Determination of Drug Solubility in Aerosol Propellants

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INTRODUCTION

There are two types of formulations administered using pressurized metered-dose inhalers (MDIs). In conventional solution-type MDIs, drug is dissolved with the aid of nonvolatile cosolvents such as ethanol, while in suspension formulations small micronized particles of undissolved drug are distributed in the propellant blend (1). When a patient actuates the valve, a precisely measured dose of drug is released and subsequently inhaled. For locally acting MDIs, large particles (or droplets) impact in the orapharynx, producing no beneficial effects. Smaller particles penetrate into the bronchioles or pulmonary regions of the lung, where they exert their therapeutic effects (2). It is therefore necessary that suspension-type MDIs are formulated with "potentially respirable" micronized particles (median diameter, approximately 3 μm) (3) and that these particles do not grow during the shelf life of the product. Growth can lead to less penetration of drug into the lung (4) and disrupt operation of the metering valve.

In the absence of interparticulate aggregation, which is usually controllable with careful choice of surfactant, a prerequisite for particle growth, also called Ostwald ripening (5), is dissolution of the predominantly "suspended" drug, at a concentration higher than its equilibrium solubility in the propellant blend. The concentration of dissolved drug in propellant may actually exceed the equilibrium solubility since smaller (predominantly submicron) particles in the suspension display a high surface curvature, leading to easier escape of drug molecules from their surface. This phenomenon is called the "Kelvin effect." Most presently marketed suspension-type MDIs contain P-11, in combination with P-12 and/or P-114. Unfortunately, P-11, with its relatively high Kauri-butanol value of 60, can induce limited drug solubility in the propellant blend, allowing particle growth to occur. Drug dissolution may be further enhanced by the presence of surfactants or small amounts of cosolvents (usually added to facilitate concentrate filling).

It is difficult to determine the extent of drug dissolution in pressurized suspension formulations by conventional methods. The suspension concentration frequently exceeds the concentration of dissolved drug by several orders of magnitude, and it is difficult to separate dissolved from suspended drug without perturbation of the equilibrium established in liquified propellants. For example, cooling a suspension after it has sedimented and sampling the supernatant is likely to reduce the observed drug solubility, while without cooling, evaporation losses can be substantial. In this report a simple filtration apparatus is presented which allows easy separation of dissolved from suspended drug, without the disadvantages presented above. Such an apparatus may prove useful to those interested in aerosol formulation. For example, significant dissolution may be predictive of particle growth during real-time storage studies of suspension formulations. The feasibility of dissolving new chemical entities in propellants without the aid of nonvolatile cosolvents could be easily assessed. Our validation studies on the apparatus are presented in this paper, in which we employed salicylic acid, an easily assayed model drug known to be slightly soluble in several liquified propellants used in the production of inhalation aerosols (1).

MATERIALS AND METHODS

Preparation of Pressurized Aerosol Units

Several series of suspension aerosols were prepared using salicylic acid (SA; City Chemical Corp, New York) at a concentration of 1.0 and 0.2% (w/w). SA was micronized prior to use using a Jet-O-Mizer fluid energy mill (Model 00, Fluid Energy Processing and Equipment Co., Hatfield, PA) operated at 70 psig using dry air. The size of the resulting powder was estimated by optical microscopy (Nikon Optiphot, Tokyo). SA was weighed directly into 2 or 4-oz plastic-coated glass bottles (Wheaton Glass, Mays Landing, NJ), the required amount of P-11 (Dymel 11, Du Pont, Wilmington, DE) added (an excess was evaporated to purge the bottle of air), and a modified, continuous BK356 valve (Bespak, Cary, NC) crimped in place (Pamasol 2005/10 crimper and propellant filler, Pfaffikon, Switzerland). P-12 (Dymel 12, Du Pont, Wilmington, DE) was pressure filled through the valve directly from the cylinder. Completed units contained P-12 and P-11 percentages of 100:0, 75:25, 50:50, and 0:100% (w/w), respectively. No surfactant was employed in these studies. Six replicates of each formulation (and corresponding blanks containing no SA) were stored under ambient temperatures (25 ± 1°C) or at 37 ± 0.5°C in an incubator.

