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A comparison of two methods to determine the solubility of compounds in aerosol propellants

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Abstract

A new on-line reverse phase HPLC method for determining the solubility of compounds in propellant based metered dose inhaler (MDI) formulations was compared with a conventional method. The new method employs a direct injection from a MDI vial into the needle injector port of a manual injector. To evaluate the two methods, beclomethasone dipropionate (BDP), 5,5-diphenyl hydantoin and 3,3′-diindolylmethane, were used as model compounds in propellant HFA-134a. Comparison was performed by analyzing known and unknown concentrations of BDP in various combinations of HFA-134a and ethanol. In addition, the solubility of 5,5-diphenyl hydantoin and 3,3′-diindolylmethane were determined in HFA-134a using both the new and the conventional methods. The two methods were found to be in good agreement with each other, with the new direct injection technique offering enhanced precision and accuracy along with considerable reduction in analysis time.

Keywords: Solubility; Aerosols; Propellant; Metered dose inhalers; Direct injection method; HFA-134a; HPLC; Comparison

1. Introduction

For many years, inhalation delivery systems have been used to deliver drugs to the respiratory tract in order to treat pulmonary diseases. Due to the diversity of inhalation dosage forms (nebulizers, dry powder inhalers, and metered dose inhalers), preformulation, as applied to the development of inhalation formulations, can be extremely broad in scope. Inhalation delivery systems, including pressurized metered dose inhalers (MDIs), are compound specific, and the physicochemical properties of a given compound can predispose the choice of the inhalation system. Early in the development process, the solubility of a drug continues to be a physical property that is routinely measured during the identification and selection of lead compounds. Especially for MDIs, the determination of drug solubility in propellants is the first step in rational formulation

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design. The solubility of a drug in the propellants principally governs the type of MDI system (solution versus suspension) chosen for development.

Dalby et al. (1991) reported the 'conventional method' for determining drug solubility in volatile propellant systems. A recent modification of this method was reported by Williams et al. (1999). The overall principle of the two methods is the same; with both utilizing a donor vial containing excess drug in the volatile propellant system, and a second empty receiving vial whose weight is pre-recorded (made of glass in Dalby et al. and made of aluminum in Williams et al.). Both vials are crimped with continuous spray valves, which enable the transfer of contents from the donor vial to the receiving vial. The donor vial is equilibrated for a period of time in order for the drug to achieve equilibrium solubility in the propellant or the MDI formulation. The donor vial is mounted on top of a gas tight filtration apparatus. Both the donor and the receiving vials have an adapter attached to the continuous valve. A filter (0.22 μm or 0.45 μm) is connected between the two adapters, to filter the excess drug from the donor vial. The receiving vial is typically kept cold with dry ice, in order to provide the necessary driving force for the contents of the donor vial to flow into the receiving vial. After transferring the contents from the donor vial to the receiving vial, the weight of the receiving vial is recorded. This vial is chilled, then either decrimped or punctured, and the contents are transferred to a pre-chilled volumetric flask. The propellant is allowed to evaporate and a suitable solvent is used for dilution. The diluted samples are then analyzed in order to quantitate the drug.

A new method for determining solubility of compounds in MDIs has been reported by Gupta and Myrdal (2004a). The method utilizes a direct injection from a MDI vial into the needle injection port of a manual injector for on-line HPLC analysis. The aim of the current investigation was to compare the new direct injection method with the conventional method for determining solubility in MDIs. In the current investigation, beclomethasone dipropionate (BDP), 5,5-diphenyl hydantoin and 3,3′-diindolylmethane (Fig. 1a–c), were used as the model compounds, and HFA-134a was used as the model propellant. BDP was quantified in various blends of HFA-134a and ethanol, and the solubility of 5,5-diphenyl hydantoin and 3,3′-diindolylmethane was determined in HFA-134a, using both methods.

