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An automated aerosol actuator: application to the uniformity testing of pharmaceutical aerosol dosage forms

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Abstract: An automated system for valve performance testing to determine net weight loss per actuation of pharmaceutical aerosol dosage forms has been developed and is described. The principal element of the system is a novel automatic aerosol actuation device. Details of the validation, comparison to manual methods of analysis and advantages are presented. The automated system has been shown to be a cost-effective, productive and facile alternative to manual testing.

Keywords: *Aerosol actuator; robotics; spray-and-weigh; automation.*

Introduction

Metered dose aerosol formulations have been employed as a viable pharmaceutical delivery system/dosage form for over three decades [1]. As the number of aerosol systems and products has increased, a variety of tests have been developed and implemented in order to study performance and insure product quality [1–6]. Many of these tests are labour intensive and/or time-consuming. Among them is the determination of valve performance or delivery. Several means of measuring this parameter are available including the use of chromatographic or spectrophotometric analyses after collection of the material delivered by actuating the device. However, a simple and commonly employed approach involves the determination of net weight of material delivered per actuation (weigh–spray–weigh). Since this testing is necessary for many pharmaceutical aerosol formulation evaluations, an automated approach was desired to address the time and labour intensive nature of the analysis. To this end, a novel automatic aerosol actuator has been developed and is described. The application of this actuator as part of an automated system for the performance of a test to determine net weight loss per actuation of an aerosol system is presented. Validation of the system by comparison to manual methodology is also discussed.

Experimental

Robot

The robotic portion of the system consisted of a robot arm used in conjunction with a COMPAQ 386 computer (Compaq Computer Corporation, P.O. Box 692000, Houston, TX 77269-2000, USA). The data were transmitted into Lotus Measure Software (Lotus Development Corporation, 55 Cambridge Parkway, Cambridge, MA 02142, USA) residing in the 386 computer, while the on-board computer of the robot controlled the robotic arm, aerosol actuator and analytical balance (AM-100, Mettler Instrument Corporation, Box 71, Hightstown, NJ 08520-9944, USA). Figure 1 shows the entire system along with a schematic drawing of the automated aerosol actuator.

The robot arm was a HERO 2000 (model ET-19-11) manufactured by the Heath Company (Benton Harbor, MI 49022, USA). The core of the base consisted of a Z-80-A microprocessor which allowed the arm to be operated from the attached teaching pendant or from a computer using a RS-232 serial port. Six

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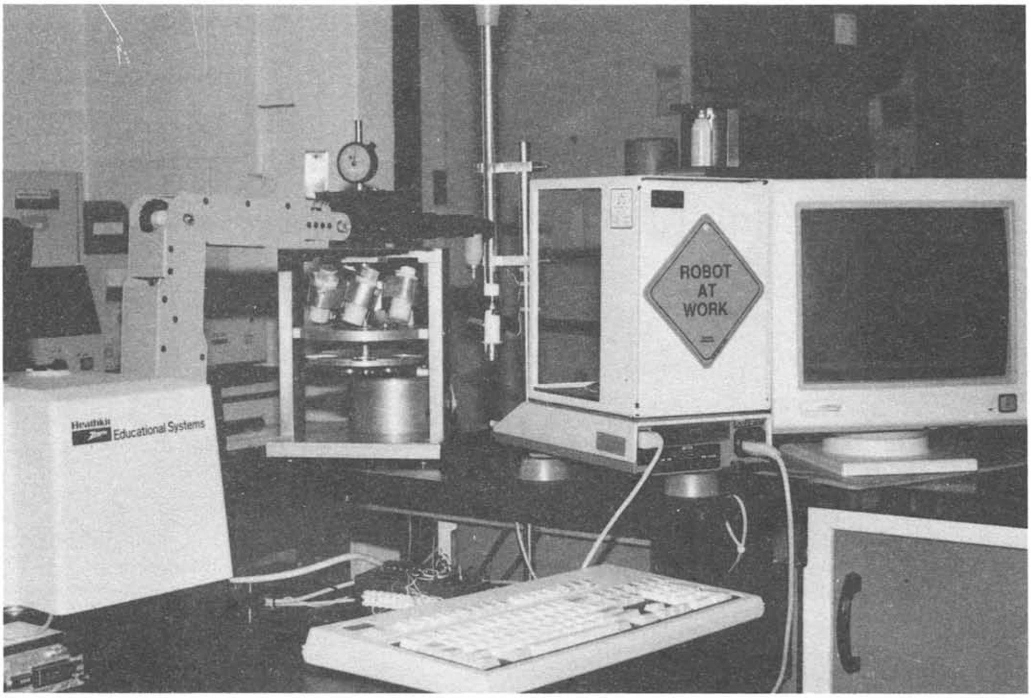
(a)



