Relative positions of stirrers and dissolution vessels may be adjusted at will. (*e*) Size of samples taken is adjustable.

The dissolution behavior of an experimental potassium chloride tablet was used to illustrate the application of this apparatus in comparison with a more laborious single dissolution flask procedure.

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Keyphrases

Dissolution apparatus—multiple testing
Apparatus, dissolution—photographs
Operating instructions—dissolution apparatus

Development and Evaluation of a Sampling Device for the Analysis of Pharmaceutical Aerosols

By SIDNEY P. TUESLEY, JOHN J. SCIARRA, and ANTHONY J. MONTE-BOVI

Various devices and techniques were studied in an attempt to obtain suitable samples of material from aerosol products. Generally accepted sampling procedures cannot be used since the aerosol product contains propellants that are extremely volatile. Several of these methods were investigated and used as the basis for assaying various aerosol products. A sampling device was developed and evaluated. The sampling device was designed in a manner that made available a sample of aerosol product that could then be assayed directly in the chamber. Openings were fitted with specially designed valves that allow for transfer of the contents without loss of volatile propellant or active ingredients. Various samples of aerosol products containing local anesthetics, steroids, and amines, were assayed by this method and found to give acceptable results. In all cases, the amount of active ingredient contained in each product could be accurately determined. The device makes possible a technique applicable to the analysis of most pharmaceutical aerosols. This method, which can be carried out with ease in a relatively short period of time, was shown to produce accurate results when used in the manner described.

THE ANALYSIS of pharmaceutical aerosols presents many unique problems to the analytical chemist. Generally encountered analytical techniques such as extractions and titrations cannot be performed without modification of the intact aerosol product. Since one or more of the components of an aerosol product may be extremely volatile, it is difficult to obtain a representative sample. The vapor pressure of the system may vary from 15 psig to about 40 psig, depending upon the nature and amount of propellant and other solvents that may be present.

All aerosol products consist of a volatile and a nonvolatile portion. The nonvolatile portion, generally referred to as the product concentrate, consists of the active ingredients dissolved, suspended, or emulsified in various solvents and other ingredients. While this concentrate may contain volatile solvents such as ethyl alcohol, acetone, *etc.*, the vapor pressure of these solvents at room temperature is considerably less than the more volatile propellants.

The propellant may consist of a compressed gas such as nitrogen, carbon dioxide, or nitrous oxide or, more commonly, of a liquified gas of the fluorocarbon type. Hydrocarbons such as propane, butane, and isobutane have not been used for pharmaceuticals at the present time. Dichlorodifluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), and trichloromonofluoromethane (propellant 11) are generally used for this purpose. The positive pressure within the container indicates the need for a sampling procedure by which active ingredients can be determined from a known amount of aerosol product. The form in which the active ingredients are found will vary accord-

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ing to the intended use of the product. This can be as a fine mist, wet spray, or foam.

Various attempts have been made to overcome the difficulties caused by the presence of the propellant. Different methods have been employed for the sampling of pharmaceutical aerosols. One commonly used method allows the propellant to escape, leaving behind the concentrate that consists of active ingredients and other nonvolatile agents used in the formulation. The solution may then be assayed and the percent active ingredient(s) in the aerosol formulation determined. This method of sampling, which has been used in a solubility study of different medicinal agents in fluorocarbon propellants by Tinney (1), involved the transfer of a filtered aliquot of a saturated solution of medicinal agent in the fluorocarbon propellant to a tared glass aerosol container. A specially designed transfer valve and actuator was used to effect the transfer. The dip tube, attached to the sample bottle, was removed from the transfer valve so that the propellant could be removed as a vapor. The total weight of the bottle containing the filtered saturated solution was determined. The propellant vapor was then removed from the sampling bottle. Following removal of the propellant, the weight of the container and valve was determined and the solubility of the medicinal agent calculated by the "weight by difference" method. This method is limited to those propellants and solvents that can be removed by vaporization at room temperature.

