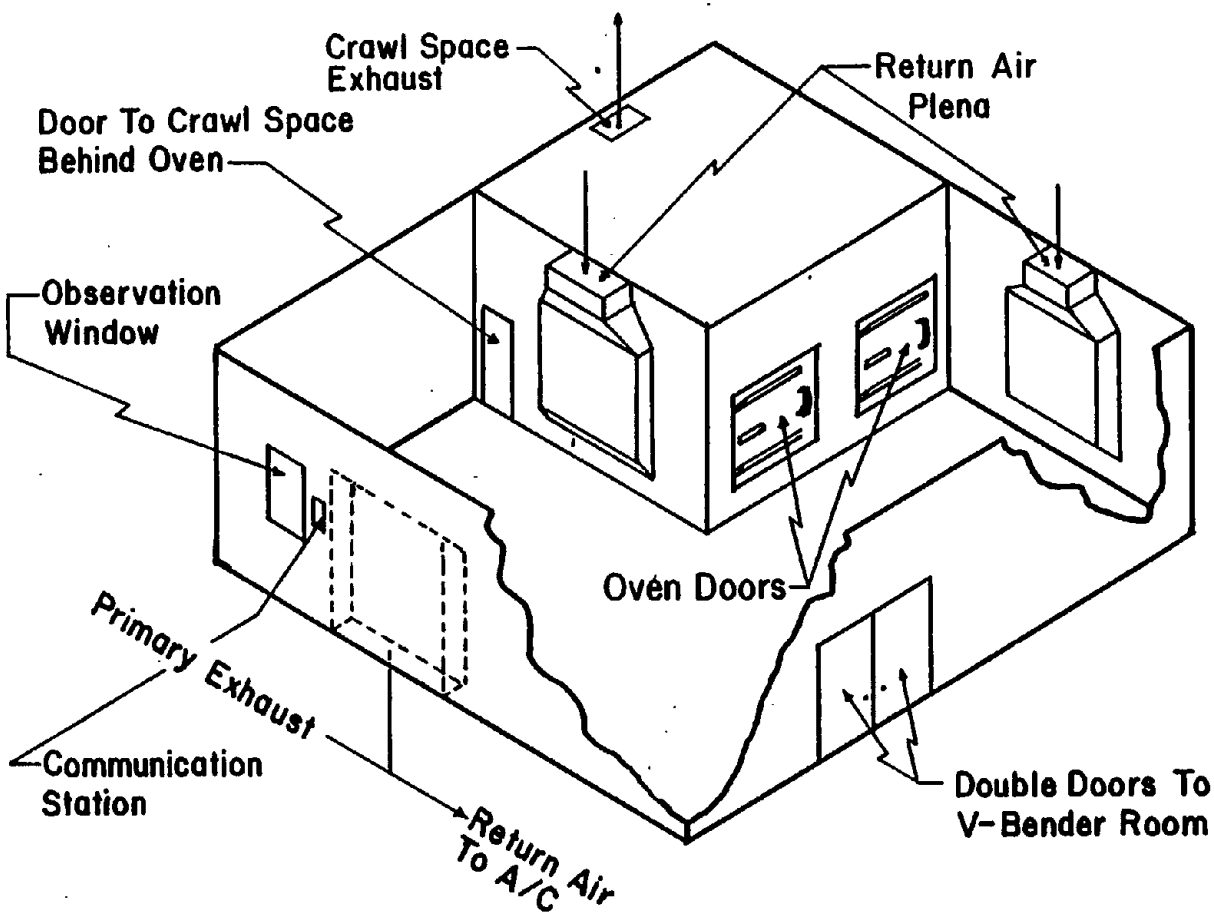

Figure 21. Oven room and ventilation controls at Plant A

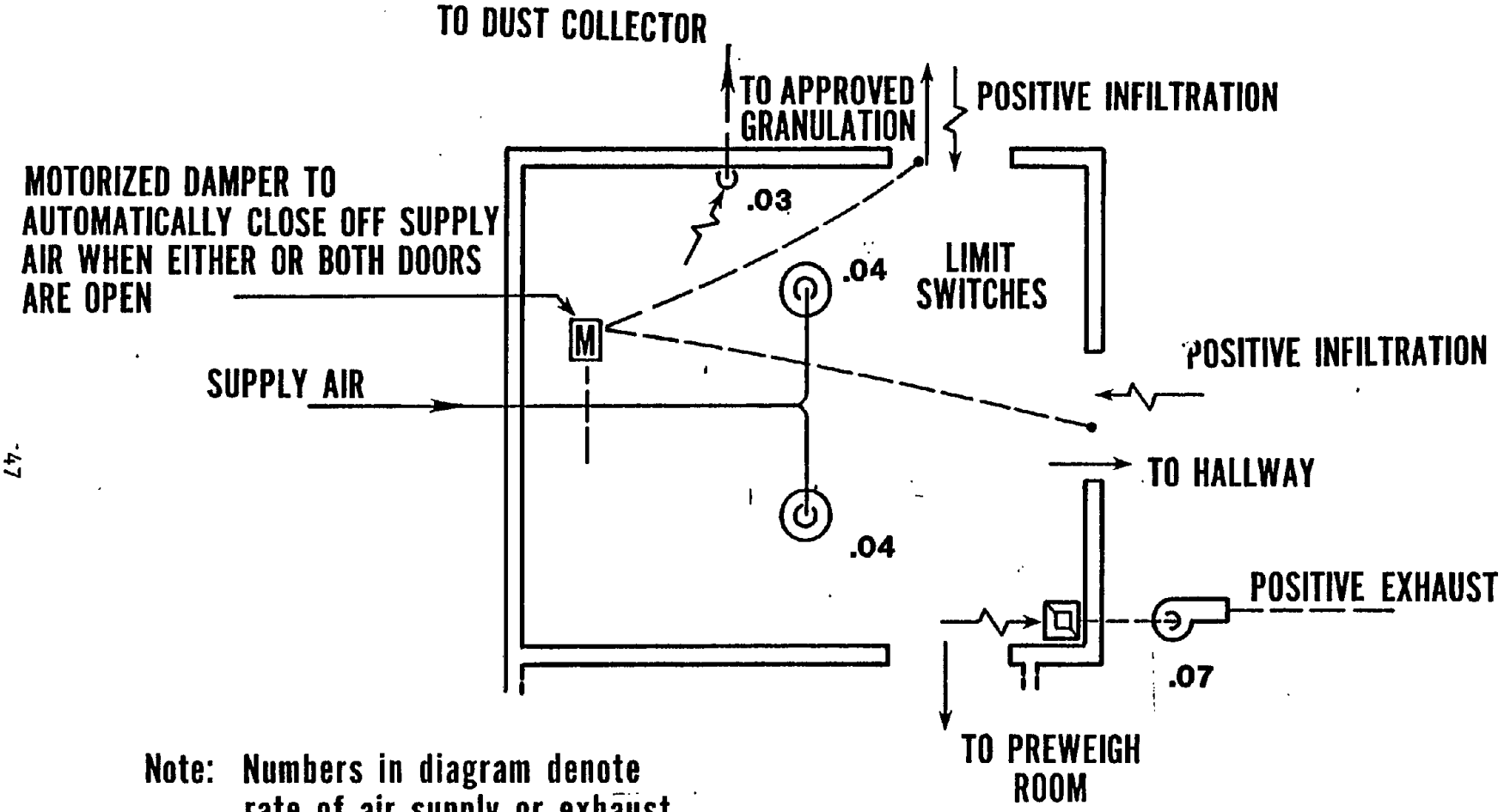

Figure 22. Plan view of processor room showing ventilation controls at Plant B

The areas (rooms) served by this unit are maintained at a negative pressure relative to surrounding areas. This is achieved through static pressure control of the inlet vanes on the primary system exhaust fan.

At Plant B, air supplied to, and exhausted from, the manufacturing rooms, corridors, and packaging rooms is handled by one of two central air handling units. Each air handling unit is similar in design with respect to filters and airflows. These air handling units, working in conjunction with localized exhaust fans, secondary recirculation air units, and a centralized dust collector, provide the required building ventilation.

All sources which are likely to produce relatively "concentrated" streams are exhausted to the dust collector. These sources include the hood in the preweigh room, local exhaust systems associated with the tableting machine, and those associated with the circular pack filling machine. The dust collector is a device with a rated particle filtration efficiency of 99.9 percent with respect to dust particles 1.0 micrometer (um) in diameter.

Air exiting the dust collector is combined with building return air before treatment and conditioning. The air passes through two prefilters and one HEPA filter with a rated removal efficiency of 99.97 percent with respect to particles at 0.3 um in diameter. A minimum of approximately 10 percent of this building air is exhausted to the outside. Fresh outside air in a quantity slightly higher than was exhausted is then mixed with the remainder (approximately 90 percent). This air is prefiltered, cooled, and HEPA filtered. It constitutes air returned to the various areas served by the system. Reheat coils and humidifiers are installed in the ductwork which serves various rooms.

At Plant C, no air recirculation is practiced. The supply air consists of air that is cleaned and conditioned as explained for Plants A and B. Particulates are removed in a baghouse.