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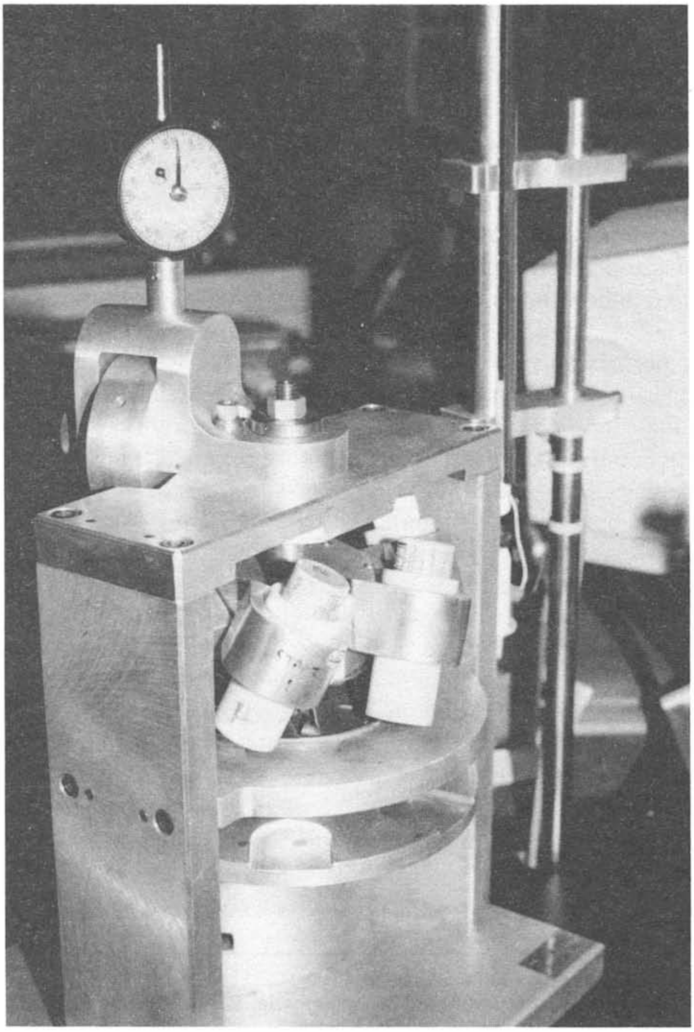

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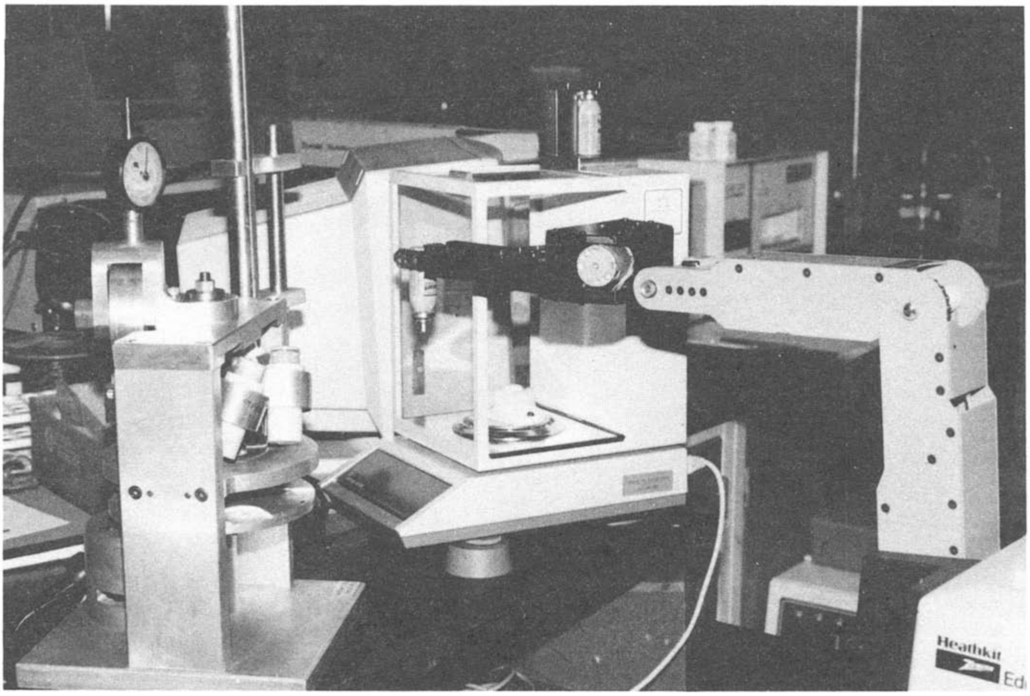

