# Labeling Suspended Aerosol Particles with Short-Lived Radionuclides for Determination of Particle Deposition

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**Abstract** □ Radiotracer techniques were developed to examine parameters that characterize pressurized aerosols designed to deliver insoluble particles suspended in the aerosol formulation. Microaggregated bovine serum albumin microspheres that were to be suspended were labeled with iodine-131 ($t_{1/2}$ = 8 d). This iodination procedure (>80% effective) is also applicable to iodine-123, which possesses superior characteristics for external imaging and further *in vivo* studies. This report shows that for pressurized aerosols containing suspended particles, each metered dose is approximately equal (not including the priming doses and the emptying doses). Increase in the delivery of the albumin particles out of the canister was best achieved by pretreating the valve assembly with a solution of 2% (w/v) bovine serum albumin in phosphate buffer. Use of a cascade impactor delineated the particle size distribution of the micropheres, with the majority of particles ranging in size from 2 to 8 μm. The data disclosed here indicate that the techniques developed with short-lived radionuclides can be used to (*a*) quantitate each metered dose, (*b*) characterize the particle size distribution profile of the aerosol contents, and (*c*) determine the extent of deposition of the particles in the aerosol canister and all of its components.

**Keyphrases** □ Radionuclides—short-lived, determination of particle deposition □ Aerosol particles—labeling with short-lived radionuclides, determination of particle deposition □ Particle deposition—determination with short-lived radionuclide labeling, suspended aerosol particles

In recent years, several reports have appeared that deal with the deposition of aerosols in the lungs of rats (1) and humans (2). Previous studies in this area have utilized liquid droplets delivered from nebulizers (3) and liquid droplets or solid particles delivered from pressurized aerosols (2, 4). Various equipment has also been developed for use in the determination of radioactive aerosol retention in the lungs of rabbits (5), as well as in studies designed to observe increased whole lung deposition of particles (6). Studies have also been performed to improve the deposition of aerosols in the lungs by controlling the breathing pattern of the patient (6). Oral adaptor extension devices have been shown to decrease the delivery of an aerosol to the oropharyngeal area (7). These devices are important not only because aerosols are used for site-specific drug delivery (2, 4), but also because the sizes of the aerosolized particles determine their distribution in the respiratory tract (2, 3).

Consequently, some studies have been performed to ascertain the amount of a compound, whether it is a solid or a liquid, that has actually been released in any individual metered dose. Several experimental techniques have been used for these determinations. In one study, weighing of a pressurized aerosol container before and after a designated number of actuations to measure the reproducibility of metered doses from a random sampling of the manufactured canisters has been reported (8). Davies *et al.* (9) have reported that there is great reproducibility and uniformity of delivery in random samples of manufactured pressurized aerosols. Those studies were performed on aerosols in a particle-size analyzer which is dependent on light-scattering techniques. In another study, the measured volume of propellant containing a known amount of particulate matter per dose has been reported (2). In yet another report, the size distribution of particles in commercially available cosmetic aerosols were delineated by microscopy, cascade impaction, and single-particle aerodynamic relaxation time analysis (10). Each of these are reliable accounts, but better quantitation can be achieved with short-lived radionuclides.

The most reliable method for the determination of reproducibility of all delivered doses from any given aerosol at any time, as well as the distribution of the size of particles released and the deposition of the compound in an aerosol canister, is by radioactive tracer methodology. Utilization of short-lived radionuclides in the assessment of quantitation techniques of aerosol particles has been reported in the past. For some time, the incorporation of a radioactive tag has been the major hindrance, due to the techniques needed for tagging the aerosol particle to be studied. Garrard *et al.* (11) have used $^{99m}$Tc-labeled $Fe_2O_3$ colloid in experimentation, whereas Moren (4), Newman *et al.* (2), and Agnew *et al.* (12) have utilized technetium-99m incorporated into synthetic polymer particles. Isawa *et al.* (13) have published results of an aerosol study in which $^{99m}$Tc-labeled serum albumin aerosols were scrutinized, although the tagging technique was not disclosed.