TABLETING

Sources of Emission

In the tableting operation, there are three potential sources of dust emission into the work area. The first source may be the operation of filling the machine hoppers with granulation. If, for example, these hoppers are filled manually by scooping powder from a drum into the hoppers, it is obvious that there are opportunities for suspension of fine dust into the work area. In evaluating the effectiveness of the hopper feed systems to be discussed later, it is useful to compare them to the uncontrolled situation just described.

The second potential source of dust emission is the feeding of the individual dies with granulation and, more importantly, the two pressure points where the upper and lower dies move toward each other to compress the tablets.

Finally, the tablet testing operations may be a source of emission. These operations may include periodic friability and gravimetric tests.

Controlled Access to Tableting

Tablet machine operators at Plants A, B, and C enter the tableting room in a manner similar to that described for the granulation production process.

Powder Feed Systems

At Plant A, the granulation feed system to the two hoppers is totally enclosed and airtight. A schematic of the feed system is shown in Figure 23. The metal drum containing granulation is securely clamped into the cage. The cover is removed and the funnel adapter/valve assembly is fastened to the rim of the drum. A tight seal is obtained there by a rubber gasket. The Y-assembly also attaches in an airtight fashion to the adapter and the two hoppers. As shown in the figure, the cage which holds the drum may be moved vertically and rotated by the especially designed hoist.

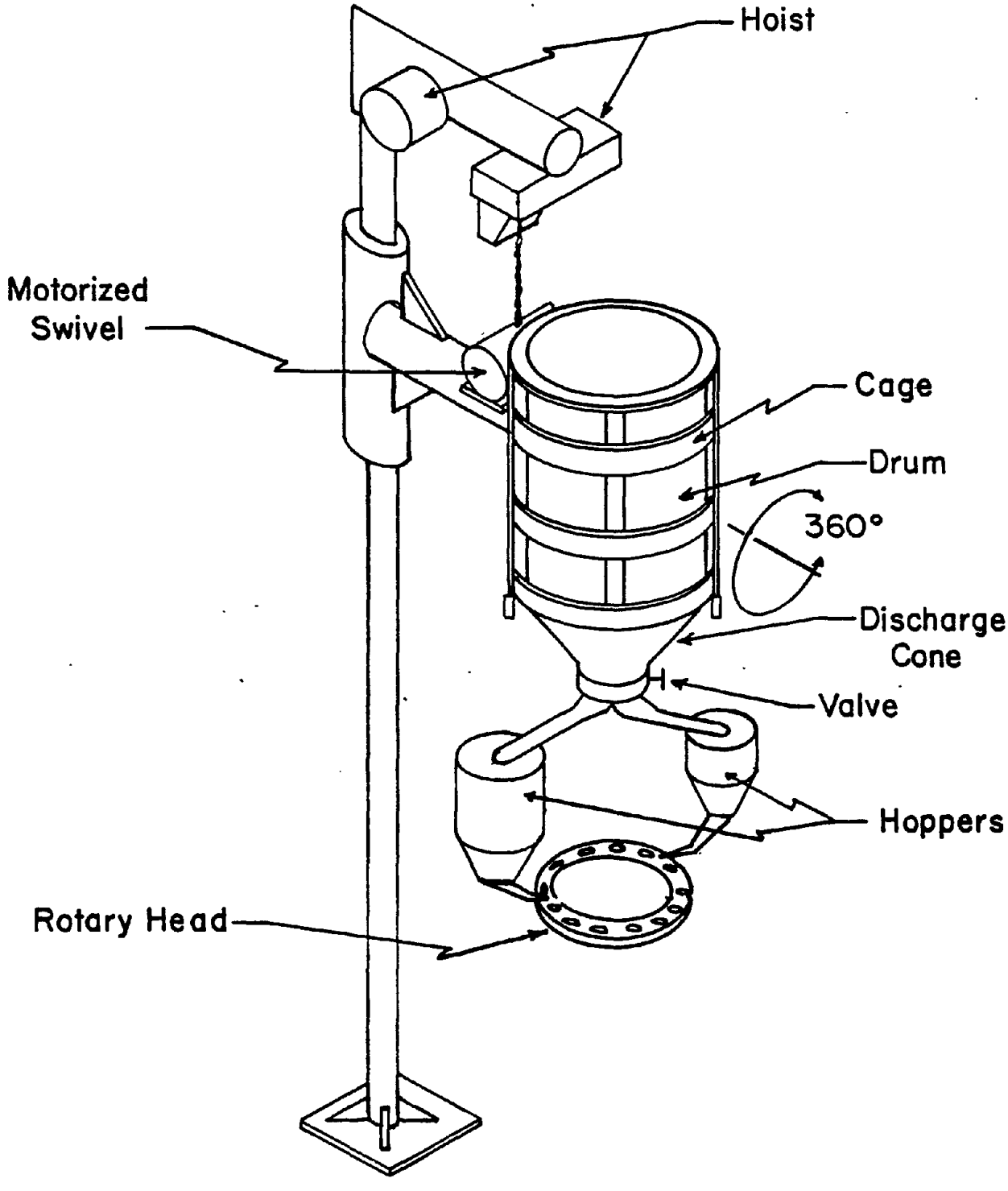

Figure 23. Tablet machine feed system at Plant A

At Plant B, the tableting machine force-flow feeders are fed with powder from a completely enclosed powder feed system shown in Figure 24. The capsule full of powder is hoisted to a mezzanine above the machine and positioned, using a hoist, over a flanged connection to the pipe which delivers granulation to the screw conveyor. Optical level sensors located at a certain level in the pipes which feed granulation to the force-flow feeders control the direction of rotation of the spiral (or screw) conveyor inside the sleeve which determines whether granulation is being fed to the right or left leg.

At Plant C, granulation is transferred from fiber drums to the two force-flow feeders of each tableting machine using a Vac-U-Max(R) vacuum system which is shown in Figure 25. A wand is inserted into a fiber drum containing granulation and when vacuum from a central system is turned on, granulation mixed with air flows to the vacuum receiver (hopper) and falls to the bottom. Particulates in the air are removed by a filter located in the receiver's top. The "V" valve, which is clamped to the bottom of the hopper, closes when vacuum is applied. The valve opens when the vacuum is released and the granulation flows to the intermediate hopper at a rate determined by the location where the "V" valve is clamped to the bottom of the hopper. The bottom end of the "V" valve extends some distance into the intermediate hopper, and when the level of powder in the hopper reaches a predetermined point, the flow stops because the bottom of the "V" valve is completely buried.

The central vacuum system serves a number of machines. A level sensor (float) in the intermediate hopper signals the central control system when the level of granulation has dropped below a preset level. In addition to this feedback from the float, the control system has been designed to "seek and find" whether any of the machines requires powder by sequentially polling the signals from the floats. If the control system detects a machine that requires granulation, it completes service to the machine that is currently occupying the control system, then switches the vacuum source to the machine which requires granulation. If two or more machines call for material at the same time, vacuum is provided to each machine sequentially for 30-second periods.