Figure 1
Photographs of the complete automated system showing (a) robot, automated actuator and balance, (b) automated actuator and (c) gripper hand. A schematic diagram of the automated actuator is also shown (d — overleaf).

additional 8042 microprocessors performed the time-consuming tasks of controlling the arm motors, allowing the Z-80-A to be dedicated to programs. An eight channel user port (eight on/off control lines) allowed control of an input from the external devices, i.e. balance, automatic aerosol actuator and sensors. The gripper was customized to facilitate gripping of the aerosol canisters. The gripper fingers were extended and the finger tips were machined to the curvature of the aerosol canister and rubber finger pads (IDL MPG and Sales Corp., Carlstadt, NJ 07072, USA) were placed over the finger tips to help ensure gripping.

Automatic aerosol actuator

The automatic aerosol actuator was designed and constructed in conjunction with staff of Arrow Tool and Die Company (Philadelphia, PA, USA). It was machined from anodized aluminium and employed commonly available micrometer and air pressure gauges as well as a commonly available electric motor. The automatic actuator functions by shaking an aerosol unit and then depressing the aerosol valve stem to open the valve and deliver the proper (i.e. metered) dose of propellant and drug through an orifice into a trap container. The actuator was designed to accommodate different metered-dose aerosol canister sizes and as many as eight metered-dose aerosol canisters at a time in the sample tray. The built-in flexibility of the automatic aerosol actuator make it unique and a versatile tool to be applied to various types of aerosol testing (e.g. valve dose delivery determinations, net total weight delivered from the valve determinations and/or unit spray content determinations).

A sample carousel with six or eight metered-dose canisters in a vertical position with valve stems pointing down rotates when turned by an electric motor. The aerosol canisters are held in sample blocks which are lifted about a horizontal axis as the carousel turns over a stationary cam. The sample blocks consist of a Teflon cylinder in a metal block. The Teflon cylinder has an open top into which the aerosol unit fits tightly. The bottom of the Teflon cylinder has a concave shaped hole drilled precisely to support the aerosol unit on the valve stem and thus positions the aerosol unit for actuation. Shaking is accomplished as the sample blocks pass over the cam and fall back to a vertical position. The cam lifts the valve tip end of the aerosol unit 1.9 cm thereby pivoting it 70° about a horizontal axis and then allows it to fall to its original position thus hitting the bottom of the sample block against a metal