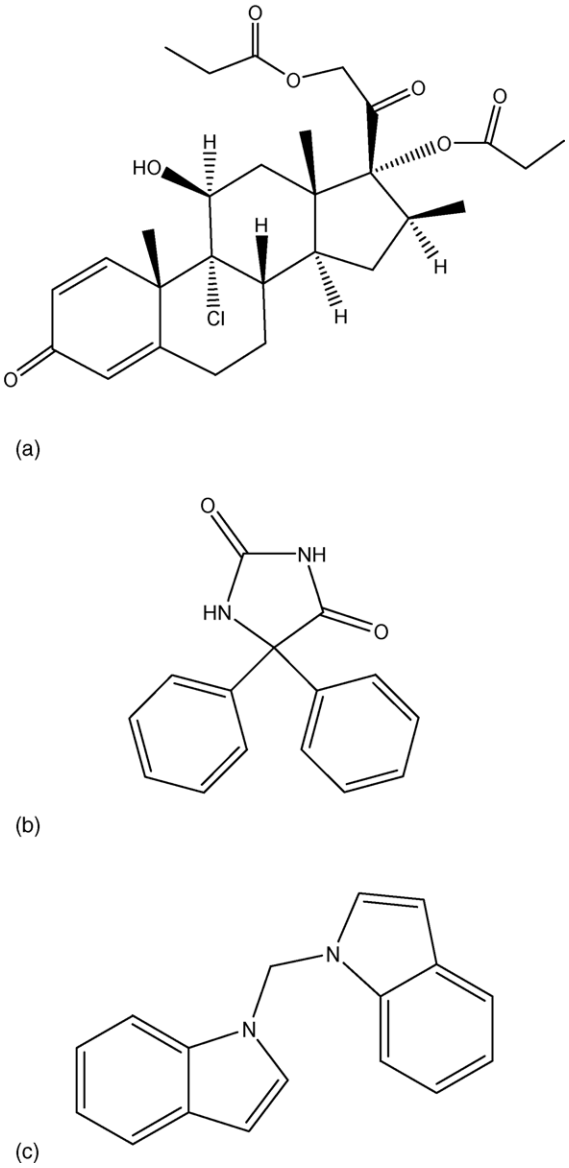

Fig. 1. Structures of the compounds used for method comparison study. (a) Beclomethasone dipropionate, (b) 5,5-diphenyl hydantoin, (c) 3,3′-diindolylmethane.

2. Materials and methods

2.1. Materials

Pressure resistant glass aerosol vials, continuous valves and beclomethasone dipropionate (BDP), were provided by 3 M Drug Delivery Systems

(St. Paul, MN). 5,5-Diphenyl hydantoin and 3,3′-diindolylmethane were obtained from RPI Corp. (Mount Prospect, IL). 1,1,1,2-Tetrafluoroethane (HFA-134a; Dymel® 134a) and ethanol (200 proof) were obtained from DuPont Chemicals (Wilmington, DE) and Aaper Alcohol and Chemical Company (Shelbyville, KY), respectively. HPLC grade acetonitrile was obtained from Aldrich Chemical Company (Milwaukee, WI).

2.2. Sample preparation

Vials that contained excess BDP were prepared at 5, 10, 15 and 20% w/w ethanol in HFA-134a. In addition, vials were made with known concentrations of BDP using HFA-134a and ethanol. These formulations were in solution and contained BDP concentrations of 0.0057% w/w, 0.0114% w/w, 0.1203% w/w and 0.7510% w/w. The first two formulations contained 5% w/w ethanol and latter two formulations contained 15% w/w ethanol. For all the formulations prepared, BDP and ethanol were directly weighed into pressure resistant glass vials. Each of these vials was immediately crimped with continuous valves (3 M Drug Delivery Systems, St. Paul, MN) using a small-scale bottle crimper (Model 3000B, Aerotech Laboratory Equipment Company, Maryland, NY). HFA-134a was pressure filled in these vials using a pressure burette (Series 3SB Pressure Filler, Aerotech Laboratory Equipment Company, Maryland, NY). Vials that contained excess BDP, 5,5-diphenyl hydantoin and 3,3′-diindolylmethane were crimped with continuous valves using the small-scale bottle crimper. HFA-134a was pressure filled in these vials using the pressure burette. All the vials were rotated at room temperature for at least 48 h prior to analysis.