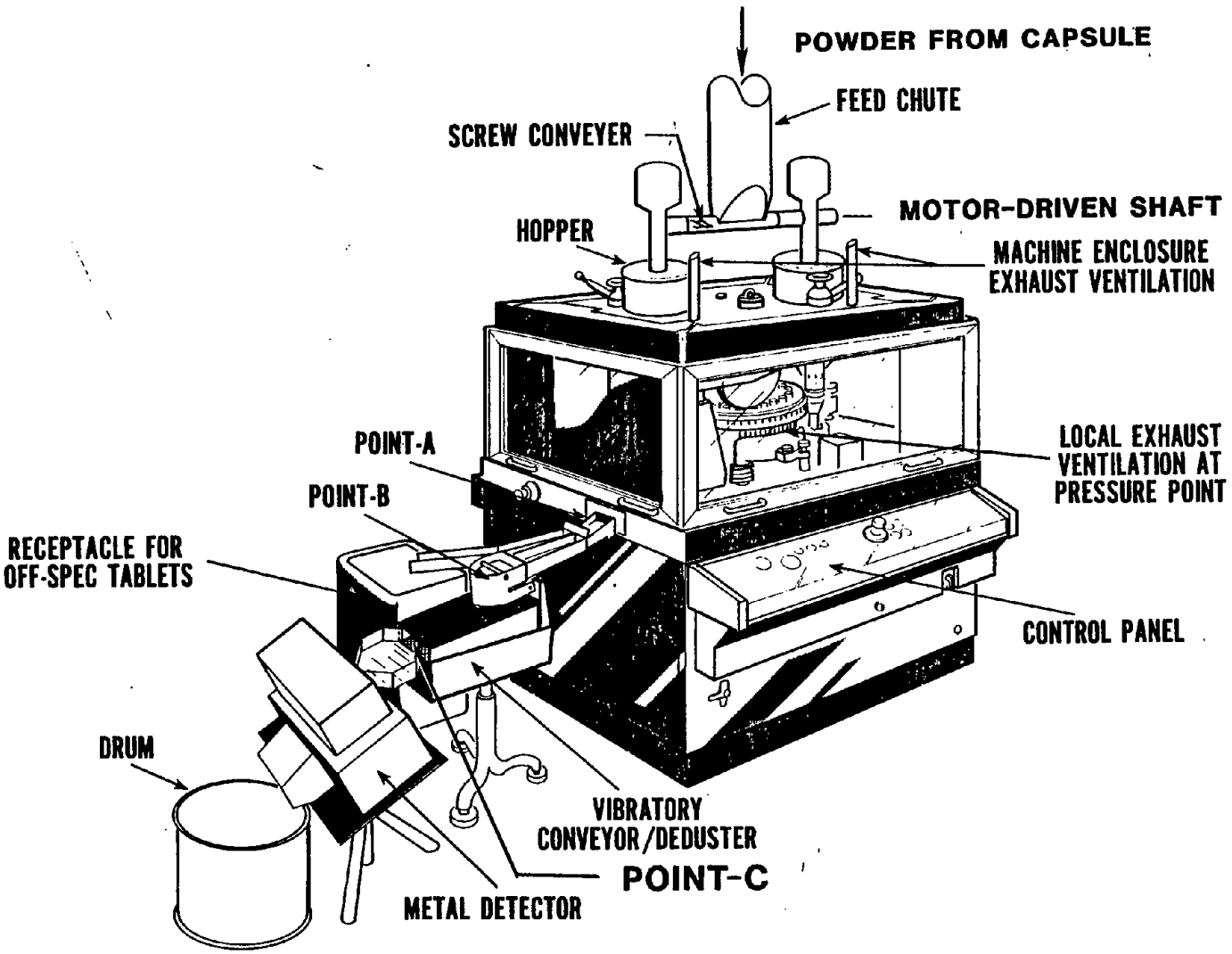

Figure 24. Tableting machine and controls at Plant B

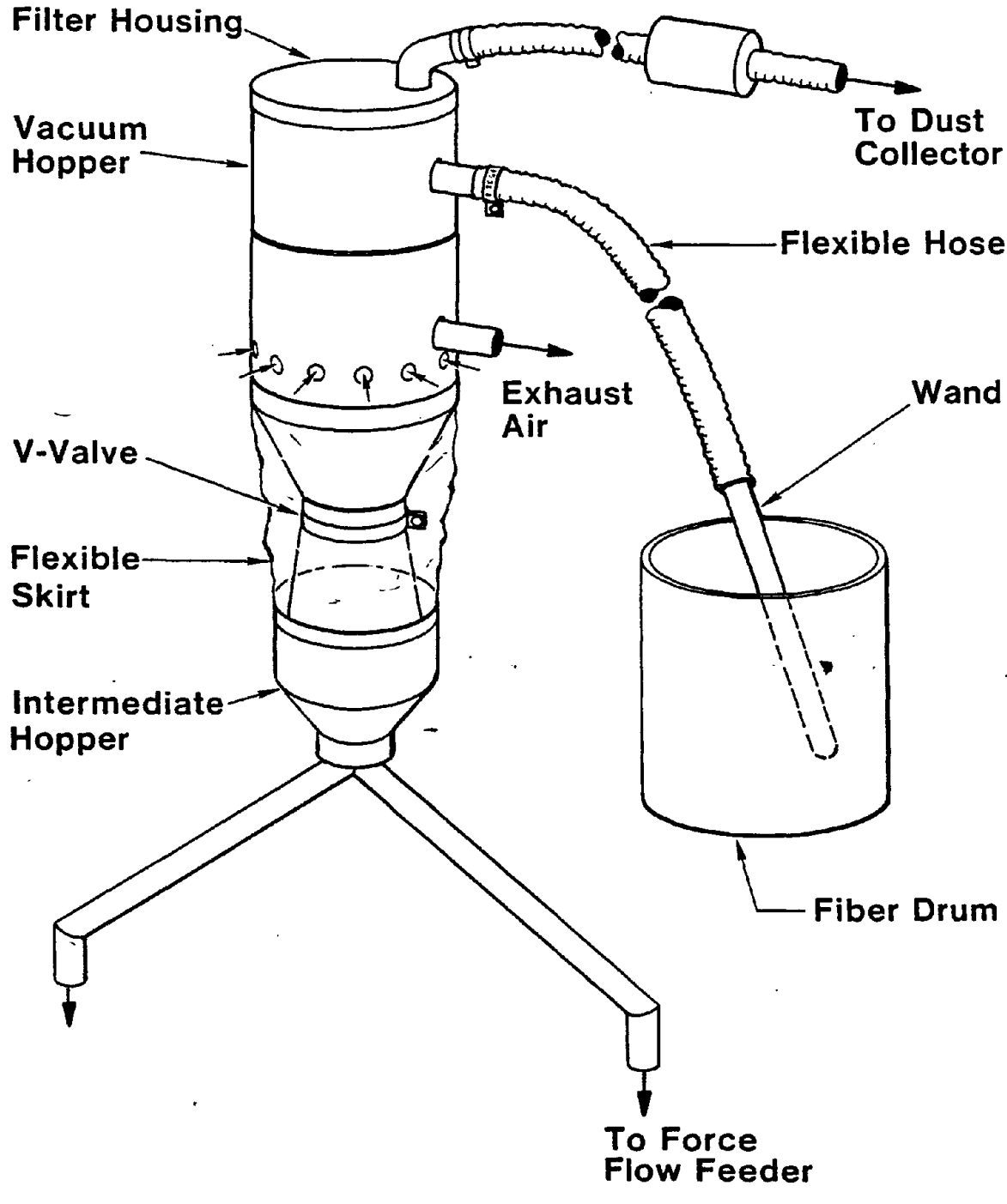

Figure 25. Tableting machine powder feed system at Plant C

At Plant D, granulation is fed to the tableting machine hoppers from a tote bin. An airtight connection between the bin and the hopper has been reported by the company.

Local Exhaust Systems

As explained earlier, granulation is transferred from fiber drums to the tableting machine feeders by vacuum at Plant C. In the absence of control, dust emissions may occur when the surface of the powder in the drum is disturbed by the wand, which is inserted into it. A ventilated semi-enclosure shown in Figure 26 is used to control dust emissions from this source. A total of 60 cfm is exhausted through the slot hood. With a fiber drum in place, control velocities between 85 and 130 fpm were measured at the farthest periphery, while a control velocity of 70 fpm was measured in the vicinity of the rubber gland.

The dust generated while the dies are filled by force-flow feeders (Plants B and D) may be at least partially controlled by enclosing the rotary head and exhausting air from the enclosure (see Figure 24) such that a negative pressure relative to the work room exists. At Plant B, an estimated 75 to 175 cfm is exhausted from that enclosure. At two points, 100 cfm are exhausted from the machine enclosure at Plant D.

Two of the more important sources of dust emissions are the two pressure points where powder in the dies is compressed into tablets. For purposes of control, local exhaust hoods of a geometry which is appropriate to the air space which is being controlled are placed at these two points. At Plant A, house vacuum is applied to two nozzles at an estimated rate of 75 cfm, distributed between two small slots, to control dust emitted from the top and the bottom of the die respectively. The nozzles in the machine at Plant B are about 2 by 0.5 inches with measured face velocities of about 500 fpm. They are located less than 2 inches away from the pressure points. An estimated control velocity of about 60 fpm may be obtained at a distance of 2 inches away from the hood.