In this study, bovine microaggregated serum albumin microspheres labeled with iodine-131 were utilized as the suspended particles of the aerosol formulation. The chemical procedure developed for the labeling of the microspheres with iodine-131 is applicable to iodine-123, which possesses superior characteristics for external imaging (14). Unlike the previously studied synthetic particles (2, 4, 12), the iodinated albumin microspheres, which are currently used in nuclear medicine, can be degraded by the body and, therefore, are available for *in vivo* experimentation.

This report describes techniques which show how short-lived radionuclides can be used in (*a*) quantitation of each metered dose, (*b*) characterization of particle size distribution by the aerosol, and (*c*) determination of the extent of deposition of the particles in the canister and all of its components.

## EXPERIMENTAL SECTION

**Iodination of Microaggregated Albumin Microspheres**—The prepared microaggregated albumin microspheres[1] were first washed with phosphate buffer (pH 8.0) for use in the subsequent experiments. The microspheres were mixed in a mixer[2] and then centrifuged in a tabletop centrifuge[3]. The supernatant was removed, and the microspheres were resuspended in the phosphate buffer. The washing process was repeated a total of five times. To determine the weight of the microspheres, a representative sample was obtained, allowed to dry, and then weighed. The weight of microspheres per volume of solution was then determined and recorded.

The microspheres suspended in the phosphate buffer were then transferred

[1] Microaggregated albumin microspheres (diameter, 3-8 μm) were suspended in a 2% Tween 80 solution in ethanol; Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N.Y.
[2] Super Mixer, model 4722; Cole Parmer, Chicago, Ill.
[3] Clinical tabletop centrifuge; IEC Co., Needham Heights, Mass.

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**Table I—Determination of the Metered Doses Actuated from an Aerosol Canister as a Function of Number of the Actuation**

| | Total Recovered Activity[b], % of dose | | |
|---|---|---|---|
| Actuation[a] | Experiment 1 | Experiment 2 | Experiment 3 |
| 1 | 1.05 | | 0.04 |
| 2 | 2.04 | 4.12 | 2.69 |
| 3 | 4.49 | 5.24 | 3.10 |
| 4 | 4.50 | 4.72 | 12.40 |
| 5 | 6.83 | 8.29 | 5.22 |
| 6 | 5.93 | 3.48 | 2.84 |
| 7 | 6.11 | 2.51 | 6.29 |
| 8 | 6.23 | 2.38 | 6.00 |
| 9 | 7.06 | 7.41 | 5.15 |
| 10 | 6.07 | 2.78 | 6.25 |
| 11 | 8.63 | 4.08 | 4.77 |
| 12 | 4.07 | 5.71 | 2.89 |
| 13 | 8.40 | 7.40 | 4.66 |
| 14 | 4.35 | 4.21 | 6.39 |
| 15 | 7.08 | 3.22 | 4.56 |
| 16 | 8.13 | 3.34 | 8.85 |
| 17 | 4.59 | 0.91 | 4.76 |
| 18 | 1.28 | 2.62 | 4.02 |
| 19 | 2.10 | 1.99 | 1.04 |

[a] A canister was filled with propellant and $^{131}$I-labeled microaggregated albumin microspheres and crimped. After temperature equilibration, the canister was emptied by releasing the contents, actuation by actuation, into appropriately labeled scintillation vials. [b] Values listed are percentages of each dose to the total activity recovered in all the actuations from each of three aerosol canisters.