2.3. Comparison of the conventional method to the new direct injection method

In order to check the precision and accuracy of the new direct injection method for the determination of solubility, a study was conducted to compare the new method to the conventional method reported by Dalby et al. (1991). Solubility of BDP was determined in various combinations of HFA-134a and ethanol using both the methods. Two types of BDP samples were evaluated: the first set of vials had excess BDP with 5%, 10%, 15% and 20% w/w ethanol. The second set of vials had known concentrations of BDP (0.0057% w/w, 0.0114% w/w, 0.1203% w/w and 0.7510% w/w) with all formulations in solution. Solubilities of BDP, 5,5-diphenyl hydantoin and 3,3′-diindolylmethane were also evaluated in pure HFA-134a. Twelve determinations were performed for each vial with unknown concentration of BDP and six determinations were performed for each vial having known concentration of BDP. Six determinations were conducted for each vial containing 5,5-diphenyl hydantoin and 3,3′-diindolylmethane.

2.3.1. Determination of solubility of compounds by conventional method

Fig. 2(a) shows the experimental setup for determination of the solubility of compounds in MDI vials by the conventional method. After equilibration, the samples were filtered through a 0.45 μm Acrodisc© PTFE syringe filter coupled to a chilled empty receiving glass vial. The receiving vials containing the filtrate were weighed and then chilled in dry ice for at least 15 min. The chilled vials were decrimped and the contents were transferred to a pre-chilled volumetric flask. The formulation was allowed to warm up, leading to the evaporation of the propellant. The receiving vial and valve were then quantitatively rinsed with the mobile phase, and the contents of the volumetric flask were diluted to volume with the mobile phase. The amount of each compound in the samples was determined by HPLC. The solubility of 5,5-diphenyl hydantoin and 3,3′-diindolylmethane in HFA-134a, and the solubility of BDP in various blends of HFA-134a and ethanol were calculated based on the total amount of formulation in the receiving vial.

2.3.2. Determination of solubility of compounds by new direct injection method

The experimental setup for the new direct injection method has been explained in previous reports (Gupta and Myrdal, 2004b). Fig. 2(b) illustrates the schematic of making an injection from a MDI vial into the needle injector port of the manual injector. In order to make a direct injection from the equilibrated MDI vial into the manual injector, the MDI vial was connected with a filtration and injection assembly (Fig. 2(b)). The injection from the MDI vial was performed by inserting the needle of the assembly through the needle port. A