Young *et al.* (2) developed a method which was applicable to the assay of an aerosol containing epinephrine bitartrate and similar agents. The gross weight of the aerosol package was first determined and then the valve closure was punctured. A hypodermic needle was inserted through the valve closure that then allowed the propellant to escape through the opening of the needle. At this point, the valve could be safely removed. The remaining suspension was then assayed spectrophotometrically. Knowing the weight of the empty container and valve, the amount of active ingredient was determined. In order to determine uniformity of dosage released from a metered valve, Young *et al.* (2) employed a somewhat different method. This method consisted of inverting an aerosol package of epinephrine bitartrate or isoproterenol sulfate over a 250-ml. glass-stoppered graduated cylinder containing 200 ml. of 0.1 *N* acetic acid. A metered dose of medication was released into the cylinder and the cylinder was immediately stoppered and shaken. An aliquot of the acid solution containing the active ingredient was assayed spectrophotometrically.

Another method that was developed for this purpose utilized an "artificial respiratory system" (2). This system was designed to measure the delivery of the active ingredient dispensed through an oral adaptor. This procedure consisted of discharging the aerosol through the oral adaptor into a funnel attached to a glass tube which was immersed into a gas washing bottle containing distilled water. A vacuum was drawn on the system. This procedure essentially simulated conditions closely related to inhalation of the medication by a patient. The solution was then subjected to spectrophotometric assay.

Sampling techniques were developed by Lawless, Sciarra, and Monte-Bovi (3) and by Rifino, Monte-Bovi, and Sciarra (4) for the analysis of various medicinal amines and volatile oils, respectively, in aerosol formulations. Their sampling technique consisted of weighing the intact aerosol package and then bubbling a given volume of the aerosol into a suitable solvent and reweighing the container. The resulting solution, brought to the desired volume, was analyzed using gas-liquid chromatography. From this, the amount of active ingredients present in the aerosol package could be determined. The method whereby an aerosol product was bubbled through a solvent had previously been developed for the analysis of moisture in aerosols by the Fischer titration method (5)

This study was concerned with the development and testing of various devices and techniques which could routinely be applied to the analysis of various pharmaceutical aerosols. The applicability of the method to different types of aerosol packages, the speed with which the sample can be obtained, and the accuracy with which the active ingredients can be removed from the pressurized package were major considerations in the development of the sampling procedures. Various commercially available pharmaceutical aerosols were assayed, using the sampling techniques developed during this study. In this manner the application and suitability of the methods could be determined.

Several materials were investigated in order to determine the suitability of the material for the sampling device. Extruded stainless steel tubing, together with Plexiglas, was fabricated into a chamber. However, difficulty was encountered in securing an efficient seal between the metal and Plexiglas. Several openings had to be drilled, tapped, and fitted with stainless steel bolts. When the device was used, the Plexiglas, under the strain of the bolts, developed cracks. Based

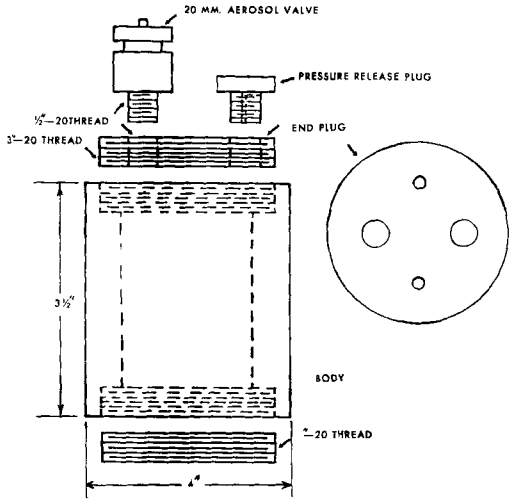

Fig. 1—Sampling chamber for aerosol products.

glass membrane and a 25-ml. buret. This was specially designed so as to allow potentiometric titrations directly within the cylinder.

Assay Procedures—The sampling device was washed with distilled water and dried with acetone prior to and following each assay. An accurately weighed sample of benzocaine NF, about 0.5 Gm., dried over phosphorus pentoxide for 3 hr., was placed into the open sampling device and 30 ml. of glacial acetic acid was added. A Teflon-coated magnetic stirring bar was placed into the container, which served to produce efficient stirring of the solution throughout the titration. The top cover of the device was screwed into place. The combination electrode was placed into one of the openings located in the top of the sampling container so that the tip of the electrode was immersed in the glacial acetic acid solution of benzocaine. A 25-ml. buret was introduced into the second opening. The electrode was connected to a Beckman Zeromatic pH meter, which had been set at the 1400-mv. range and adjusted to 0 mv. at the start of each titration. The benzocaine solution was then titrated with 0.1 *N* perchloric acid in glacial acetic acid. The equivalence point was determined potentiometrically and the milliliter of titrant represented at this point was obtained from a first derivative plot of $dmv./dml.$ *versus* ml. of titrant added. The procedure was repeated several times and these results are shown in Table I.