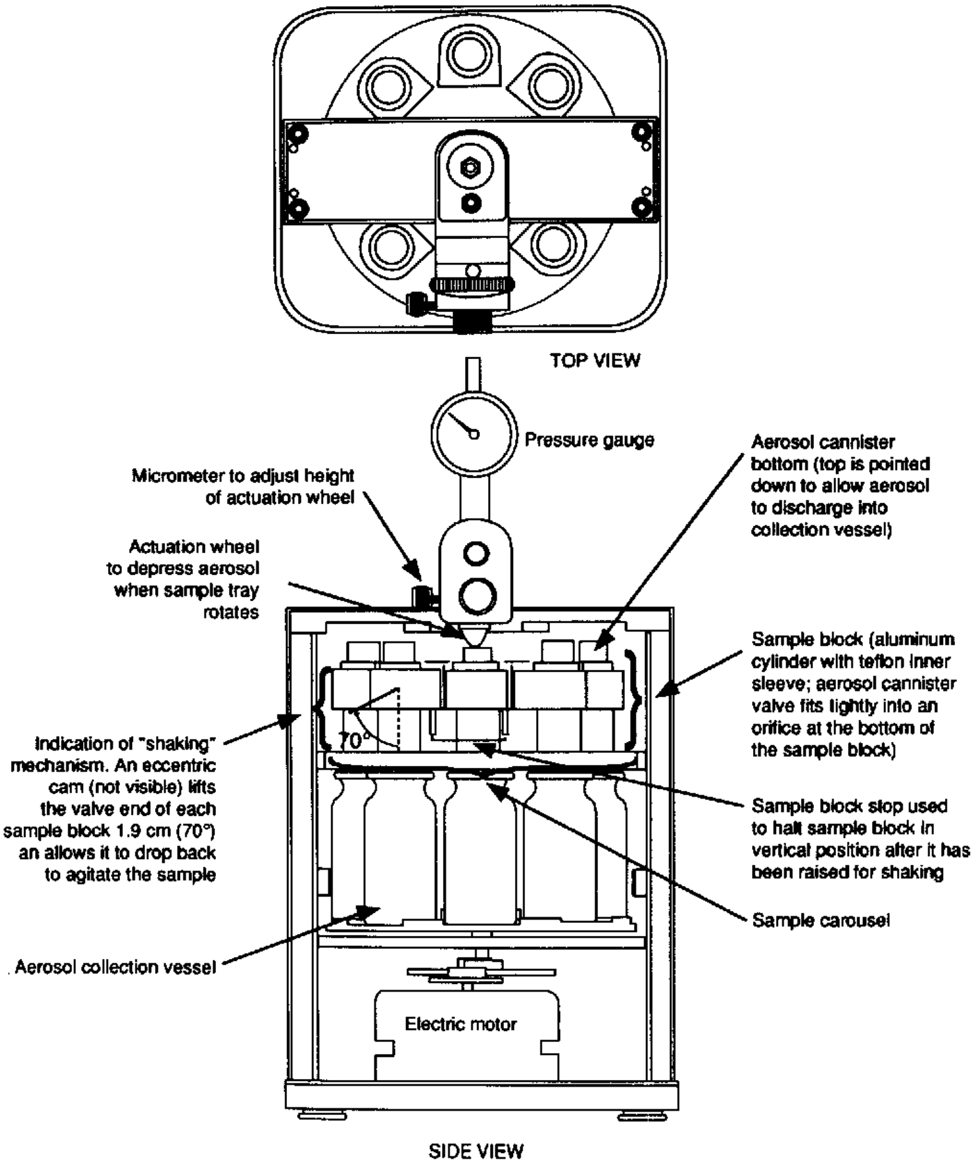

Figure 1(d)

plate and agitating the sample. Each aerosol unit on the sample tray is shaken four times per tray revolution (i.e. every 42 s).

The actuation mechanism consists of an adjustable actuation wheel and positioning arm. The positioning arm holds the actuation wheel at the correct angle to position it halfway between the stopping points of the sample carousel. As the sample tray rotates, the actuation wheel rolls over the bottom of an aerosol canister (positioned in the sample block with the valve stem down) forcing the valve stem inward a precise and reproducible distance and thus actuating the valve. An adjustable cam allows the height of the actuation wheel to be adjusted for aerosol units of different size and/or to optimize actuation pressure.

In order to obtain proper actuation and/or to achieve correct interaction with the robot, an aerosol canister must be precisely positioned in the automatic actuator. The positioning mechanism consists of a star wheel, cam follower, and a microswitch. The cam follower is mounted on a steel plate which is turned by the electric motor one revolution every seven seconds. As the cam follower turns, it enters a star wheel slot for 3 s. The aerosol samples are rotated on a sample tray as the cam follower turns in the star wheel slot. As the cam follower exists the slot, rotation stops with the samples precisely positioned. The cam follower then moves along to the next star wheel slot. For each revolution the microswitch is momentarily depressed by the cam follower. The microswitch output is read by the robot computer to determine the power turn off point for the electric motor after the completion of each actuation and to determine the time which was required to complete the turn. This time interval is used to detect positioning errors. For example, if the rotation time is too great, the cam follower has moved too far and a positioning error has occurred. If a positioning error is detected by the computer, testing is automatically stopped.