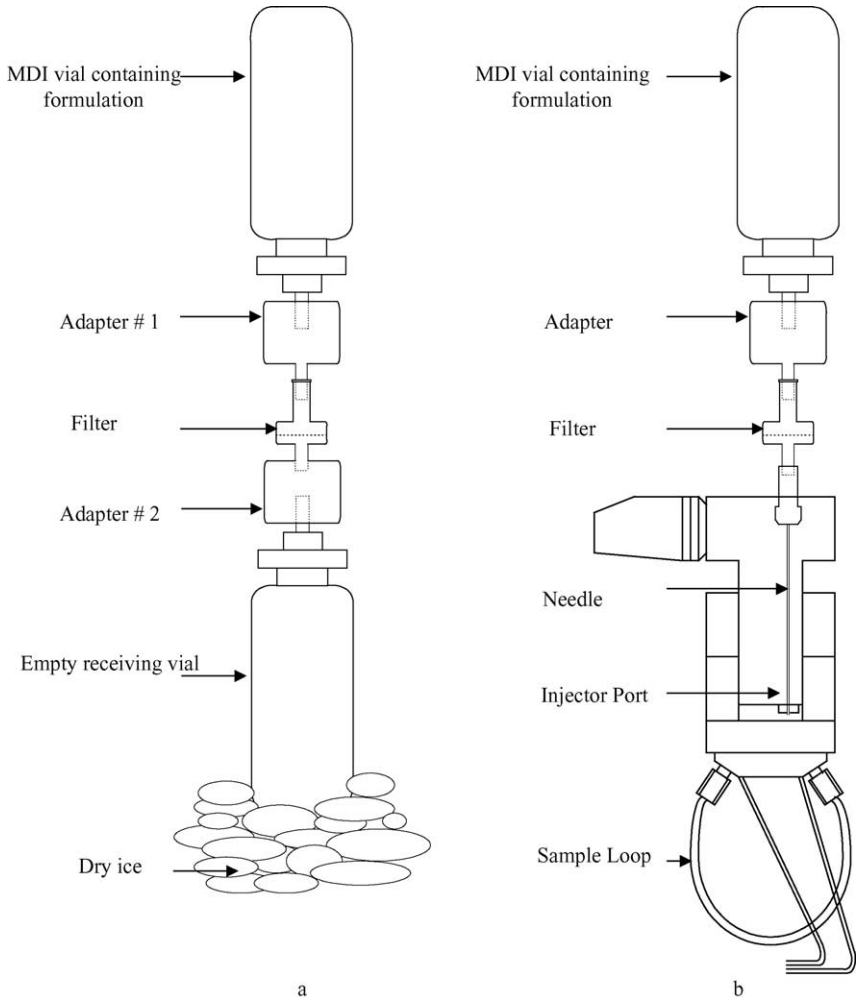

Fig. 2. (a) Conventional method for determination of drug solubility in MDIs. (b) MDI vial assembly injection into the manual injector needle port.

suitable adjustment of the backpressure regulator was devised, such that the backpressure in the waste line was approximately 60 psig for each injection. The same backpressure regulator setting was used for all the subsequent injections. The injector was kept at the LOAD position, and after 3–4 s of actuation of the MDI vial, the loop was overfilled. The injector was immediately turned to the INJECT position and the excess formulation was allowed to discard through one of the waste lines.

In order to make replicate injections after the first injection, the backpressure valve was opened to relieve the backpressure and discard any formulation to waste. The loop was then rinsed with excess 100% acetonitrile. In order to perform the next injection, the backpressure regulator was adjusted to the initial setting and the injector was brought to the LOAD position. A new injection was performed in the same manner as the first injection and the process was repeated using a new filter each time.

2.4. Sensitivity of the new direct injection method

The new direct injection method was found to be sensitive for the quantitation of compounds in MDI formulations. For BDP (λ_{max}: 240 nm) the upper limit

of detection was found to be approximately 0.008% w/w, beyond which the linear concentration-absorption range of Beers law (Martin, 1993) was exceeded at the λ_{max}. In order to investigate the accuracy, repeatability and similarity of data analysis at multiple wavelengths (at which the compound absorbs relatively less), the data for 5,5-diphenyl hydantoin (λ_{max}: 210 nm) and 3, 3′-diindolylmethane (λ_{max}: 220 nm) were analyzed at multiple wavelengths. The results from the direct injection method were compared with the results of the conventional method for the three compounds.

2.5. Dilution of the concentrated samples

Since the solubility of BDP in the cosolvent samples was higher than 0.008% w/w, a dilution step was included in the procedure, prior to the direct injection. The formulations with known concentration of BDP (0.0114% w/w, 0.1203% w/w and 0.7510% w/w) and the solubility samples with unknown concentration of BDP (containing 5%, 10% and 15% w/w ethanol) were diluted with HFA-134a, prior to analysis by the direct injection method. The dilution was performed by transferring a small and known quantity of the concentrated samples to a receiving MDI vial crimped with continuous valve. The initial transfer of the concentrated samples to the receiving vial was done by using a set of custom adapters. A known quantity of HFA-134a was then pressure filled in the receiving vial. The diluted samples in the receiving MDI vial were then analyzed by the new direct injection method. The original concentration was then calculated based upon the appropriate dilution factor.

2.6. Data analysis at multiple wavelengths

The solubilities of 5,5-diphenyl hydantoin and 3,3′-diindolylmethane in HFA-134a were quantitated at multiple wavelengths by both methods. Data for 5,5-diphenyl hydantoin were analyzed at 210 nm (λ_{max}), 220 nm and 230 nm while data for 3,3′-diindolylmethane were analyzed at 220 nm (λ_{max}), 265 nm and 283 nm. The wavelengths were chosen as representative cases in order to cover a wide range of wavelengths at which the data can be analyzed. The linear concentration-absorbance range was not exceeded at any of these selected wavelengths. This exercise was done to illustrate that a different set of wavelengths may be chosen depending upon the compound to be analyzed, in order to facilitate analytical detection without the need for dilution.