Determination of Salicylic Acid Solubility

The apparatus (shown in Fig. 1) consisted of two leakproof couplings, one connected to the valve stem of the aerosol unit containing the suspension formulation to be sampled (in an inverted position with no dip-tube) and the other to an airtight receiving container. The receiving container consisted of a crimped and purged (using P-11) glass aerosol bottle fitted with a continuous valve and was preweighed prior to use. Between the couplings a stainless-steel filter unit (micro-syringe filter housing containing a 25-mm-diameter GVWP 0.22-μm filter sandwiched between stainless-steel support screens, Millipore, Bedford, MA)

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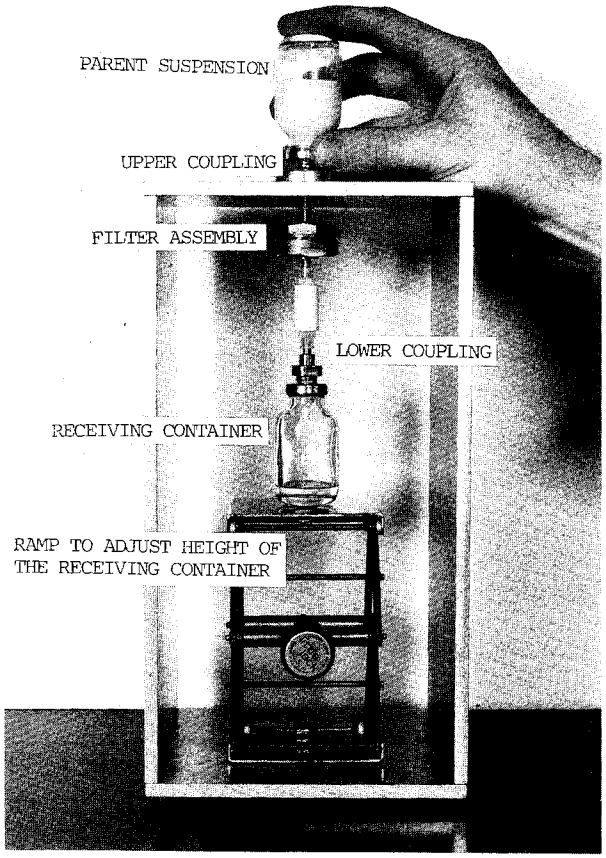

Fig. 1. Annotated photograph of the filtration apparatus in use.

separated dissolved SA in propellant from undissolved SA. The couplings and filter assembly were confined within a frame which held all the components in place.

The receiving container was positioned on the ramp to produce a gas-tight seal with the lower coupling. Pressure exerted by the ramp on the valve stem kept the valve in the open position. The aerosol unit containing the SA suspension was then pressed gently into the upper coupling, opening its valve and causing suspension to flow into the filter assembly. Propellant and any dissolved SA passed the filter and was collected in the receiver. When sufficient propellant accumulated (typically about 5 g), the ramp was lowered, closing the receiving valve, and the parent suspension detached from the upper coupling. The receiving pressure pack was reweighed and purged of propellant (by venting the vapor only), and the valve removed. Residual SA in the receiving container was dissolved in 0.01 *M* aqueous sodium hydroxide (Fisher Scientific, St. Louis, MO), diluted to fall within the linear region of a Beer Lambert plot (correlation coefficient = 1.0000, $n = 6$), and assayed by UV spectroscopy (Varian DMS 1000, Palo Alto, CA) at 295 nm. Control formulations containing no SA were assayed for comparison.

RESULTS AND DISCUSSION

The particle size distribution of micronized SA was found to consist of 99.7% (by length) <12.5 μm, with 52% <2.5 μm. The results and discussion presented below, in paragraphs a, b, and c, are some validation experiments designed to test the utility of the apparatus alongside some results which are intended to exemplify the use of this apparatus to obtain solubility data useful to an aerosol formulator. Obviously, these validation experiments relate only to a single batch of SA; a different initial fraction of particles less than the filter cutoff size or a different drug may necessitate a separate series of validation experiments. In some cases it may be necessary to use a specific drug assay, for example, when a surfactant or elastomer extractable contains a chromophore having significant absorption at the analytical wavelength.

Equipment Validation

(a) Salicylic acid concentrations in P-12 were determined in the presence of excess SA at several time points (Fig. 2). From the last five time points of this preliminary experiment, the mean equilibrium solubility was determined to be 173 μg SA/g P-12. The standard deviation (SD) of these determinations was 4 μg SA/g P-12. This constant concentration indicates that equilibrium solubility was reached within approximately 30 min as evidenced by a horizontal asymptote. In subsequent experiments all solubilities were determined at least 30 min after preparation of the aerosol unit. The time to reach equilibrium may be different with other drug–propellant combinations and is also dependent on temperature.

(b) Micronized SA was suspended in P-12 at concentrations of 1 and 0.2% (w/w); the apparent solubility of SA was 187 μg/g (SD = 9μg/g) and 189 μg/g (SD = 6 μg/g) for the 1 and 0.2% (w/w) parent suspensions, respectively. These results were not significantly different from one another (using a *t* test, $P \leq 0.05$). Because SA was initially suspended at concentrations 10 and 50 times in excess of the measured solubility (for 0.2 and 1.0% w/w, SA aerosols, respectively), this indicates that suspended particles <0.22 μm contributed negligibly to the concentration of SA determined to be dissolved. The 1% parent suspension might have been expected to produce a greater apparent solubility than the 0.2% suspension if SA particles less than the pore size of the filter (<0.22 μm) contributed significantly to the measured solubility (it should contain five times the mass of particles able to penetrate the filter).