The robot starts and stops the actuator by turning the power to an electric motor on and off. The position of the motor shaft is monitored by means of a microswitch which is open and closed as the motor turns. The microswitch output is read by the robot computer to determine the power turn off point of the electric motor after the completion of each actuation and to determine the time which was required to complete the revolution. This is the previously noted time interval which is used to detect positioning errors.

The robot communicates with the computer via a RS-232 serial port. A terminal program is used to load programs between the robot and the computer. Communication between the robot and the computer does not exist when Lotus Measure is running. Multitasking software enables both tasks to be viewed in windows on the same screen. The robot program requests input of number of aerosol units to be tested, number of total actuations, number of waste actuations, and number of repetitive weights.

Balance communication

The robot computer sends a high logic level to the balance via the handshaking line 2 s after an aerosol unit has been placed on the balance. The balance sends a high logic level to the robot computer after the data has been transferred to Lotus Measure to signal that the aerosol unit may be removed from the balance. The handshaking line remains high until after Lotus Measure has completed communication with the balance. The computer requests data from the balance via the send line, and the balance sends data to Lotus Measure over the data line after it is stable and only after the robot has completed handshaking. The Lotus Measure program monitors the weight sent from the balance to determine when an aerosol unit is placed on or removed from the balance. A weight increment must exceed 50 mg in order for it to be recorded in the Lotus Measure table, and a weight must drop by 50 mg to signal the Lotus Measure program that the aerosol unit has been removed from the balance. Through this chain of events, weight is accepted into the Lotus Measure table only after the weight has exceeded 50 mg, the robot has completed its movements, and the balance stability requirement is met. The robot removes the aerosol unit only after the stable weight has been recorded.

Spray–weigh–spray

Validation of the automated system for the analysis of valve performance testing was performed by recording data both manually and with the automated system. Two different proprietary valve types (A & B) and canister sizes were tested. These combinations were chosen since they are typical of the valve/canister combinations encountered when testing developmental aerosol formulations in our laboratories. Valve type A had the larger canister which was tested for 230 actuations while valve type B had a smaller canister unit which was tested for 138 actuations.

Initial weights of the aerosol units were performed manually. The manual testing procedure consisted of 20 waste actuations, only the last of which was weighed, followed by three repetitive sprays for which each actuation was followed by a weighing. The aerosol sample was shaken thoroughly between each actuation. The last waste actuation together with the three repetitive weights yielded by calculation of weight differences, three weight losses per actuation. A 5 min delay period was given every 10 actuations to avoid effects due to cooling of the canister from expanding propellant.

The automated system and the manual measurement were performed on the same balance using the same number of waste and repetitive actuations and weighings. With the automated actuator, there was a 42 s delay period between each waste actuation and approximately a 1 min period during which the robot moved the aerosol units from the actuator to the balance and back for each weighing.

Three metered-dose units were tested concomitantly both manually and with the automated system. Lotus Measure was programmed to automatically produce from the raw data: a weight difference per actuation, average weight loss for each unit, standard deviation, relative standard deviation, grand mean, and a plot weight loss versus actuation number.

For all data generated using the automated system, the system was allowed to run unattended for the duration of the analysis.