2.7. HPLC assay

For BDP, the HPLC system consisted of a Waters 2695 Separations module (Waters, Milford, MA) coupled with a Waters 2487 dual wavelength absorbance detector. 5,5-Diphenyl hydantoin and 3,3′-diindolylmethane were analyzed using a Waters 2690 Separations module coupled with a Waters 996 PDA. For analysis by the new direct injection method, the Waters 2695 and Waters 2690 Separations module were connected with a Rheodyne Model 7725 (Rheodyne, L.P. Rohnert Park, CA) manual sample injector. Sample analyses for the three compounds were performed by a reverse phase HPLC assay, using a 150 mm × 4.6 mm, 5 μm Apollo C18 column, maintained at ambient temperature. Quantitation was conducted based on peak area using a five-point standard curve prepared daily. Since the sample loop delivers formulations based on volume, density correction was required for the different standards and formulations injected by the direct injection method. With the knowledge of the solvents used for preparing the standards and formulations, the density of these solutions was calculated as a linear combination of the densities of the constituent solvents. Based on the density correction, the formulation mass dispensed from the sample loop was calculated.

For analysis of BDP by the conventional method, acetonitrile:water (70:30, v/v) was used as the mobile phase, at a flow rate of 0.8 mL/min with an injection volume of 50 μL. For analysis by the new direct injection method, acetonitrile:water (80:20, v/v) was used as the mobile phase, at a flow rate of 0.9 mL/min, with an injection volume of 5 μL. Ultraviolet detection was conducted at 240 nm. 5,5-Diphenyl hydantoin and 3,3′-diindolylmethane were analyzed using acetonitrile: water (90:10, v/v), at a flow rate of 1.0 mL/min, with an injection volume of 5 μL, for both the conventional method and the direct injection method. Retention time was 2.9 min for 3,3′-diindolylmethane and 2.7 min for 5,5-diphenyl hydantoin.

Table 1
Comparison of the methods using known and unknown concentrations of BDP

Sample	Concentration (% w/w)	*N*	% Recovery		S.D.		C.V. (%)	
			Conventional	Direct injection	Conventional	Direct injection	Conventional	Direct injection
Known concentration								
1	0.0057	6	101.16	99.96	10.83	1.68	10.7	1.68
2	0.0114	6	100.06	99.15	2.50	3.03	2.50	3.05*
3	0.1203	6	100.47	102.45	7.06	3.05	7.03	2.97*
4	0.7510	6	100.10	102.72	3.34	2.07	3.34	2.02*
Unknown concentration								
1	0	12	0.0080	0.0081	0.00043	0.00023	5.32	2.89*
2	5	12	0.2719	0.2760	0.0155	0.005	5.72	1.84*
3	10	12	0.5457	0.5393	0.0250	0.015	4.59	2.78*
4	15	12	0.8676	0.8633	0.0380	0.017	4.43	2.01*

'*N*' is the number of samples analyzed for the conventional method and the number of injections performed for the new method. '% Recovery' is the percent drug recovered, 'S.D.' is the standard deviation and 'C.V.%' is the coefficient of variation. The values marked with '*' were obtained by using a dilution step prior to direct injection by the new method.

3. Results for the method comparison

Results for the comparison of the conventional method with the new direct injection method are summarized in Tables 1 and 2.

3.1. Conventional method

Table 1 lists the percent recovery along with the standard deviations (S.D.), of the four known concentrations of BDP, when analyzed by the conventional method. The coefficient of variation (C.V.%) was taken as a measure of the precision and accuracy of the method. The values of the coefficient of variation (%) ranged from 2.5 to 10.7. Table 1 also lists the solubility (% w/w) of BDP in different blends of HFA-134a and ethanol (i.e. unknown concentration), when analyzed by the conventional method. The coefficient of variation (%) ranged from 4.43 to 5.72.

Table 2 lists the percentage w/w solubility of 5,5-diphenyl hydantoin and 3, 3′-diindolyl methane, along with the S.D. and C.V.%, when analyzed by the conventional method. Data for 5,5-diphenyl hydantoin were analyzed at 210 nm, 220 nm and 230 nm and the C.V.% ranged from 5.67 to 5.92. Data for 3,3′-diindolyl methane were analyzed at 220 nm, 265 nm and 283 nm and the C.V.% ranged from 20.00 to 22.89.

3.2. New direct injection method

Table 1 lists the percent recovery along with the S.D. of the four known concentrations of BDP when analyzed by the new direct injection method. The values of the C.V.% ranged from 1.68 to 3.05.