to a 1.0-mL glass vial with a magnetic spin-vane stirrer[4] and capped with a plastic cap containing a multiple-delivery rubber septum. The radionuclide was introduced into the closed system, and then *N*-chloro-4-methylbenzenesulfonamide sodium salt[5] (5 mg dissolved in 0.5 mL of buffer solution) was added such that the total concentration was 1-10 μg of microspheres. The reaction was stirred continuously for 5 min on a magnetic stirrer[6], and then sodium metabisulfite[7] in buffer solution (10 mg/0.25 mL) was added, so that the final ratio was 5 μg of sodium metabisulfite[7] to 10 μg of microspheres. The contents of the vial[4] were mixed for an additional 5 min and then transferred quantitatively to a conical centrifuge tube by repeated washings of the vial[4] with the phosphate buffer. The sample was then centrifuged for 8 min, the supernatant was removed, and the labeled microspheres were washed two more times with fresh phosphate buffer.

To determine the efficiency of iodination of the microspheres, two test methods were used. In the first method, the iodinated microspheres were precipitated with 20% trichloroacetic acid[8] and then centrifuged and washed repeatedly with the phosphate buffer. The radioactivity found in the precipitate was considered to be bound to the albumin microspheres. A second test involved the use of a dialysis bag[9] in phosphate buffer. The radioactivity remaining in the dialysis bag and in the total dialysate after 62 h was quantitated.

**Preparation of the Aerosol Containers**—The iodinated microspheres were suspended in ethanol[10] for use in the modified aerosol canister[11]. The canister was fitted with an insert made of aluminum, stainless steel, or plastic[12] so that when filled it would deliver 20 metered doses of 65 μg/dose (the similar commercially available canister is designed to deliver 200 metered doses).

The freshly prepared albumin microspheres[1] were placed in the plastic[12] insert in a canister and supercooled to −65°C in an acetone-dry ice bath. The propellant, dichlorodifluoromethane[13] (1.3 g), was added, and the valve[14] was put in place and crimped[15]. The closed canister was placed in a warm water bath, *i.e.*, 55°C, to test for crimping leaks. After successfully passing the leak test, the canister was allowed to equilibrate to room temperature for use in the deposition studies.

**Determination of the Radioactive Species**—By testing the interaction of the canister insert, valves, and contents singly and combined, determination of the radioactive species was attempted. That is, attempts were made to check whether the quantitated activity was due to free iodine, iodinated propellant, or the labeled microspheres. By varying the different parameters, the radioactive deposition was proven.

*Experiment 1*—Three aluminum canisters were filled with propellant and a known, weighed amount of unlabeled albumin microspheres, crimped closed, and then allowed to equilibrate to room temperature after successfully passing the leak test. The contents of each were then actuated into scintillation vials for later determination by the ninhydrin assay for the amount of protein present.

*Experiment 2*—Again, three aluminum aerosol containers were used, with the first containing $^{131}$I-iodinated microspheres and propellant. After crimping, the canister was warmed to room temperature, cooled to −60°C, and then opened. After evaporation of the propellant, the activity was quantitated. The second canister contained only [$^{131}$I]NaI and unlabeled microspheres. Propellant was added, the system was crimped hydraulically and allowed to warm to room temperature. After supercooling (−60°C) the aerosol container, the valve assembly was removed, and the contents were permitted to evaporate. The final canister in this portion of the experiment contained only [$^{131}$I]NaI and propellant that was allowed to evaporate without the crimping, warming, and cooling procedure.

*Experiment 3*—One of the two canisters containing iodinated microspheres and propellant was crimped closed, heated to 50°C, cooled to −60°C, and opened by removing the valve to allow the contents to evaporate. The other canister was filled with iodinated microspheres and propellant, which were then allowed to evaporate at room temperature.

**Metered Dose Determinations**—The canister was shaken manually for dispersion, and subsequently, the contents were emptied into plastic scintillation vials[16] lined with gauze. After each actuation, the canister was shaken vigorously for 2-3 s. The end of the valve stem was held with needle-nose pliers, and each metered dose was delivered into a separate appropriate vial. The collection of actuations was continued until the canister was empty. The canister was then dismantled, the inside of the plastic[12] insert was washed exhaustively, and the valve was dismantled to quantitate the deposition of the radioactivity.