Results and Discussion

A plot of manual and robotic data for valve

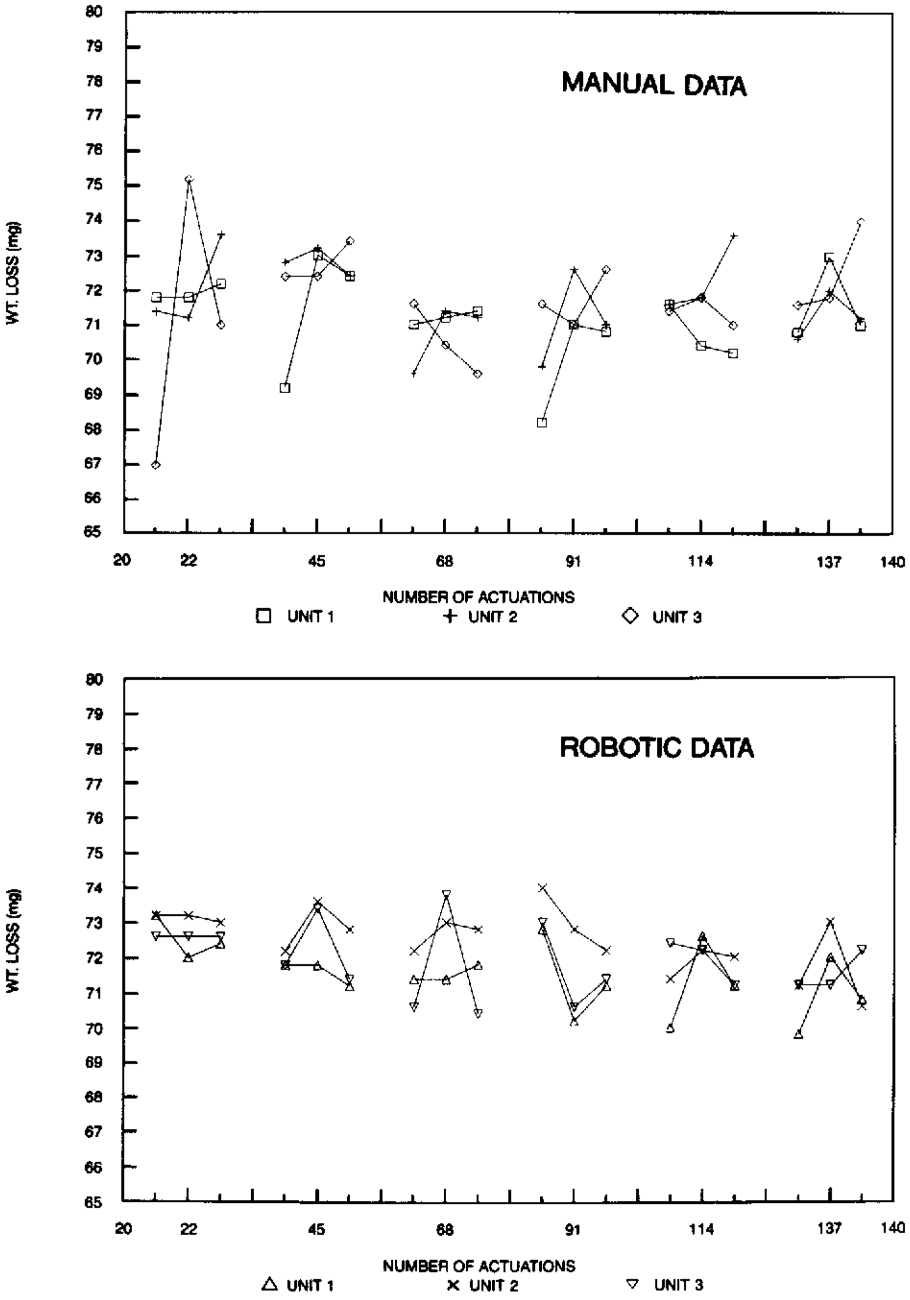

Figure 2
(Top) Data generated by an analyst. Weight loss per actuation for valve A as a function of actuation number. Three different samples were tested. (Bottom) Data generated by the automated (robotic) system. Weight loss per actuation for valve A as a function of actuation number. Three different samples were tested.

A showing weight loss per actuation versus actuation number is shown in Fig. 2. For six different aerosol units tested by each method, the data generated by the automated method was more precise than the manually generated data. With 138 actuations each, the average standard deviation was 0.91 and 1.36% for the automatic and manual methods, respectively. For the six aerosol units grouped together in a single data pool, the standard deviation was calculated to be 1.53% for the manual method and 1.58% for the automated method. This data indicates that the variation intrinsic to the aerosol units themselves was greater than the variation of either of the methods. The mean weight loss per actuation was 71.34 mg for the automated method and 71.87 mg for the manual method. The difference in the means