Table 2
Method comparison data for 3,3′-diindolylmethane and 5,5-diphenyl hydantoin

Compound	Wavelength (nm)	Solubility (% w/w)		S.D. ($n = 6$)		C.V. (%)	
		Conventional	Direct injection	Conventional	Direct injection	Conventional	Direct injection
5,5-Diphenyl hydantoin	210	0.001212	0.000952	6.65E−05	4.28E−05	5.80	4.49
	220	0.001400	0.001112	7.94E−05	4.67E−05	5.67	4.20
	230	0.001404	0.001016	8.31E−05	3.93E−05	5.92	3.87
3,3-Diindolyl methane	220	0.004335	0.003941	9.80E−04	1.03E−04	22.89	2.62
	265	0.004202	0.004071	8.40E−04	9.16E−05	20.00	2.25
	283	0.004153	0.004159	8.35E−04	1.05E−04	20.12	2.52

'S.D.' is the standard deviation and 'C.V.%' is the coefficient of variation.

Table 1 also lists the solubility (% w/w) of BDP in different blends of HFA-134a and ethanol (i.e. unknown concentration), when analyzed by the new direct injection method. The C.V.% ranged from 1.84 to 2.89.

Table 2 lists the percentage w/w solubility of 5,5-diphenyl hydantoin and 3,3′-diindolyl methane, along with the S.D. and C.V.% when analyzed by the new direct injection method. Data for 5,5-diphenyl hydantoin were analyzed at 210 nm, 220 nm and 230 nm and the C.V.% ranged from 3.87 to 4.49. Data for 3,3′-diindolyl methane were analyzed at 220 nm, 265 nm and 283 nm and the C.V.% ranged from 2.25 to 2.62.

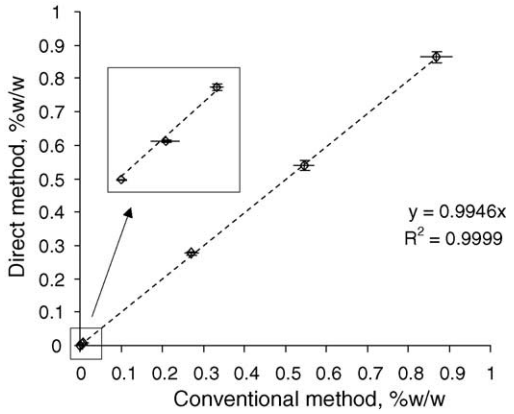

Fig. 3. Comparison of solubility values (% w/w) obtained by using the conventional method with the direct injection method. The horizontal error bars represent the standard deviations for the values obtained by using the conventional method and the vertical error bars represent the standard deviations for the values obtained by using the direct injection method.

4. Discussion

The present study compares two methods for determining the solubility of compounds in propellant based MDI formulations. The conventional method for determination of the solubility of compounds in propellants has been widely used (Dalby et al., 1991; Warren and Farr, 1995; Tzou et al., 1997; Williams et al., 1999; Dickinson et al., 2000). The new direct injection method (Gupta and Myrdal, 2004a) is the first direct on-line reverse phase HPLC method for determining solubility of compounds in closed MDI vials. The method utilizes a direct injection of the MDI vial into the needle injection port of a manual injector and hence does not require the MDI vial to be opened (decrimped or punctured). Based on the solubility data for three model compounds, it is evident that the two methods are in agreement with each other (Fig. 3). The solubility values obtained using both methods were not significantly different, although the coefficients of variation for the data obtained by using the new method were found to be lower than the conventional method.

The process of using the conventional method is both time consuming and laborious. Although the actual process of transferring the drug from one vial to another takes very little time, the entire process of cooling the receiving vial and glassware, decrimping the receiving vial, transferring the contents for dilution, and then sample preparation for the analysis of the drug content, is time consuming. Thus, the generation of a single data point involves significant analyst time and labor, as well as relatively large compound and solvent quantities. On the other hand, the new method involves a direct injection from a MDI vial, thereby, eliminating the need for additional sample manipulations and reducing analysis time. Fig. 4 shows a chromatogram of BDP with six injections within 30 min by using the new direct injection method. All six peaks are identical and offer six solubility data points with minimal time and effort. Since the conventional method involves transferring contents from one vial to another vial, and a subsequent transfer for dilution (into a volumetric flask), it is technique dependent. There is a potential to lose formulation/drug during the quantitative transfer of contents. Sample loss can also occur during propellant boiling/evaporation. This can lead to variable results in replicate analysis. The new method does not require any of these transfer steps therefore reducing the operational errors, which directly results in consistent and reproducible results.