**Cascade Impaction**—Filled and leak-tested aerosol canisters containing the radiolabeled albumin microspheres[1] were also used in the second experiment. An appropriate oral adaptor was fitted onto the canister and the valve stem, and subsequently, the aerosol was actuated in a cascade impactor[17]. A pressure of 18 psi was applied to the cascade impactor with a vacuum pump[18]. The canister was shaken before each actuation into the impactor, and the vacuum was run for an additional 5 min after the last actuation to ensure complete impaction. The glass slides for collecting the sized particles were removed and washed with 3 M NaOH[19]. All washings were collected, and the radioactivity was quantitated.

## RESULTS AND DISCUSSION

This study was undertaken to examine several parameters which characterize pressurized aerosols in which the drug used is in the form of an insoluble particle suspended in the aerosol formulation. These parameters include (*a*) accurate quantitation of metered doses, (*b*) characterization of the size distribution of particles ejected from the aerosol, and (*c*) the deposition profile of the aerosol particles in the canister and component parts.

To achieve these goals, microaggregated bovine albumin microspheres (ranging from 3 to 8 μm in diameter) were labeled with iodine-131 by the general methods of McConahey and Dixon (15), Greenwood *et al.* (16), and Hughes and Straessle (17) adapted for use with microspheres in this experiment. The microspheres, which were suspended in phosphate buffer (pH 8.0), were placed in a glass vial[4], and the radioactivity, in this case [$^{131}$I]NaI, was added. *N*-Chloro-4-methylbenzenesulfonamide sodium salt was added, the mixture was stirred for 5 min, and the reducing agent, sodium metabisulfite, was added to halt the iodination procedure. The radiolabeled microspheres were then washed with phosphate buffer to remove any residual radioactivity.

To ascertain that the iodine was covalently bonded to the protein backbone, the microaggregated albumin microspheres were precipitated with trichloroacetic acid. The total radioactivity found in the supernatant and in the precipitated protein indicated an 80-90% efficiency of iodination. To further determine the covalent linkage of the iodine to the microspheres, an identical sample of the microspheres was dialyzed[9]. The results indicate that 12% of the total radioactivity was found in the dialysate and the dialysis bag, confirming that the majority (>80%) of the radioactivity is associated with the microspheres.

[4] Minivial and stirrer; Reliance Glass Work Co., Bensenville, Ill.
[5] Chloramine-T; Eastman Kodak Co., Rochester, N.Y.
[6] Model PC-351; Corning Glass Works, Corning, N.Y.
[7] Mallinckrodt, Inc., Paris, Ky.
[8] J. T. Baker Chemical Co., Phillipsburg, N.J.
[9] Spectropor Membrane Tubing (molecular weight cut off ~3500); Spectrum Medical Industries Inc., Los Angeles, Calif.
[10] U.S. Industrial Chemical, Louisville, Ky.
[11] Cebal canister; Lederle Laboratories.
[12] Teflon, Dupont.
[13] Freon-12; Racon Inc., Wichita, Kan.
[14] Valois valve; Lederle Laboratories.
[15] J & G Crimper, Paterson, N.J.
[16] Packard Instrument Co., Downers Grove, Ill.
[17] Delron DCI; Delron Research Products Co., Powell, Ohio.
[18] Gast Manufacturing Co., Benton Harbor, Mich.
[19] Fisher Scientific Co., Fair Lawn, N.J.