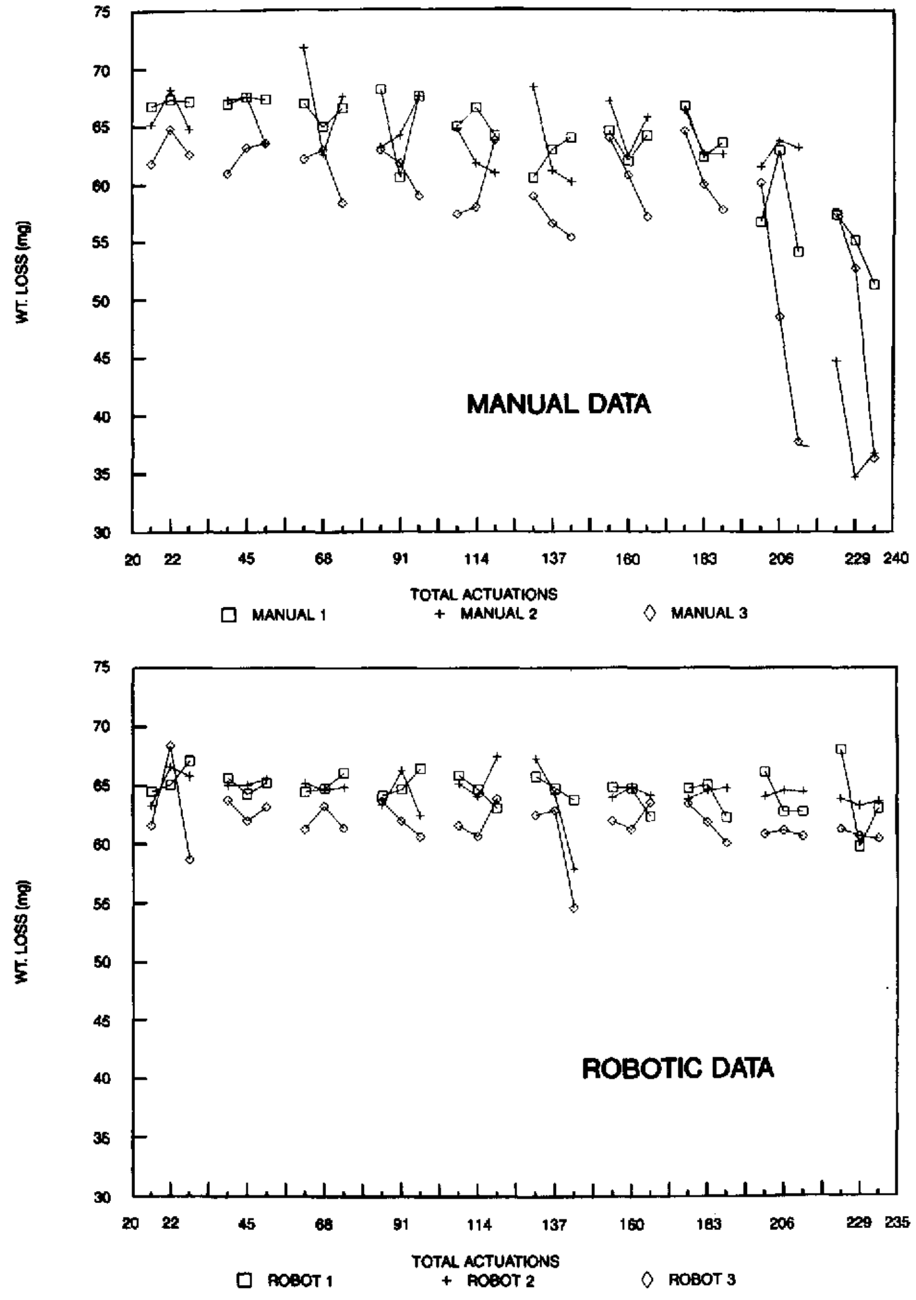

Figure 3
(Top) Data generated by an analyst. Weight loss per actuation for valve B as a function of actuation number. Three different samples were tested. (Bottom) Data generated by the automated (robotic) system. Weight loss per actuation for valve B as a function of actuation number. Three different samples tested.

was 0.53 which falls within the 95% confidence interval for data recorded by equivalent methods.