TABLE I—ASSAY OF BENZOCAINE NF IN DIFFERENT SOLVENT SYSTEMS

	Benzocaine in Glacial Acetic Acid		Benzocaine in Ethanol and Propylene Glycol		Benzocaine Aerosol		
	Determination No.						
	1	2	1	2	1	2	3
Weight of sample, Gm.	0.4419	0.4037	3.9698	4.0395	4.3827	6.4826	4.7262
Benzocaine in sample, Gm.	0.4419	0.4037	0.4054	0.4417	0.2799	0.4090	0.2982
0.1 *N* perchloric acid, ml.	26.8	24.2	24.7	26.75	16.6	25.2	18.0
Benzocaine found, Gm.	0.4437	0.3997	0.4080	0.4419	0.2792	0.4163	0.2973
Recovery, %	100.18	99.02	100.6	100.04	99.76	101.8	99.7

upon these preliminary results, Teflon was selected as the material of choice for construction of the chamber.

EXPERIMENTAL

Construction of the Sampling Device—This sampling device was constructed from a 3-in. piece of Fluoroflex "T" tubing having an internal diameter of 2.5 in. and external diameter of 3.5 in. The top and bottom of the sampling container were constructed from Fluoroflex "T" sheeting, 0.5 in. in thickness. The inside walls of the tube were threaded 0.5 in. down on each end. Both the top and bottom plates for the container were cut and threaded to match the threads of the sampling tube. The ends were than screwed into the cylinder and tightened, making a pressure-tight seal. Teflon tape was used on the threads to ensure an efficient seal. A piece of Fluoroflex "T" was machined to the same configuration as the neck and mouth of a standard uncoated glass aerosol bottle and fitted with a 20-mm. aerosol valve.[1] This assembly was then fitted into one of the openings on the top cover as shown in Fig. 1. The openings in the top plate were large enough to accommodate a Corning semimicro combination electrode with triple-purpose

[1] The valves used in this study are referred to as the "male-female" valves and were of the type used on various "mother-daughter" aerosol packages. A female-type valve was attached to the sampling device. Other standard aerosol valves can also be used provided a section of tubing or transfer actuator is attached to the valve stem.

Solutions of benzocaine NF were then prepared in a solvent mixture of 55% by weight of ethanol USP and 45% by weight of propylene glycol USP. These solutions were then placed into the sampling cylinder and assayed in a manner similar to the above described method. These results are also shown in Table I.

Having determined the suitability of the sampling device as a titration vessel, a sample aerosol product was prepared. This aerosol contained 6.3088 Gm. benzocaine NF, dissolved in a mixture of 55% by weight of ethanol USP and 45% by weight of propylene glycol USP. A sufficient amount of solvent was added to bring the total weight to 50 Gm. Propellant, consisting of a mixture of propellant 12/114 (40:60) was added to produce a total weight of 100 Gm. This formulation was packaged into a glass aerosol container and fitted with a female-type aerosol valve.

Thirty milliliters of glacial acetic acid was placed into the open sampling device and the top cover sealed into place. The two openings in the top cover were sealed with the two plugs, one containing the aerosol valve and the other the pressure release plug. The entire unit was then weighed and chilled

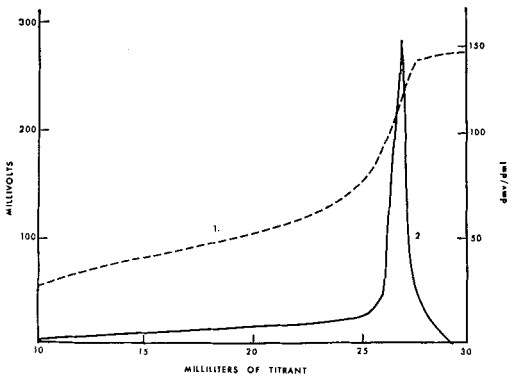

Fig. 2—Titration curve for benzocaine aerosol using 0.1 N perchloric acid as titrant. Key: 1, standard titration curve; 2, first derivative plot.