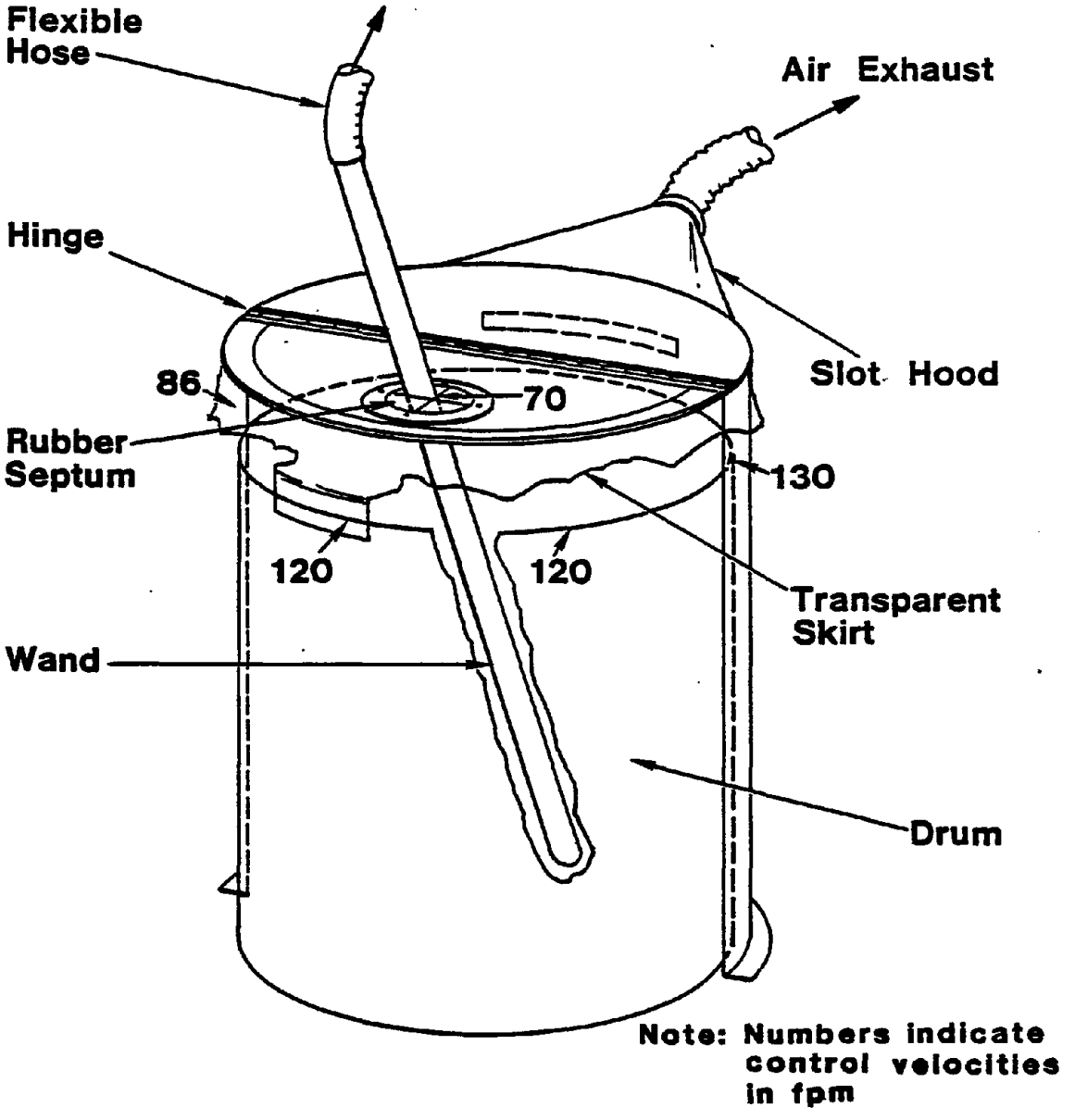

Figure 26. Dust control for transfer of granulation from fiber drums to tablet machine feeders at Plant C

At Plant C, two hoods are used to serve the dual purpose of ventilating the pressure point as well as the enclosure. Air is exhausted from each hood at the rate of 225 cfm. The estimated control velocities at 3 inches away from the hood face in the vicinity of the pressure points are about 150 fpm.

Compressed tablets normally exit the tableting machine along chutes which feed deduster/conveyor mechanisms which in turn deliver them to their eventual receptacles. At Plant A, the deduster/conveyors consist of a vibratory conveyor. The tablets move along a perforated plate. Exhaust ventilation is applied to this plate at an estimated rate of 50 cfm. At Plant B, the chute feeds a conveyor, which also acts as a deduster, with a covered top. The tablets move along a surface also consisting of a perforated plate. Air is exhausted through a plenum directly below the plate. Control velocities on the order of 300 fpm were measured at point A (see Figure 24) where the tablets exit the rotary head enclosure, 100 fpm directly above the partially open area B where the tablets enter the conveyor, and about 100 fpm at the open area C where the tablets exit the conveyor.

At Plant C, the deduster conveyor consists of an airtight housing within which a cylindrical ribbon-type spiral wrapped in a screen rotates. The spiral causes the tablets to turn over as they advance forward, allowing loose dust to fall through the screen. The dust exits the housing and accumulates into a plastic bag attached to the bottom of the housing. In the past, the deduster housing was ventilated at a rate of 120 cfm.

General Ventilation

General dilution ventilation is employed at Plant A to control dust emissions from the rotary head while the dies are filled by the feed frame and to provide additional dust control for the compression step.

The general ventilation controls associated with the tableting operation at Plant A are shown in Figure 27. The room is maintained at negative pressure (ten hundredths of an inch of water minimum) with respect to non-controlled surroundings. Air is supplied at a rate of 1.1 RVPM. About 1.2 RVPM is

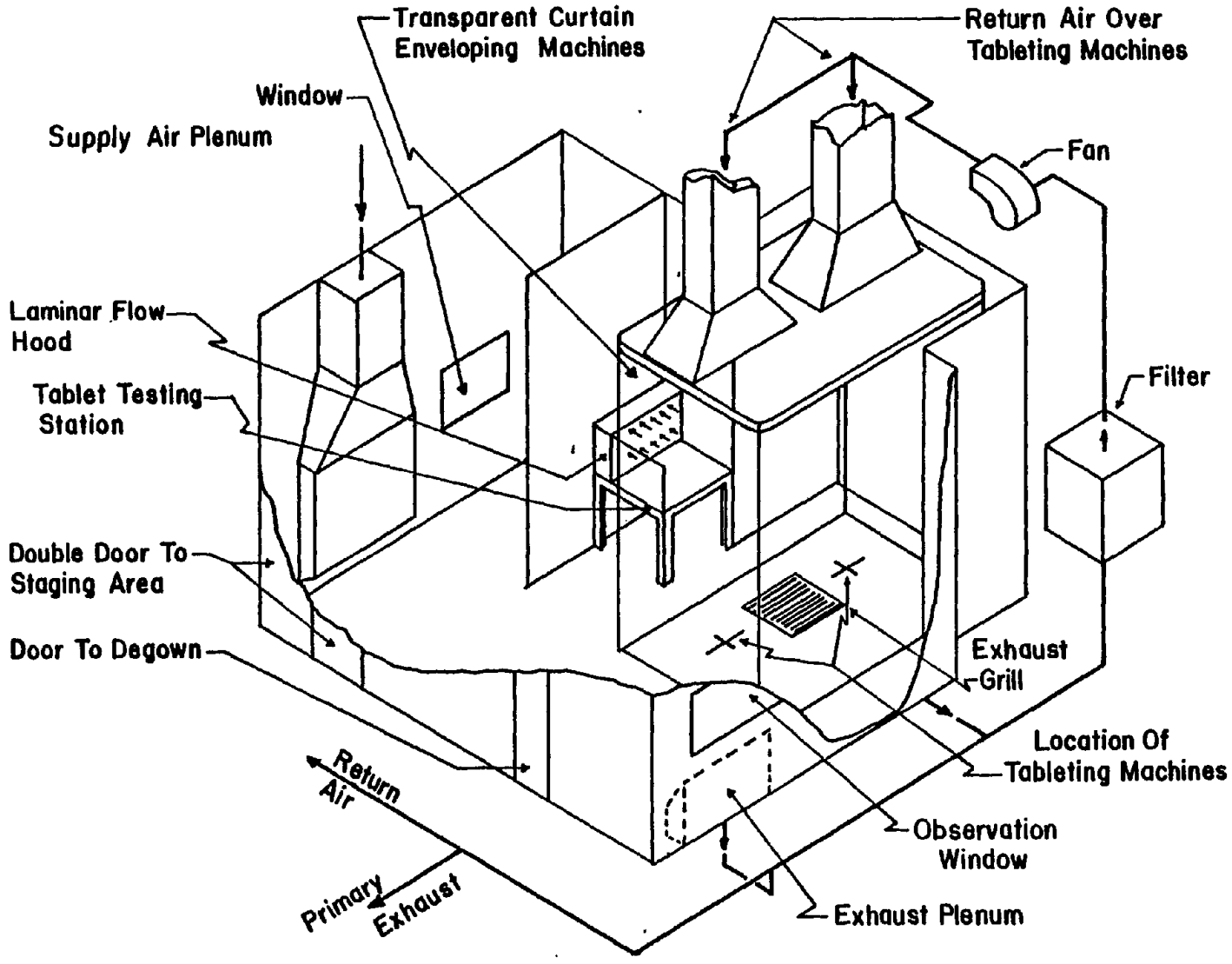

Figure 27. General ventilation in tableting at Plant A

exhausted by the air plenum on the other side of the room. The area in which the two tableting machines are located is enclosed by curtains made from transparent plastic film. Air within this enclosure is exhausted from a grille in the floor at a rate of 0.45 RVPM. This air is filtered and returned to the overhead plena on top of each tableting machine.

The general ventilation scheme in the tableting room at Plant B is shown in Figure 28. Fresh air is supplied at the rate of 0.34 RVPM, of which 0.26 RVPM is distributed through grilles in the ceiling. The area immediately above the tableting machine is ventilated with about 0.08 RVPM of fresh air and 0.11 RVPM that is recycled after removal of dust. About 0.28 RVPM is exhausted to the air handling system through a slot at floor level while 0.075 RVPH is exhausted to the dust collector from the local exhaust devices that are associated with the tableting machine and previously discussed. A portion of the exhausted air is recycled and the dust is removed by three filter banks in series. The first two consist of "prefilters," while the third is a HEPA filter. Under normal conditions, the doors to the room are closed. An air balance around the room indicates that more air (about 0.0125 RVPM) is exhausted than supplied in order to maintain a positive infiltration into the room. When a door to the room is opened, switches attached to the door cause the motorized supply air damper to close so that positive infiltration of air from the corridor is maintained.