**Table II—Effect of Various Treatments Involving Aerosol Valves and Canister Contents on the Delivery of Iodinated Microspheres [a]**

| Canister | Valve Treatment | Surfactant | Percent Radioactivity In Valve | In Insert [b] |
|---|---|---|---|---|
| 1 | | 2% (v/v) Tween 80 in EtOH | 79.9 | 8.9 |
| 2 | 2% (w/v) BSA [c] in phosphate buffer pipetted into valve | 2% (v/v) Tween 80 in EtOH | 51.4 | 11.3 |
| 3 | 4% (w/v) BSA [c] in phosphate buffer pipetted into valve | 2% (v/v) Tween 80 in EtOH | 89.8 | 4.5 |
| 4 | 10% (w/v) Tween 80 in phosphate buffer pipetted in valve | 2% (v/v) Tween 80 in EtOH | 57.5 | 5.8 |
| 5 | 4% (v/v) Tween 80 in phosphate buffer pipetted in valve | 10% (v/v) Tween 80 in EtOH | 89.9 | 4.3 |
| 6 | 10% (v/v) Tween 80 in phosphate buffer pipetted in valve | 10% (v/v) Tween 80 in EtOH | 83.5 | 6.9 |
| 7 | | 2% (v/v) Tween 80 in EtOH | 94.1 | 1.9 |
| 8 | | 10% (v/v) Tween 80 in EtOH | 83.2 | 7.9 |
| 9 | Silylated with 1% (v/v) organosilane [d] in dioxane by immersion | | 77.4 | 10.2 |
| 10 | Silylated with 1% (v/v) organosilane [d] in methanol by immersion | | 75.1 | 4.2 |
| 11 | Silylated with 1% (v/v) organosilane [d] in distilled water by immersion | | 74.5 | 4.8 |
| 12 | 2% (w/v) BSA [c] in phosphate buffer pipetted into valve | | 54.6 | 6.2 |
| 13 | 5% (w/v) BSA [c] in phosphate buffer pipetted into valve | | 59.2 | 8.5 |
| 14 | 10% (w/v) BSA [c] in phosphate buffer pipetted into valve | | 71.2 | 8.7 |
| 15 | Silylated with 100% (v/v) trimethylchlorosilane by immersion | | 82.9 | 6.4 |

[a] Numbers represent percent of total radioactivity delivered from the aerosol. [b] Teflon; DuPont. [c] Bovine serum albumin. [d] Prosil-8; PCR Research Chemicals, Inc.

When the labeled microspheres were photographed[20] under a microscope[21] before and after the labeling process, it was found that their spherical geometry remained unaltered by the iodination procedure.

The labeled microspheres were introduced into an aerosol canister[11] (a plastic insert was used to decrease the fill volume), the propellant[13] was added, and the canister was crimped closed with the valve[14] in place. Leak tests in warm water provided proof of good crimps with no gas leaks, and the filled canisters were subsequently allowed to equilibrate to room temperature for 15 min before use in the experiments.

Experiments were devised to determine the reproducibility of each metered dose from the canister. The aerosol container was shaken; each actuation was collected in individual scintillation vials[16] lined with gauze and quantitated.

The percentage of the total radioactivity collected from each actuation is listed in Table I. In all three experiments, the first three actuations (necessary to prime the valve) had suboptimal amounts of solid particles, as indicated by the smaller amounts of radioactivity delivered. The last three doses also showed lower amounts of radioactivity. The total radioactivity released from the canister represented only 5% of the total quantitated. The majority of the activity was found in the valve. Several attempts were made to improve the delivery of the labeled microspheres from the aerosol canister. These included impregnation of the valve with (*a*) 2, 5, or 10% bovine serum albumin in phosphate buffer, (*b*) 4 or 10% Tween 80 in phosphate buffer, and (*c*) 1% organosilane[22] in dioxane, methanol, or distilled water. The best results (Table II) were obtained when the valve was impregnated with 2% bovine serum albumin in phosphate buffer. A total of 0.4 mL was applied directly into the valve, and it was allowed to air dry at room temperature for 1 h before use. Approximately 50% of the total activity was found in the valve after the albumin pretreatment, indicating an improvement in delivery of the labeled microspheres of ~40%.