by placing it into a freezer or dry ice chest for about 10–15 min. A sample of benzocaine aerosol was then injected into the sampling chamber by inverting the sampling device over the upright aerosol container and fitting the valve stem of one valve into the valve opening located on the other container. By pushing the sampling device down, both valves will open allowing the product from the container to flow into the sampling device due to the difference in pressure between the two containers.[2] For the purpose of this study the standard type "male-female" or "mother-daughter" valves were used since these valves allow for transfer of contents from one aerosol container to another without the use of adaptors. Since most commercially available pharmaceutical aerosols do not make use of this valve, an adaptor must be used.

About 5.0 Gm. of aerosol product was allowed to flow into the sampling device. The actual amount acquired is dependent upon the nature of the active ingredient(s) and the type of assay used. This must be determined on an individual basis. The sampling device is than allowed to return to room temperature, dried of any moisture which may have condensed on the surface, and reweighed. The difference between the two weighings indicates the weight of sample.

The propellant was removed from the container by turning the pressure release plug one turn. The aerosol valve and pressure release plug are removed from the top cover and the openings fitted with the electrode and buret as previously described. The remaining solution was then titrated with 0.1 *N* perchloric acid and the equivalence point determined potentiometrically, and the milliliter of perchloric acid was obtained from a first derivative plot as illustrated in Fig. 2. From this result the amount of benzocaine in the formulation was calculated. These results are also indicated in Table I.

Various commercially available pharmaceutical aerosols were assayed using this sampling device and the appropriate assay. The aerosols utilized in this study are indicated in Table II. These products were selected on the basis of being representative of various types of aerosols requiring different analytical procedures for assay.

[2] This procedure is applicable for those aerosols containing a dip tube. Where no dip tube is present, the positions of the sampling device and aerosol container are inverted so that a liquid sample is obtained. Aerosols used in the upright position contain a dip tube attached to the valve housing while those used in the inverted position do not have a dip tube. Certain aerosols containing a dip tube and special valve can be used in either position.

Table II—Representative Pharmaceutical Aerosol Products

Active Ingredient	Concn.	Amount/ Dose, mg.
Epinephrine bitartrate[a]	7.0 mg./ml.	0.3
Ergotamine tartrate[a]	9.0 mg./ml.	0.36
Isoproterenol HCl[b]	2.5 mg./ml.	0.125
Prednisolone[c]	0.332 mg./Gm.	Non-metered
Cyclomethycaine HCl[b]	2.645 mg./Gm.	Non-metered
Pramoxine HCl[c]	10.0 mg./Gm.	Non-metered
Epinephrine HCl[a]	8.3 mg./ml.	0.3
Tetracaine[b]	10.0 mg./Gm.	0.5

[a] Suspended in vehicle of propellent with dispersing agents. [b] Solution in vehicle of propellant, ethanol, and other agents. [c] Solution in vehicle of propellant and other agents.

These products were separated into two groups; those that could be assayed by a potentiometric technique and those that utilize a spectrophotometric method. All of these aerosols contained a valve fitted with a stem. In order to effectively transfer material to the sampling container, a small piece of polyethylene tubing was fitted over the stem and attached to the sampling device. A transfer actuator could also be used.

Potentiometric Method—The aerosol product was sampled by determining the tare weight of the sealed sampling device containing 20 ml. of glacial acetic acid and fitted with the valves previously described. After chilling the device a sample of product was injected into the chamber. The weight of sample was determined by allowing the contents to reach room temperature and then reweighing the container. Where the aerosol product was fitted with a metered valve, the number of doses injected was recorded. In this manner the quantity of active ingredient dispensed each time the valve was depressed could be determined. The propellant was allowed to escape through the pressure release valve. The valves were removed from the top and replaced with the buret and electrode. The active ingredient was then assayed by titrating the nonaqueous solution with 0.01 *N* perchloric acid in glacial acetic acid as previously described.

Aerosol products containing tetracaine, epinephrine bitartrate, epinephrine hydrochloride, pramoxine hydrochloride, and cyclomethycaine hydrochloride were assayed by this method and the results are shown in Tables III and IV.