(c) As a final validation experiment the influence of filtrate weight on apparent solubility was determined by cal-

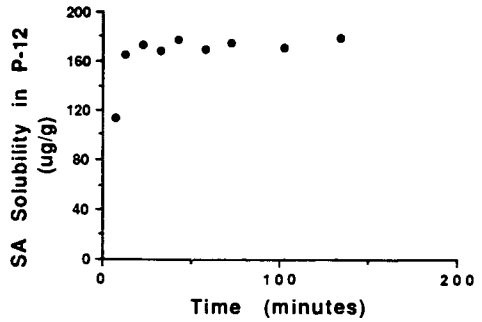

Fig. 2. Salicylic acid solubility in P-12 as a function of post-preparation time.

culating apparent solubility from mean filtrate weights of 4.5 g (SD = 1.2 g) and 8.9 g (SD = 1.0 g) from each of six formulations containing 1% (w/w) SA in P-12. Apparent solubility was 180 μg/g (SD = 7 μg/g) and 182 μg/g (SD = 10 μg/g) for the 4.5- and 8.9-g filtrate weights, respectively. These determinations were not statistically different according to a t test ($P \leq 0.05$). This final validation study was considered necessary because of the possibility of propellant cooling during sampling, and subsequent SA precipitation might have been expected to reduce the apparent solubility when larger samples of suspension were filtered; however, this was not found to be the case.

(d) Six replicate filtrate samples from parent suspensions containing 1% (w/w) SA in propellant consisting of 100:0, 75:25, 50:50, and 0:100% (w/w) P-12 and P-11, respectively, were obtained after 1, 2, and 12 weeks. The apparent SA solubility estimated from these samples is shown in Table I. Blank formulations (containing no SA) produced small apparent SA solubilities, probably as a result of valve elastomer extractives absorbing at the same wavelength as SA. As the proportion of P-11 in the propellant was increased, the apparent SA solubility increased; this is shown in Fig. 3, which was constructed from pooled data in Table I for each propellant blend independent of sampling time. No clear trend emerged in the solubility of SA in P-12 at each time point, however, in the remaining propellant blends (which all contained some P-11), a trend of decreasing SA solubility over time was noted. Further, with increasing P-11 content the decrease in solubility became greater. These variations do not appear to be temperature dependent and are not consistent with preferential loss of P-12 vapor during storage (which would be expected to increase the apparent solubility). One explanation of this observation is that, over time,

Table I. Apparent SA Solubility (μg/g) in Various Propellant Blends as a Function of Time[a]

Propellant P-12:P-11 (%, w/w)	Time (weeks)[b] 1	2	12	Blank[c]
100:0	193.50 (12.20)[d]	167.45 (12.37)	175.65 (14.59)	16.00
75:25	348.06 (19.95)	310.08 (11.45)	304.15 (20.60)	11.95
50:50	536.70 (14.20)	485.61 (10.18)	458.69 (17.87)	12.84
0:100	1137.10 (30.10)	957.62 (54.18)	857.00 (125.36)	13.01
Ambient temp. during expt.	26°C	24°C	24°C	

[a] All parent suspensions contained 1% (w/w) salicylic acid.
[b] Samples were also taken after 10 weeks but are not reported since the results showed an unusually low solubility and more variability. We were unable to confirm the experimental validity of these results.
[c] Blanks consisted of three replicates of each propellant blend (one determination at each time point) and contained no salicylic acid. Apparent solubilities are probably the result of elastomer extractives from valve components which absorb at the same wavelength as SA.
[d] Values in parentheses represent standard deviation (n = 6).

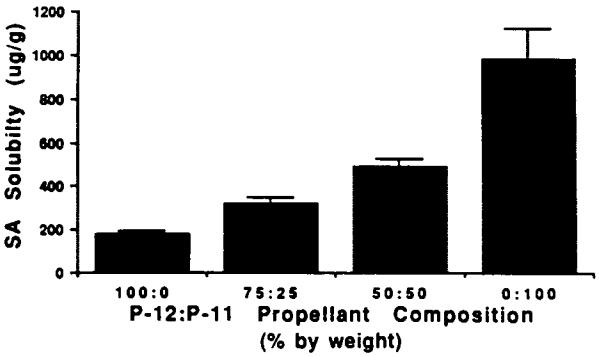

Fig. 3. Effect of altering the P-12:P-11 ratio on the solubility of salicylic acid (μg SA/g propellant). The solubility of SA in each blend is the mean of 18 determinations. Error bars represent standard deviation.