The amount of protein present in unlabeled microspheres delivered from the aerosol canister was determined using the ninhydrin assay (4.31 mg), indicating that ~20% had been actuated out of an untreated aerosol container. This value is higher than the reported value of 5% for the radiolabeled microspheres released from the canister by acutating the valve. Further experiments with (a) labeled microspheres and propellant, (*b*) unlabeled microspheres, [$^{131}$I]NaI, and propellant, and (*c*) [$^{131}$I]NaI and propellant demonstrated that iodine-131 alone was not responsible for the activity present in the valve assembly, but the iodinated microspheres represented the radioactive species quantitated.

To determine the particle size distribution of the aerosol, a cascade impactor[17] was utilized. Either 2 or all 20 actuations (metered doses) were passed through a cascade impactor[17] subjected to a vacuum of 18 psi[18]. Due to the aerodynamic design of this particle size analyzer, the microspheres exhibited a size distribution profile as shown in Table III. Stage 1, with the largest opening, collected the heaviest or largest particles, whereas stage 6 collected those particles which traveled the fastest, that is, the smallest particles. The size determination provided by the cascade impactor[17] showed that the majority of particles (stages 3-5, Table III), had sizes ranging from 2 to 8 μm.

Dismantling of the emptied canister and quantitation of the residual radioactivity constituted the final aspect of the study. The valve was removed from the canister and separated into six component parts. Approximately 90% of the total radioactivity in the aerosol container was found in the valve[14], with the spring accounting for the highest amount counted (95%). Impregnation of the valve decreased the amount of radioactivity in the spring to 46%. Radioactivity was also present in the plastic[12] insert, and direct counting of the insert with the residue present led to quantitation of the particles that had not been aerosolized (2-10%).

The major drawback in this study was the tendency of the $^{131}$I-labeled albumin microspheres to adhere to the various components of the aerosol container. A substantial amount of the total radioactivity was located in the valve apparatus, and therefore, this type of suspended microsphere aerosol system is not practical for drug delivery. However, the data obtained concerning the quantitation of metered doses and the determination of size distribution of particles illustrate the usefulness of tracer methodology in aerosol research.

Table I shows that reasonably equal doses can be delivered in actuations 5-16. The first four primer doses delivered lesser quantities of the formulation. This is probably due to the fact that these primer doses rid the valve of any water in the stem after the leak test and fill the valve chamber with the propellant. The last three doses shown are also smaller. As the pressure decreases, the quantity of particles delivered becomes less because the weight of the microspheres is too great for the amount of propellant remaining.

In the particular valve system utilized, each metered dose delivered is 65 μg. Therefore, determination of a single dose by the conventional weighing-by-difference method would be difficult.

**Table III—Determination of Particle Size Distribution Profile of Microspheres Delivered from an Aerosol [a]**

| Cascade Impactor Stage | Known particle Size Impacted, μm | Particle size, % of total [b] Experiment 1 | Experiment 2 |
|---|---|---|---|
| 1 | 32 | 15.18 | 16.59 |
| 2 | 16 | 9.14 | 11.30 |
| 3 | 8 | 23.02 | 24.06 |
| 4 | 4 | 24.59 | 17.42 |
| 5 | 2 | 14.73 | 15.80 |
| 6 | 1 | 9.21 | 10.59 |
| Filter paper | 0.5 | 4.14 | 4.24 |

[a] Data were obtained from $^{131}$I-labeled microaggregated albumin microspheres pulled through a cascade impactor with 18 psi pressure applied by two in-line vacuum pumps. [b] Values listed are percentages of total radioactivity recovered on all six glass slides of the impactor plus the filter paper at the bottom of the cascade impactor.

[20] Model N35A camera; Nikon.
[21] Reichert microscope, Vienna, Austria.
[22] ProSil-8; PCR Research Chemicals, Inc., Gainesville, Fla.

The variability of the amount delivered per actuation could be due to inadequate shaking of the aerosol container. The method of collection of the labeled microspheres could also cause the valve stem to be blocked, thus detrimentally affecting the results.