Spectrophotometric Method—Essentially the same method as described in the previous section was developed for the aerosols assayed spectrophotometrically. In most cases, part of the solvent used in the assay was added to the sampling device which was then weighed. The aerosol sample was injected into the tared and chilled container in a manner similar to that previously described and the weight of sample determined by reweighing the container after the contents attained room temperature. The propellant was allowed to escape and the contents were transferred to a volumetric flask. The sampling container was rinsed with solvent until all of the active ingredient was removed. The rinsings were added to the volumetric flask, necessary reagents added, and the solution was then

TABLE III—ASSAY OF METERED AEROSOLS BY POTENTIOMETRIC TITRATION

Active Ingredient →	Tetracaine		Epinephrine Bitartrate		Epinephrine HCl	
	Determination No.					
	1	2	1	2	1	2
No. of sprays	30	20	30	30	30	30
Amt. of active ingredient, mg.[a]	15.0	10.0	9.0	9.0	9.0	9.0
0.01 *N* perchloric acid, ml.	5.65	3.77	2.61	2.63	4.18	4.14
Amt. found, mg.	14.9	9.95	8.96	9.04	9.18	9.10
Recovery, %	99.4	99.53	99.62	100.4	102.0	101.0
Amt./dose, mg.	0.497	0.498	0.299	0.301	0.306	0.303

[a] Calculated on basis of labeled amount.

TABLE IV—ASSAY OF NONMETERED AEROSOLS BY POTENTIOMETRIC TITRATION

Active Ingredient →	Cyclomethycaine HCl		Pramoxine HCl	
	Determination No.			
	1	2	1	2
Wt. of sample, Gm.	10.6140	14.1880	3.0865	3.6942
Amt. of active ingredient, mg.[a]	28.0	37.47	30.81	36.94
0.01 *N* perchloric acid, ml.	7.085	9.45	9.325	14.2
Amt. found, mg.	28.04	37.42	30.71	36.95
Recovery, %	100.13	99.87	99.67	100.02

[a] Calculated on basis of labeled amount.

TABLE V—SPECTROPHOTOMETRIC ASSAY OF SEVERAL METERED PHARMACEUTICAL AEROSOLS

Active Ingredient →	Ergotamine Tartrate			Isoproterenol HCl		
	Determination No.					
	1	2	3	1	2	3
No. of sprays	10	10	10	40	40	40
Amt. of active ingredient, mg.[a]	3.6	3.6	3.6	5.0	5.0	5.0
Absorbance of active ingredient, A_U	0.129	0.127	0.130	0.59	0.585	0.598
Absorbance of standard, A_S	0.192	0.192	0.192	0.596	0.596	0.596
Amt. found, mg.	3.599	3.543	3.627	4.95	4.91	5.02
Recovery, %	99.98	98.42	100.75	99.16	98.15	100.34
Amt./dose, mg.	0.360	0.354	0.363	0.124	0.123	0.125

[a] Calculated on basis of labeled amount per dose.

brought to the desired volume. Aliquots of the solutions were then assayed using an appropriate spectrophotometer.

Isoproterenol Hydrochloride Aerosol—This aerosol was assayed using a modification of the official method of assay (6). A Beckman DU spectrophotometer was used and the absorbance of the solution at 279 mμ was determined. The absorbance (A_U) was then compared to the absorbance (A_S) of USP isoproterenol hydrochloride reference standard and the amount of isoproterenol hydrochloride in the sample calculated. These results are shown in Table V.

Ergotamine Tartrate Aerosol—Approximately 25 ml. of tartaric acid solution (1 in 100) was added to the sampling chamber that was then sealed, weighed, and chilled. The desired number of doses of ergotamine tartrate aerosol was added, the solution mixed and reweighed after having come to room temperature. This was then treated in a manner similar to the procedure followed for isoproterenol hydrochloride aerosol, and the absorbance (A_U) at 550 mμ was determined, using a Bausch and Lomb Spectronic 20, according to the USP method of assay (7). This result was then compared to the absorbance (A_S) of a standard solution of USP ergonovine maleate reference standard. The amount of ergotamine tartrate in the aerosol sample was calculated using the conversion factor of 1.488 which is the ratio of one-half the molecular weight of ergotamine tartrate to the molecular weight of ergonovine maleate. Table V also indicates these results.