At Plant C, an estimated 0.7 RVPM is exhausted from each of the tableting rooms. With the door to one of the rooms two-thirds open, a differential pressure of 0.02 to 0.04 inch of H_2O was measured (using a magnehelic gauge) between the corridor and the room indicating a strong positive infiltration of air into the room. With the door closed, a reading of 0.04 inch H_2O was obtained.

PACKAGING

At Plant A, the engineering controls in each of two rooms where packaging machines are located include general and local exhaust ventilation, a device

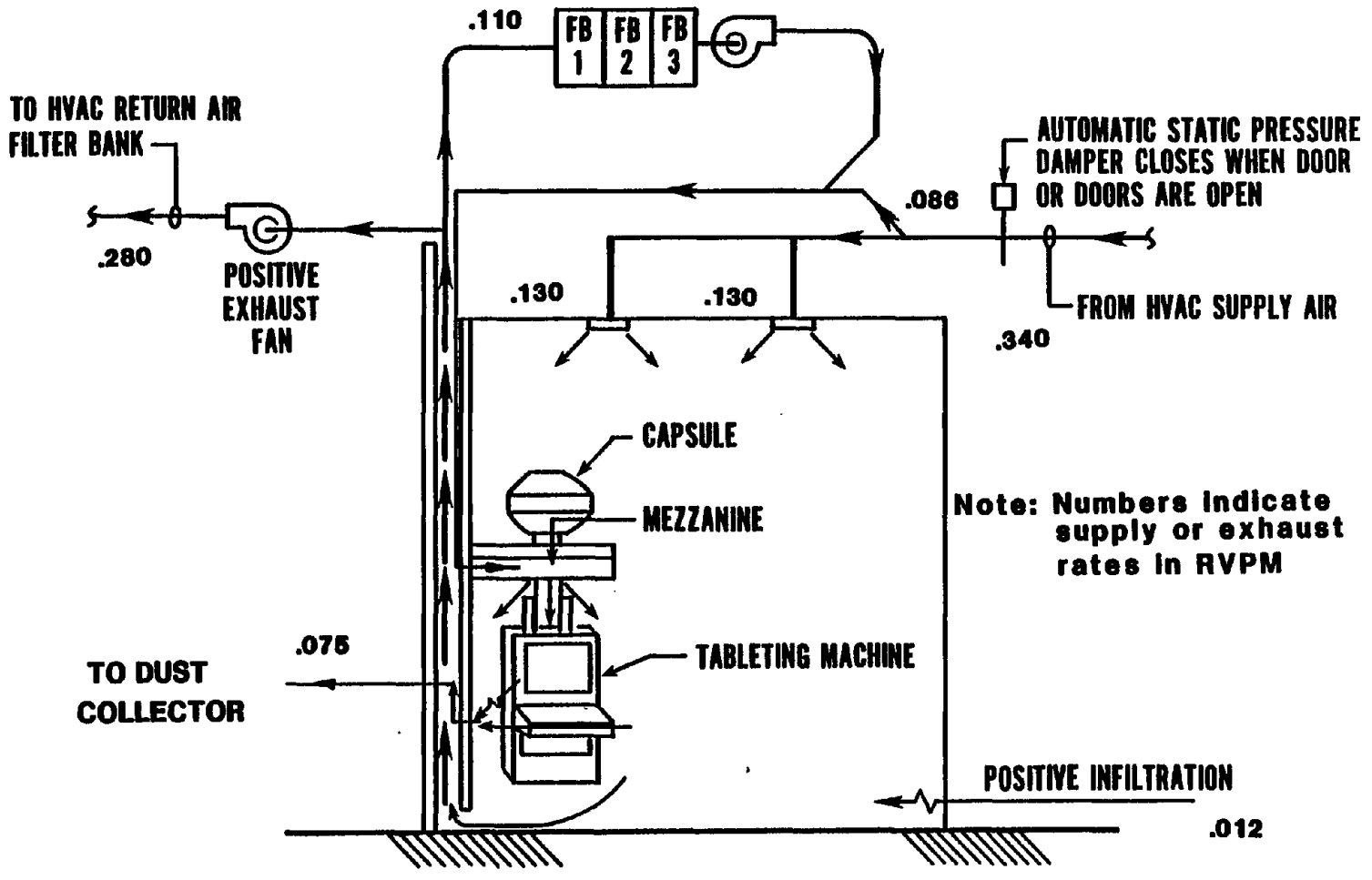

Figure 28. General ventilation in tableting at Plant B. (Rates in RVPM)

for dedusting of tablets, and an alarm which indicates whether the negative pressure in the room has been broken.

Air-conditioned air is supplied to each room. One hundred percent is exhausted through a Rotoclone(R) to the outside. The Rotoclone(R) consists of a fan in a cast iron housing with an inlet section wherein water sprays remove the dust carried by the air. The room is maintained at a slight negative pressure by exhausting more air than is supplied. A photohelic alarm has been installed to indicate to the operator when negative pressure is not maintained.

A vacuum machine with a filter controls dust at specific areas in the Hassia packaging machines. These points include the vibratory conveyor and the brush feeder.

The dedusting device removes loose dust associated with the tablets. The operator spreads the tablets over the perforated tray. Air is drawn by vacuum over the tablets and through the tray to entrain the loose dust. Lateral exhaust is also provided to capture dust that may be generated in the course of dumping and spreading the tablets over the perforated tray.

The packaging machines generate a significant amount of heat which may be stressful to workers in this area in the absence of controls. Additional air cooling units have, therefore, been installed to reduce air temperature.

At Plant B, there are a number of local exhaust ventilation controls incorporated into the pack filling machine. The three hoppers containing OC and placebo tablets are covered and are exhausted at an estimated rate of 15 cfm each through "elephant trunk" hoses that are attached to the covers. The bottom parts of the three vibratory conveyors which transfer tablets from the hoppers to the device which feeds the chutes with tablets are ventilated at an estimated rate of 25 cfm each. The conveyors are covered with rectangular hoods through which the air is exhausted at an estimated rate of 25 cfm.

Air is exhausted from the enclosed space between the end of the conveyors and the device which feeds the chutes at an estimated rate of 100 cfm. Air velocities in the range of 100 to 150 fpm were measured in the annular spaces between stationary and moving parts. The space in front and in back of the tubes connecting the chutes to the "blocks" which positively feed the individual circular packs is ventilated by two small circular hoods at an estimated rate of 120 cfm through each. Control (air) velocities between 50 and 80 fpm were measured in a vertical plane which intersects the horizontal plane of the conveyor. Capture velocities between 30 and 40 fpm were measured at the fringes where contaminants are not very likely to be dispersed.

Clean air is supplied to the filling room from four grilles in the ceiling at a rate of 0.2 RVPM. Air is exhausted from the room to the air handling system at a rate of 0.17 RVPM from two exhaust grilles. An additional 0.07 RVPM is exhausted to the dust collector from three locations. One of these is the manifold which provides local exhaust ventilation at various points in the pack filling operation. The balance of the air (0.04 RVPM) enters the room through positive infiltration from the adjacent room where packaging is completed. Similar rates of air supply and exhaust are also used in that area.

At Plant C, local exhaust systems have been installed to control dust emissions from three sources. The first source is that associated with scooping tablets from fiber drums in the packaging machine hopper. The control consists of a semi-circular slot hood. The second controlled source is the machine hopper/conveyor which feeds the nine spiral chutes with tablets. Air velocities between 30 and 50 fpm were measured in the recesses of the hopper cover which permit ventilation air to infiltrate the hopper.

The feed table cover has been tapped at one point where air is exhausted. Air velocities between 20 and 50 fpm were measured in the open areas on top of the Uhlman tablet feeder. Finally, capture velocities between 390 and 720 fpm were measured at the point where tablets enter the spiral chutes.

WORK PRACTICES

GENERAL REMARKS

Work practices that are effective in reducing exposures are the result of effective training and education programs. Company A maintains a training center where training sessions for the development of a variety of job-related skills, including those pertaining to performing job duties in a safe manner, are prepared and presented. Permanent staff and modern equipment and facilities are available for the preparation and presentation of audio/visual materials for training sessions. Also available are special areas where workers may individually study various components of the training sessions. Procedures have been written for a number of important process- and safety-related items.

New employees at Company B receive on-the-job training and indoctrination in good manufacturing practices (GMP's) and safety. Manuals have been written and these are available for use by both new and old employees. On-the-job training consists of a gradual introduction of the new worker to the job together with a gradual building of his/her competence. The first time that a worker is assigned to a given operation, he/she observes it being performed by a senior technician. The second time involves active participation with the senior technician. The third time he/she performs the work while being observed or monitored by the senior technician. Usually, the new worker is able to perform the job duties adequately the fourth time.

Workers in the estrogen area are educated in the health effects of exposure to estrogens by a company physician and the company safety specialists. They also explain the importance of complying with safety requirements. Work practices are regularly audited by supervisors. Discussions of training requirements and manufacturing operations are held once a month.

At Plant C, there is a wide variety of audiovisual and written manuals on subjects related to safety. There are training media on the use, care, and maintenance of respirators. Others include information on Material Safety

Data Sheets (MSDS) which explain their contents. A manual which includes MSDS's on hazardous materials used in the plant is also available for supervisors to use in conjunction with the audiovisual training material on the subject.