The cascade impactor, which was used to delineate the particle size distribution profile, showed that the majority of microspheres had sizes ranging from 2 to 8 μm. The size profile seen in Table III lists microspheres with sizes greater than the reported prepared size of 3 to 8 μm, indicating aggregation of the smaller particles into heavier larger clusters. These aggregates were deposited onto the glass slides of the first two stages of the impactor, as dictated by the aerodynamic parameters of this particle-size analyzer. Again, the radiotracer method proved superior to the classical weighing-by-difference procedure for quantitation of the amount of particulate matter present on each slide after only one actuation of the aerosol.

The deposition of the microspheres onto the components of the valve constituted the final portion of this study. Untreated valves permitted the release of ~5–10% of the total radioactivity. By pretreating the valves with albumin solutions, the adherence of the iodinated albumin microspheres to the plastic parts of the valve and the metal spring was significantly decreased. The delivery of the activity from the treated canister, however, was found not to exceed 50% of the total dose. These results indicate that much more work must be done before microspheres utilized as a drug delivery system can be released effectively from present aerosol canisters.

## CONCLUSIONS

The advantages of radiotracer methodology described in the study of aerosols are multifold: (*a*) single doses of an aerosol delivered from a canister can be analyzed, rather than multiple doses as required in previous studies, (*b*) short-lived isotopes can be disposed of easily after the passing of an appropriate decay period, and (*c*) by proper choice of the radionuclide label, rapid and accurate data may be obtained both in *in vivo* and *in vitro* studies. Since aerosols are designed to deliver a metered amount of drug to the patient, the elucidation of the size of the dose and its deposition in the patient is an important consideration. The technique outlined here should prove to be useful in answering these problems.

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# Effects of Solvent Medium on Solubility III: Hydrophilic–Lipophilic Character Exhibited by Some Functional Groups Having Oxygen or Nitrogen in Ethanol–Water


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**Abstract** □ Solubility data of nine derivatives of the structure $p$-$X_1$—$C_6H_4$—$X_2$ in ethanol-water at 25°C are reported. The correlation of such sets of data by $\log S_y = P_y \cdot \log S_x + C$ yields the medium effect parameter $P_y$ for a variety of functional groups possessing either oxygen or nitrogen. $P_y$ accounts for the hydrophilic-lipophilic character exhibited by each group.



**Keyphrases** □ Solubility—effects of solvent medium, hydrophilic-lipophilic character, ethanol-water □ Solvent medium—effects on solubility, hydrophilic-lipophilic character, ethanol-water □ Hydrophilic-lipophilic character—effects of solvent medium, solubility, ethanol-water


The existence of linear relationships between the logarithms of the solubility equilibria of structurally related crystalline compounds, as they vary with changes in solvent or solvent composition has been shown previously (1, 2). Such linear free energy relationships (LFER) are conveniently expressed by:

$$\log S_y = P_y \cdot \log S_x + C \qquad \text{(Eq. 1)}$$

where $S_y$ and $S_x$ are sets of solubility data of compounds $A_y$ and $A_x$, respectively. By taking a proper solvent condition as reference, Eq. 1 becomes:

$$\log S_y - \log S_y^0 = P_y(\log S_x - \log S_x^0) \qquad \text{(Eq. 2)}$$

or

$$\Delta\log S_y = P_y \cdot \Delta\log S_x \qquad \text{(Eq. 3)}$$

The medium effect parameter $P_y$ depends on the structural difference between $A_y$ and $A_x$ on the one side and on the effects of the solvent change on the solubility of the substrate series (*i.e.*, on the sign of $\Delta\log S$) on the other. To illustrate this point, Fig. 1 shows a typical LFER plot of a pair of $p$-aminobenzoic esters which pass through a solubility maximum when they move from the first to the last solvent condition. There, as the solvent system increases in lipophilicity, the solubility




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