Prednisolone Aerosol—About 30 ml. of ethanol USP was added to the sampling chamber. The chamber was sealed, weighed, and chilled. A sample of prednisolone aerosol was injected and the chamber was allowed to come to room temperature and reweighed. This was then treated in a manner similar to the isoproterenol hydrochloride aerosol and the absorbance (A_U) at 525 mμ was determined using a Bausch and Lomb Spectronic 20 according to the USP method of assay (8). This result was then compared to the absorbance (A_S) of USP prednisolone reference standard, and the amount of prednisolone in the aerosol was calculated. These results are shown in Table VI.

TABLE VI—SPECTROPHOTOMETRIC ASSAY OF NONMETERED PHARMACEUTICAL AEROSOLS CONTAINING PREDNISOLONE

Active Ingredient	Prednisolone Determination Number 1	2	3
Sample weight, Gm.	3.2604	3.5874	4.2604
Amt. of active ingredient, mg.[a]	10.83	11.19	14.14
Absorbance of active ingredient, A_U	0.452	0.497	0.595
Absorbance of standard, A_S	0.545	0.545	0.545
Amt. found, mg.	10.79	11.87	14.20
Recovery, %	99.68	99.67	100.39

[a] Calculated on basis of labeled amount.

DISCUSSION

The results obtained in this study indicate the applicability of the sampling chamber to the routine

sampling and analysis of several different types of pharmaceutical aerosols. Since the container can be easily closed to make a pressure-tight seal, there is practically no loss of product concentrate or propellant. The transfer from original container to sampling device can be achieved rapidly and accurately.

The sampling device was constructed from Fluoroflex "T" in order to provide a chamber that would be compatible with almost all medicinal materials, solvents, and reagents used in various assay procedures. This material allows for close tolerances and is strong enough to withstand the pressure of the intact aerosol samples when injected into the chamber. The sampling chamber was designed so that it can be easily disassembled for cleaning while the adaptor for the aerosol valve and the pressure relief valve were designed for easy removal so that the sample could be removed or titrated directly in the chamber.

This system was found to be especially applicable to those materials which are assayed by a potentiometric titration, thus eliminating the need to transfer material from the chamber. The value of the chamber and this type of analysis becomes of increasing importance when small amounts of active ingredients are involved. Benzocaine was chosen as the material to test the sampling device since it is found in many aerosol formulations and is suitable for a nonaqueous potentiometric titration. The end points of the titrations for this material were determined potentiometrically since the use of visual indicators were not possible due to the opaque nature of the Fluoroflex "T." However, the chamber can be redesigned to provide a window for titrations utilizing a visual indicator for the end point. The possibility of interference in the titrations due to the presence of dispersing agents, suspending agents, or other adjuncts in the formulation was considered. The benzocaine aerosol consisting of benzocaine in propylene glycol and ethyl alcohol was accurately prepared, with and without the propellant, and titrated. No interference in the titration was observed as indicated by the results.

For the analysis of commercially available aerosol products, the labeled quantity of the medicinal agent present was compared to the quantity found upon analysis of the sample. In all cases, the labeled quantity of drug and the amount of drug found upon analysis varied by no more than 1%; that is, recovery was 99% or better.

Spectrophotometric analysis was performed on various aerosols so that the accuracy of the chamber could be determined for those products requiring a transfer of active ingredients. As can be noted from the results obtained, over 99% of material was recovered. These results indicated the suitability of the sampling chamber for assays requiring transfer of materials from the sampling chamber to another container such as a volumetric flask.

SUMMARY

The sampling chamber proved to provide a simple, fast, and accurate method for the sampling of a variety of aerosol products. No limitations were found in the device with the aerosol products assayed. Those products selected were chosen on the basis of the type of assay which could be used and that they represent different types of aerosols. In addition to allowing for efficient sampling, the chamber was found to be quite suitable as a titration vessel, thus eliminating the need of transferring the material after removal of the propellant to another vessel. All of the aerosol products assayed by this method gave acceptable results. Further study will involve the use of this chamber for solubility determinations of medicinals in fluorocarbon propellants, analysis of water-based aerosols, and for use with aerosol foams.

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Keyphrases

Aerosols—pharmaceutical
Sampling device—aerosol analysis
Potentiometric analysis
UV spectrophotometry—analysis
Colorimetric analysis