At Plant D, procedures have been written for a number of activities. One procedure calls for documenting the use, maintenance, and cleanup of process equipment. Two other procedures describe in detail the protective equipment (respiratory and clothing) which are required in various activities. Another procedure requires periodic inspection of ventilation system components.

In the next few sections, work practices pertaining to (1) administrative controls, (2) ventilation systems audits, (3) ingress to and egress from high-risk areas, and (4) respiratory protective equipment will be described.

ADMINISTRATIVE CONTROLS

At Company A, workers involved in the production of granulation and in tableting are rotated to other jobs so that exposure to these materials occurs, at most, one day a week. Packaging line inspectors at Plant A are scheduled in the tablet blistering room on a rotating basis at a frequency of once every 12 to 13 working days if one line is operating, and a frequency of once every 5 days when two lines are operating. The blister packaging equipment operator is not rotated, but permanently assigned to the job.

At Company B, workers involved in production of granulation and tableting must stay out of these high-risk areas and perform entirely different activities for 48 hours for every 10 hours worked there. Fertile females are excluded from high-risk activities because Company B considers steroids to be teratogenic.

Job rotation is also practiced at Plant C.

VENTILATION SYSTEMS

At Plant A, weighing of active ingredients must be performed within the confines of the hood. The hood is fitted with a meter which indicates proper airflow into the hood (about 500 cfm). The worker should check the velometer reading before use. In the areas of the blender and oven rooms, the negative pressure controls must be checked daily by inspection of the pressure gauges. The ventilation system must be manually switched to total exhaust (no recirculation) whenever granulating liquid is present (wet milling and loading the dryers in the oven room, and wet mixing in the blender room).

At Plant D, the air handling system is monitored daily in accordance with a procedure written for this purpose. Smoke tubes are used to check the direction of airflows between various process areas and adjacent locations. With a door slightly ajar, the worker places the smoke tube in the vicinity and determines the direction of airflow. A floor plan which specifies the correct direction of the airflow is provided. The procedure specifies that incorrect airflows are to be corrected and that management be notified if such airflows cannot be corrected. A report is to be filled out at the end of each inspection.

At Plant D, there is also a written procedure for inspection of local exhaust systems and for the review of plans to install or modify such systems. The inspection procedure specifies the objectives of the inspections, who is to perform the inspections, how they are to be performed, the frequency (bimonthly), and reporting requirements. The inspection is to assure the structural integrity and proper functioning of ductwork, fans, and filters, and the detection of exhaust ventilation system failures or defects. Data concerning these items must be entered on an inspection form. A space is also provided for recommended follow-up action if necessary. Filters must be replaced when the pressure drop across them exceeds 1.5 inches of mercury. Fans and belts are to be inspected for wear.

Ductwork is to be inspected for leaks. Ventilation measurements to be performed consist of face velocity measurements whereby one reading is taken

for each square foot of hood face. If the average measured face velocity is 75 percent of the design (standard) value or less, remedial action is taken.

INGRESS TO AND EGRESS FROM HIGH-RISK AREAS

At Plant A, granulation and tableting area operators are required to activate the house vacuum system for dust collection at local exhaust systems previously described before entering the process area. The exterior surfaces of drums and tools are to be cleaned before being taken out of the production facility. Thorough showering with a mild lotion soap is mandatory upon leaving the degown room. The access area is designed so that the shower room cannot be bypassed when going from the degown room to the change room.

At Plant B, workers in granulation and tableting must pass through the water shower to remove dust particles from outside surfaces of respiratory and other protective equipment as they leave the process areas.

At Plant D, workers enter an air lock, where they put on protective equipment, before entering process areas. Upon exiting these areas, they wash their gloves, brush vacuum their protective clothing, and wipe off their shoes on a shoe-cleaning machine after removing booties.

Workers at Plant D are to wash face, hands, and forearms when exiting process areas during the shift. They are to shower at the end of the shift and sign a shower log.

PERSONAL PROTECTIVE EQUIPMENT

At Plant A, there are written procedures which specify the respiratory and other protective equipment to be used by workers in granulation production, tableting, and packaging. There are also written procedures which specify the servicing and calibration of the respiratory airline monitor. Since disposable protective clothing is used at Plant A, the procedures require that the clothing not be reused. No instances of such reuse have been observed. The used clothing is dumped into a trash bag lined with plastic. When full,

it is heat sealed and placed in clearly labelled fiber drums destined for land filling.

At Plant B, procedures have been written which specify protective equipment required for each category of risk (or job). Additionally, all batch sheets (which are used by workers who mix the batch) include detailed requirements for personal protective equipment. Regularly scheduled "refresher" sessions include movies on the use, maintenance, and storage of respirators; information on new equipment is also presented at these sessions.

At Plant C, the manual on respiratory protection describes in detail the reasons why respirators are required, namely, health effects. It specifies the type of protective gear required when handling hazardous dust and volatile organic chemicals. The manual also specifies the limitations of respiratory protective equipment, for example, the powered air-purifying respirator is not to be used in oxygen deficient atmospheres. Also included in the manual are detailed procedures pertaining to the inspection and maintenance of PPE.

Similar procedures are in effect at Plant D. The procedure on PPE specifies what to wear and where to put it on. A separate detailed description of PPE requirements for each activity has been written.

MEDICAL AND ENVIRONMENTAL MONITORING

MEDICAL MONITORING

At Plant A, workers in the steroid facility are provided with periodic physical assessments which include EKG, an X-ray, pulmonary function test, and a battery of blood tests (SMA-23). This is performed annually for workers over 40 years of age, once every 2 years for workers that are 30 to 40 years of age, and once every 3 years for workers between 20 and 30 years of age. An extensive history and physical assessment is performed by company nurses specifically trained for this function at the beginning of employment. Workers in the steroid facility are also examined by a physician once every 2 weeks specifically for symptoms of overexposure.

At Plant B, medical monitoring of employees is conducted routinely. Physical examinations are administered only to workers who may exhibit symptoms of overexposures to steroids. Every 6 months, each worker fills out a questionnaire to determine whether overexposures may have occurred.

ENVIRONMENTAL MONITORING

Fixed Area Monitoring Systems

At Plant A, periodic monitoring of steroid levels in various areas is performed. An area monitoring system designed by the company is used to monitor concentrations at fixed locations in various areas within the steroid facility. The air samples are drawn through 37 mm glass-fiber filters in cassettes using vacuum generated by a steam jet ejector. Constant airflow is obtained by using critical orifices. The filters are then taken to the laboratory for analyses, in the same manner as personal samples. This system is useful in detecting departures from expected levels, and in indicating the need for corrective action.

A similar system is in use at Plant C.

Sampling Activities

Monitoring of workers in granulation production, tableting, and packaging has been conducted by both NIOSH and the companies participating in the study. At Plant A, both NIOSH and the company obtained side-by-side breathing zone samples of workers in granulation production and tableting over a period of 4 days (4 shifts). Packaging operations were idle during the NIOSH survey. Therefore, only data generated by Company A will be reported for the packaging operation.

At Plant B, breathing zone samples were obtained by the company for workers in granulation production (2 shifts) and tableting (2 shifts) during the NIOSH survey. Additional data on granulation, tableting, and packaging were provided after the survey. Side-by-side area samples were simultaneously taken in the three areas by both NIOSH and the company during the survey. These samples were used to verify statistical agreement between Company B's and NIOSH's sampling and analytical methods.

Two surveys were conducted by NIOSH at Plant C. Breathing zone samples for workers in granulation production and tableting were obtained during 5 shifts in the course of the first survey. The second survey was conducted to document the engineering controls. Company officials mentioned that steroid levels did not materially change in granulation production and packaging. These levels were lower in tableting as a result of control modifications. Data summaries on breathing zone levels were provided by Company C. Only the estrogenic component was reported.

NIOSH did not conduct a detailed survey at Plant D; however, the company provided information on the operation, including data on breathing zone levels.

It must be emphasized again that the breathing zone levels reported characterize the engineered safeguards in the manufacturing operations and do not represent actual worker exposures. As will be described in the next chapter, the workers in granulation production, tableting, and packaging don

respiratory protective equipment. Actual exposures would therefore be the breathing zone levels divided by the protection factor.

Breathing Zone Levels of Steroids

Breathing zone samples outside respiratory protective equipment were obtained during dry milling and wet milling of granulation and during cleanup at Plant A. The data are listed in Tables 1, 2, and 3, respectively. Sources of variability in the data include: (1) differences in work practices between individuals, (2) proximity to the sources of exposure varies since not every worker in the processing area performs identical tasks, and (3) a minor leakage in some equipment may occur on one day but not on other days. These caveats notwithstanding, the geometric mean (GM) and geometric standard deviation of the data for the three activities were calculated with a view to obtaining a geometric mean level for workers in this area and a geometric standard deviation which is a measure of the variability of the data. The results of these calculations are given in Table 4.

Table 1. Air Concentration Levels Outside Protective Equipment During Dry Milling at Plant A, mcg/cu.m.