crystal growth occurs by the process of Ostwald ripening (5). Therefore, the initial solubilities (determined after 1 and 2 weeks) may be slightly higher than the solubility measured at 12 weeks. Further evidence for this is provided by Fig. 4, which shows an apparent increase in SA particle size recovered from the filter after 7 hr and 127 days compared to initially micronized SA. The disappearance of small particles and growth of larger particles are particularly apparent in the 127-day sample. Alternative explanations for the initially higher SA solubility include a change in the physical form of the drug induced during micronization or temperature-induced supersaturation. Numerous drugs are known to undergo such polymorphic changes during milling (6,7).

(e) One percent (w/w) SA aerosols in pure P-12 and pure P-11 were stored at 37°C for 1 week. The use of one-component propellants was designed to prevent possible complications which might be introduced by selective leakage of the more volatile propellant (P-12 in this case) at the elevated storage temperature. In P-12 and P-11 the solubility of SA at 37°C increased to 319 μg/g (SD = 34 μg/g) and 1402 μg/g (SD = 74 μg/g), respectively, compared to controls stored at ambient temperature, which showed SA solubilities of 168 μg/g (SD = 12 μg/g) in P-12 and 958 μg/g (SD = 54 μg/g) in P-11. This clearly shows the utility of testing suspension aerosol formulations under cycled storage conditions in an attempt to predict the likelihood of crystal growth. Temperature cycling during suspension aerosol formulation screening for physical stability is a common practice.

CONCLUSIONS

The filtration apparatus allowed the reliable measurement of drug solubility in volatile, liquified propellant blends at ambient and elevated temperatures. Using this simple method it should be possible to identify suspension formulations in which Ostwald ripening is likely to be a problem, without the expense of protracted stability testing. Such a method might be useful in screening propellant blends for their drug and surfactant solubilizing potential and/or for determining the feasibility of preparing high-volatility solution MDI formulations containing little or no cosolvent.

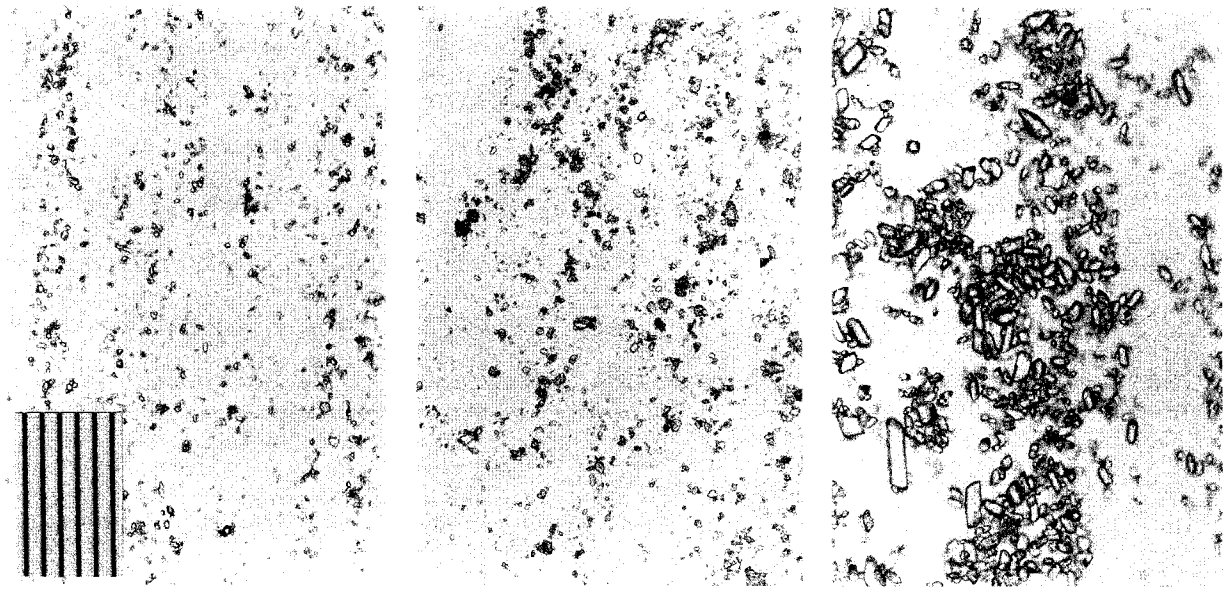

Fig. 4. Photomicrographs of SA crystals (a) immediately after micronization, (b) after 7 hr in P-12, and (c) after 127 days in P-12, at approximately 24°C. The distance between each division is 10 μm. All photomicrographs were taken at the same magnification.

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