A plot of manually and automatically generated data for valve B showing weight loss per actuation versus actuation number is shown in Fig. 3. The weight loss per actuation for the manual testing was low for the last 25% of the actuations tested. The manual testing was repeated by the same analyst and this trend for low actuation weight was verified. The automated data collection system did not generate this trend. As is commonly the case with aerosol testing, the apparent difference in product behaviour was attributed to operator artifacts for the manual method. Degree of sample agitation, speed of repeated actuations, hand temperature, can orientation, etc., can all contribute to actuation performance. Figure 4 shows a plot of manual and automated data normalized and plotted together on the same graph. Normalized data was produced by taking the ratio of experimental to theoretical weight change and multiplying this ratio by one for automated data and by negative one for manual data. When the absolute value of the ratio is equal to one, the weight change per actuation agrees with theory. As was noted above, the manual data was shown to deviate and was less than theory for the last 25% of the actuations. Further investigations after the comparison study showed that this deviation could be avoided when a 10 min delay was imposed after every 10 actuations. The automated data did not show low actuation weights presumably because the programmed delay periods provided adequate time between actuations. To avoid introducing bias caused by the low actuation weights in the manual method, statistics were calculated excluding the low data points and comparing the same range of robotic data. The standard deviations of the methods were observed to be 2.33 and 3.41 for the automated and manual methods, respectively. Mean weight losses per actuation were calculated to be 63.88 mg for the automated method and 63.74 mg for the manual method. The difference in the means is 0.14 mg which falls within the 95% confidence interval for data recorded by equivalent methods.

Conclusions

An automated aerosol actuator has been generally described along with its specific application as part of a robotic system for testing the performance of aerosols to determine net weight loss per actuation. The com-

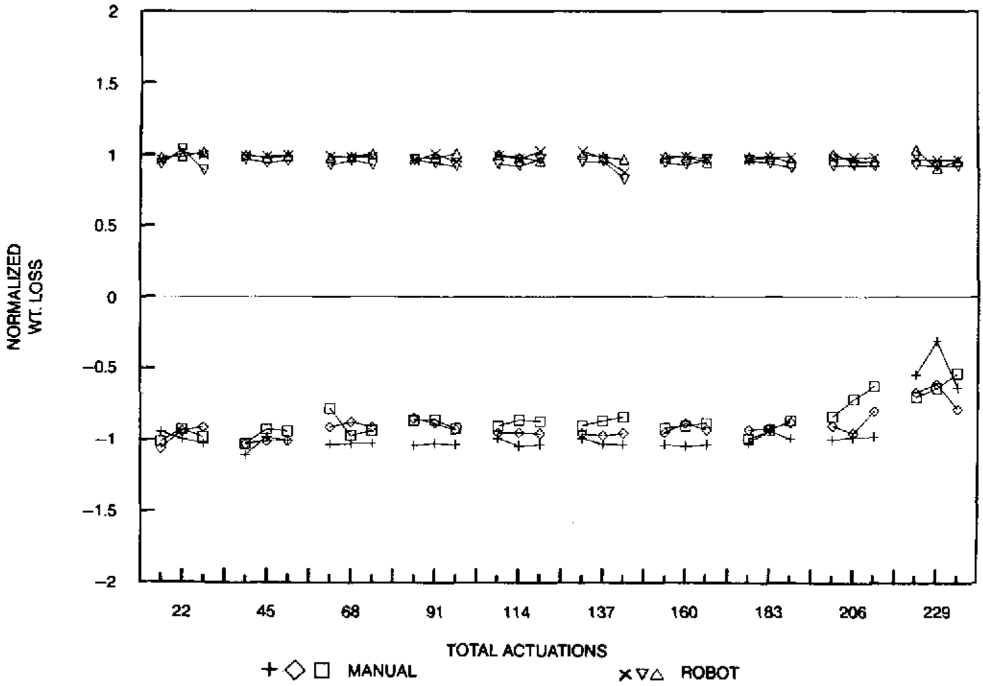

Figure 4
Normalized weight loss per actuation as a function of actuation number: analyst and robotic data. An absolute normalized value of one indicates that experimental data agrees exactly with the theoretically predicted value.

plete automated system has been demonstrated to provide equivalent results on similar samples as those obtained when a previously validated, existing manual method was used. Implementation of the automated method in our laboratories has resulted in a significant saving of manpower allowing for the more effective use of analysts. The system, once loaded with samples, runs unattended for the duration of the analyses. The automated system has been shown to be a reliable, productive and facile alternative to manual testing to determine weight loss per actuation for aerosol products. It is also important to note that the automated actuator can be applied to other types of pharmaceutical aerosol testing (e.g. unit spray content) in which repeated actuations of the sample must be performed in a controlled and reproducible manner.

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