Day	Worker	Estrogen	Progestogen
1	A	0.56	9.12
	B	0.84	13.40
	C	0.52	6.11
2	D	4.19	73.40
	E	1.23	23.39
	F	1.50	29.72
3	G	0.83	13.63
	H	0.49	7.71
	I	1.98	34.90
4	J	2.67	45.5
	K	3.61	63.92
	L	2.55	46.40

Table 2. Air Concentration Levels Outside Protective Equipment During Wet Milling at Plant A, mcg/cu.m.

Day	Worker	Estrogen	Progestogen
1	A	0.48	12.27
	B	0.60	6.53
	C	1.2	27.70
2	D	0.49	7.96
	E	--*	--*
	F	0.34	8.12
3	G	2.53	63.84
	H	0.40	9.38
	I	--*	--*

* No samples taken.

Table 3. Air Concentration Levels Outside Protective Equipment During Cleanup at Plant A, mcg/cu.m.

Day	Worker	Estrogen	Progestogen
1	A	--	--
	B	0.31	1.96
	C	0.11*	2.30
2	D	0.12*	0.83
	E	0.28	1.23
	F	0.12*	0.47
3	G	0.75	2.19
	H	0.18*	0.93
	I	0.18*	1.91
4	J	0.24*	3.94
	K	1.65	20.36
	L	0.24*	3.08

* Concentration based on half the detection limit which is 50 ng.

Table 4. Geometric Means (GM) and Geometric Standard Deviations (GSD) for Air Concentrations in the Production of Granulation at Plant A, mcg/cu.m.

	Estrogen		Progestogen	
Activity	GM	GSD	GM	GSD
Dry Milling	1.36	2.14	22.71	2.34
Wet Milling	0.67	2.04	13.60	2.29
Cleanup	0.26	2.28	2.00	2.68

Air concentrations outside of protective equipment in tableting are inherently much lower than those in processing. The worker usually spends most of his time performing periodic weight and friability tests on tablets from both machines. He usually enters the enclosed area of the machines to obtain sample tablets and to perform machine adjustments while the machine is running. Top-of-helmet exposure data were obtained for the tablet machine operator and these are reported in Table 5. The geometric means and geometric standard deviations are reported in Table 6.

Table 5. Air Concentration Levels Outside Protective Equipment in Tableting Room at Plant A, mcg/cu.m.

Day	Worker	Estrogen	Progestogen
1	M	0.23	0.44
2	N	0.05*	0.05*
3	O	0.07	0.15
4	P	0.09	1.01

* Based on detection limits.

Table 6. Geometric Means (GM) and Geometric Standard Deviations (GSD) for Air Concentrations in the Tableting Room at Plant A

Estrogen		Progestogen	
GM, mcg/cu.m.	GSD	GM, mcg/cu.m.	GSD
0.09	1.92	0.24	3.69

Data summaries provided by Plant A indicate that breathing zone levels for packaging area workers are in the range of non-detectable to 0.37 mcg/cu.m. for the estrogen and 0.1 to 1.8 mcg/cu.m. for the progestogen. The mean levels for the two steroids were 0.11 and 0.72 mcg/cu.m. based on 35 samples.

At Plant B, only company-generated data on breathing zone levels during the NIOSH survey for workers in granulation and tableting were obtained. These are reported in Table 7.

Table 7. Breathing Zone Levels of Steroids for Workers in Granulation Production and Tableting at Plant B

Day	Operation	Sampling Rate, Liters Per Minute	Duration of Sampling, Minutes	Concentration, mcg/cu.m.	
				Estrogen	Progestogen
2	Granulation	3.3	409	0.1971	12.89
3	Granulation	3.3	281	0.5974	20.83
4	Tableting	3.3	319	0.0230	0.98
5	Tableting	3.3	259	0.2200	3.76

The small number of personal samples taken in each area does not allow an accurate computation of the mean breathing zone level for each job category and obtaining an accurate estimate of the confidence limits pertaining thereto. However, the data are useful in qualitatively estimating the order of magnitude of exposures in each location. With these limitations in mind,

workers in granulation production had a geometric mean breathing zone level of 16.4 mcg/cu.m. with respect to the progestogen, while those in tableting had a geometric mean level of 1.92 mcg/cu.m. The corresponding levels for the estrogen were 0.34 and 0.071, respectively.

Breathing zone levels of steroids in packaging are much lower than those in granulation and tableting. Most area samples obtained by NIOSH during the survey indicated non-detectable levels. Three workers at the front end of the packaging line, where the blister packs are filled and sealed, exchange positions every one-half hour. Only one of these positions is close to the sources of dust. One breathing zone sample obtained for this position by the company indicated a level of 0.48 mcg/cu.m. for the progestogen and a level of 0.02 for the estrogen at Plant B.

The results of sampling at Plant C during the first NIOSH survey are reported in Table 8. Also reported in Table 8 are the data provided by the company after the second survey. Close agreement between the NIOSH and company data has been demonstrated in the past.

Company officials at Plant D provided the results of sampling conducted over a period of three days. These data are summarized in Table 9. For workers in granulation and tableting, the values reported are time-weighted averages of three or four individual samples for each worker over the entire sampling time. In terms of dosage, Granulation Operator No. 1 received 63 percent of the total dose during the first 112 minutes of the shift while wet mixing a batch. For Operator No. 2, 81 percent of the dose was received while manually scooping excipients and active ingredients into the blender over a period of 117 minutes. The group leader's breathing zone levels were evenly distributed between the three samples taken and the activities he was engaged in during the shift.

Inspection of the data from four plants seems to indicate, at least qualitatively, that the true geometric mean breathing zone level in granulation most probably lies toward the lower end of the 10 to 100 mcg/cu.m. range with respect to the progestogen. A small fraction of the data (assuming

Table 8. Summary of Worker Breathing Zone Levels at Plant C.

Activity	Source of Data	Number of Samples	Estrogen, mcg/cu.m. Range	Estrogen, mcg/cu.m. Geometric Mean	Progestogen, mcg/cu.m. Range	Progestogen, mcg/cu.m. Geometric Mean
Granulation	NIOSH	6	0.470 - 1.92	1.04	2.39 - 65.5	15.03
	Company	10	0.087 - 3.29	1.19		
Tableting	NIOSH	8	less than 0.020 - 0.290	0.052	0.120 - 5.31	1.13
	Company	5	0.049 - 0.229	0.101		
Packaging	Company	6	0.001 - 0.055	0.028		

Table 9. Summary of Typical Breathing Zone Levels at Plant D.

Activity	Job Title	Total Sampling Time, min	Breathing Zone Levels, mcg/cu.m.		Remarks
			Progestogen	Estrogen	
Preweighing	Preweighing Coordinator	45	9.6	ND	
Granulation	Operator No. 1	357	12.0	ND	Wet mix, discharge blender dry mix
	Operator No. 2	365	15.0	ND	Scoop actives into blender
	Group Leader	360	41.0	0.27	Wet mix, scrapes sides of dryer bowls, discharge blender
Tableting	Operator	320	4.8	ND	a) Compress tablets and mill rejected ones
	Leader	347	10.4	0.09	a) Compress tablets and mill rejected ones
Packaging	Machine Operator	317	0.2	ND	Operate blister packaging machine
Picking and Shelling	Machine Operator	320	1.2	ND	Sort loose tablets to remove damaged ones
	Machine Operator	328	0.8	ND	Hand-operated small press, to remove tablets from packs. Sorted loose tablets to remove damaged ones
Quality Control	Laboratory Analyst	9	1.8	ND	Ground tablets with mortar and pestle. Weighed powder and balance

a) not simultaneously

numerous measurements are taken) would lie above 100 and another small fraction would lie below 10. The corresponding levels for the estrogen would probably be about 1/25 those of the progestogen, although ratios of progestogen to estrogen between 50:1 and 20:1 have been observed in actual data. The true geometric means would most probably lie in the 1 to 10 mcg/cu.m. range for tableting and 0.1 to 1 for packaging with respect to the progestogen. The same remarks about the scatter of the data and the true geometric means for the estrogen in granulation most probably apply to tableting and packaging.

There are a number of significant factors which affect interplant variability of data. Some of these are:

- Compositions of products are variable. Some products have more steroids than others.

- Production rates in granulation, tableting, and packaging vary.

- The levels of control vary. Air supply rates and capture velocities of ventilation systems together with the effectiveness of material transfer systems vary.

- There are inherent differences in granulation production, and tableting and packaging machinery.

PERSONAL PROTECTIVE EQUIPMENT

INTRODUCTION

Workers in granulation production, tableting, and packaging are further protected from exposure to steroids by use of respiratory and other protective equipment described in this chapter. Actual worker exposures to these materials depend upon the protection factors afforded by the protective equipment, work practices, and personal hygiene requirements.

This study was primarily concerned with the engineering and work practice components of hazard control techniques. However, for the sake of completeness, personal protective equipment in use at Plants A, B, C, and D will be described in the following paragraphs.

PLANT A

Granulation

Workers in the excipient dump room wear dust respirators (3M No. 8710) for protection against what is considered to be nuisance dust.

Workers in the processing area must don PPE in the change room and the degown room before entering the blender area, the oven room, or the process weigh room. In the change room, the workers remove their street clothing and put on Tyvek undershirts and undershorts. They may, at this point, wear either an unhooded or a hooded Tyvek coverall. If a hooded coverall (American Hospital Supply) is chosen, then shoe covers are worn and these should be taped to the legs of the coverall. Then a belt with a vortex cooling assembly (3M, W2862) attached to it is put on. The hooded coveralls are not completely closed while gowning is taking place. The worker proceeds to the degown room and attaches the vortex unit to an air supply to verify that sufficient airflow is obtained. Then a flexible hose attached to the vortex unit is inserted into a side opening in the suit. The suit material and hose are taped at this point to prevent leakage of outside air. Finally, surgical gloves (Derma-Thin, Best

Manufacturing Company, No. 1005) are worn and these are taped to the sleeves to prevent leakage. The worker then connects the vortex assembly to an air supply point via a 15- or 20-foot-long rubber hose fitted with quick-disconnect fittings at both ends. This is effectively an air-supplied suit. If an unhooded Tyvek coverall is chosen, the worker dons a vest (3M, W2802-6) and a detachable hood (3M, W5220-6, for example), which provides equivalent protection.

Published data on protection factors suggest a protection factor of 2,000 for this combination (Reference 5, Page 54). The company collected data that show a protection factor of 1,000 or better.

When removing the PPE, the worker enters the degown room and removes the detachable hood or opens the hooded coverall. Then the order of removal is: (1) vortex cooling unit, (2) detachable vest (if unhooded coverall is used), (3) coveralls, (4) shoe covers, and (5) gloves. The worker then removes disposable underclothing and enters the shower room.

When wet milling operations are completed, the processing area is hosed down before workers leave for a short break. Only unhooded Tyvek coveralls, shoe covers, gloves, and dust respirators are required when they re-enter the area for cleanup.

Tableting

Requirements here are similar to those in processing. Underclothing, unhooded Tyvek coveralls, gloves, and overshoes are worn. Respiratory protective equipment consists of a Racal air-purifying respirator including a helmet, with a HEPA filter (AS905) blower, and a battery Pak worn also as a backpack. The HEPA filter removes 99.97 percent of particles 0.3 microns in diameter. Theoretically, this should give a protection factor of about 3,300. However, the protection factor of such respirators is compromised by complex turbulent air currents which entrain some particulates back into the breathing zone.

NIOSH has generated field data on such respirators which suggest a protection factor of 205 (geometric mean based on 23 observations).[6] The measurements were made at a lead smelter where both particulates and fumes were found. A lower confidence limit (LCC) of 128 was obtained for the protection factor, while the upper confidence limit was found to be 325. Work conditions in a lead smelter are much more rigorous than those encountered by the tablet machine operator at Company A, and a higher protection factor may be obtained under these conditions. Company-generated data indicate a value of 100 for the protection factor.

PLANT B

Workers performing high-risk activities don air-supplied vinyl suits and disposable rubber gloves. The vinyl suits have overshoes attached. The worker exits the high-risk area through the suit wash where jets of water wash the dust off the suit before it is taken off.

For moderate-risk activities, the worker dons a disposable suit, rubber gloves, and shoe covers. A respirator which is approved for dusts, fumes, and mists having a TLV not less than 0.05 mg per cu.m. is also worn.

Workers in low-risk activities wear disposable rubber gloves and disposable dust respirators approved for protection against fibrosis and pneumoconiosis.

Air-supplied suits have an estimated protection factor of 2,000 or more.[5] Achieving the higher levels is dependent upon maintaining the outside as well as the inside surfaces of the suit free from contamination. Also important is maintaining the clean air distribution and delivery hoses and associated connect/disconnect fittings free from contamination.

PLANT C

There are two types of respirators in use at Plant C. In granulation and tableting, the 3M Whitecap powered air-purifying respirators are used. This respirator is a combination of a backpack consisting of a fan and HEPA filter,

which is connected by a hose to a helmet with a face shield and shroud. Air is drawn from the workroom and filtered in the HEPA filter before delivery to the helmet. Protection factors for this respirator are similar to the Racal in use at Plant A. Protective clothing includes woven cloth coveralls, which are frequently changed, and disposable surgical rubber gloves.

For low-risk activities, the 3M Brand 8710 dust/mist respirator is used.

PLANT D

Workers in granulation production, tableting, blister pack filling operations use 3M Whitecap W5005 airline respirators. The air supply is regulated by the W-2800 air-regulating valve assembly. Protective clothing consists of a coverall worn over a jumpsuit, booties worn over shoes, and rubber gloves.

MSA Comfo II half-mask respirators are worn in blending and compressing of placebo tablets and while OC tablets are analyzed in the lab.

MSA Ultra Twin (full-facepiece) respirators are worn by (1) maintenance workers in granulation and tableting and (2) while protective clothing is being laundered. Process areas are washed down and cleaned prior to maintenance work.

SUMMARY AND CONCLUSIONS

Tablet-making operations are common in the pharmaceutical industry. They are used to manufacture a wide variety of drugs. OC tablet-making processes were studied as an example of such operations where stringent health hazard controls are required to control dust which contains very potent estrogens and progestogens.

The manufacture of OC tablets involves preweighing and batch mixing of ingredients to form a granulation, compression of the granulation into tablets, and packaging. Since it is very important to maintain product uniformity, quality control procedures usually require that assays be performed at each step in the process. These and other considerations mandate the use of batch processing in tablet-making operations.

In all of the plants visited, the four elements of health hazard control are well represented. These are engineering controls (ventilation, automation, etc.), work practices (training and education, and performance audits), environmental and medical monitoring of workers, and personal protective equipment.

The engineering controls that were characterized included the use of hoods for preweighing the pure steroids, local and general ventilation, material transfer systems in granulation and tableting, and powder feed systems in tableting. Capture velocities between 50 and 100 fpm were measured for preweigh hoods. Capture velocities of 50 to 300 fpm were measured for various local exhaust systems designed to control dust at or near the source in granulation and tableting. General ventilation is used to dilute steroid levels in process areas and/or provide supply air for local exhaust systems. The air that is exhausted may be recirculated after filtration in HEPA filters to remove dust and conditioning (humidity and temperature). A number of vacuum-type and gravity-type powder feed systems are in use both in granulation production and in tableting. The gravity-type systems that were observed were totally enclosed and as such did not appear to present any

problems in operation. For high-speed tableting operations (as at Plant B), positive feed devices (screw conveyors and force-flow feeders) are necessary.

Good work practices which further diminish the potential for dust generation are the result of effective training and audit programs. Detailed procedures have been written at all plants studied pertaining to each significant aspect at each job category. There are written procedures for the proper use, inspection, and maintenance of respirators. Others are concerned with auditing the performance of ventilation systems (both general and local). Still others are designed to prevent the tracking of the steroids to other plant areas. Personal hygiene (frequent showering and changing of protective clothing) is emphasized.

Environmental and medical monitoring of employees is practiced at all plants. Steroid levels are periodically measured both at fixed locations within a process area and in the breathing zone of workers. Protection factors of respiratory protective equipment are determined by simultaneously sampling the air inside and outside such equipment. The results of some of the measurements conducted by NIOSH and the companies indicate the following levels (in mcg/cu.m.) in the breathing zone of workers outside of respiratory protective equipment with respect to both the progestogen and the estrogen.

	Granulation		Tableting		Packaging	
	Estrogen	Progestogen	Estrogen	Progestogen	Estrogen	Progestogen
Plant A	0.80	13.9	0.09	0.24	0.11	0.72
Plant B	0.34	16.4	0.07	1.92	0.02	0.48
Plant C	1.04	15.0	0.05	1.13	0.03	--
Plant D	0.15*	18.9	0.14*	7.10	0.04*	0.20

* Based on half the detection limit of 0.05 mcg per filter.

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APPENDIX A

ANALYTICAL PROCEDURES

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

The procedure described below outlines a typical analysis of air samples by high performance liquid chromatography (HPLC). This procedure is concerned with the synthetic steroids mestranol, norethindrone, and ethinylestradiol.

The samples are typically extracted with acetonitrile and agitated on a sonic bath at 60°C for 1 hour. The samples are filtered through FALP filters, concentrated by solvent evaporation, and analyzed by HPLC.

The HPLC conditions are as follows:

Column - Waters Radial Pak A in a radial compression module
Solvents - 40 percent acetonitrile/60 percent water isocratic
Flow rate - 3 mL/min

The eluting peaks are measured by two UV detectors and one fluorescence detector in series. The UV detectors (Waters 450) are set at 190 nm for detection of norethindrone and 254 nm for detection of mestranol. The fluorescence detector is a Schoeffel FS970 set at 210 nm excitation with a 340 nm emission filter.

RADIOIMMUNOASSAY

The filters are extracted with a suitable solvent (e.g., diethyl ether) and an aliquot is placed in assay tubes. Appropriate anti-serum solution and a radioactive tracer are added to samples and standards.

After thorough mixing and incubation, bound and free steroids are separated, and the bound steroid is placed in scintillation vials and the radioactivity measured. Suspected contaminants (e.g., progestins) are checked for cross-reactivity since these are usually present on the same filters.