The conventional method is sample intensive. For generating multiple data points, contents of the donor vial can only be transferred to a limited number of receiving vials. Once the receiving vial is decrimped, the entire sample is lost. As a result, generation of multiple data points with a single donor vial is limited. Since the new method utilizes a very small sample size for solubility determination (150 μL–200 μL) and the MDI vial is not opened, the same vial can be used numerous times to generate multiple data points. The ability

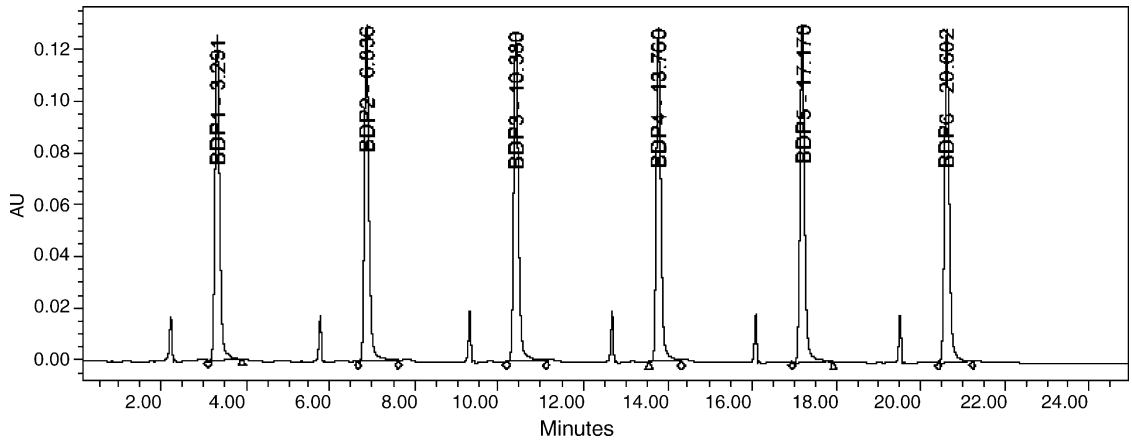

Fig. 4. Chromatogram of BDP using the new direct injection method. Six injections were performed during a period of 30 min.

to monitor the same sample over time offers significant advantages in terms of generating various stability profiles.

The direct injection method was also found to be a sensitive analytical method. The limit of quantitation (LOQ) of BDP was estimated as ten times the variation in the measured response (ICH Q2B, 1997) and was calculated to be 26.75 ng/mL (0.00000219% w/w). For BDP (λ_{max}: 240 nm) the upper limit of detection was found to be approximately 0.008% w/w, beyond which the linear concentration-absorption range of Beers law (Martin, 1993) was exceeded at the λ_{max}. Due to the sensitivity of the new direct injection method, a similar situation may arise for compounds that are highly soluble in pure HFA-134a or have a high solubility when a cosolvent is used along with the propellant. When such compounds are analyzed by liquid chromatography using a UV detector, there is the potential that the linear concentration-absorbance limit of Beers law (Martin, 1993) might be exceeded. The high sensitivity of the method may present a potential limitation for the analysis of compounds having high solubility in the propellants alone or along with other formulation excipients. Two practical solutions to this situation were presented, including dilution of the samples prior to direct injection and analysis of the data at a wavelength other than the λ_{max}. In order to check the feasibility of both these options, a systematic investigation of the dilution method and data analysis at a wavelength other than λ_{max} were performed. From the results, it was evident that when BDP was analyzed using a dilution step along with the direct injection method, the percent recoveries for the two methods were not different. In addition, the data for 5,5-diphenyl hydantoin and 3,3′-diindolylmethane were analyzed at two wavelengths other than the λ_{max}. The wavelengths were chosen such that the compounds absorbed relatively less at these wavelengths and hence offered a means of reduced sensitivity for detection. For the direct injection method, the coefficient of variation (%) for the solubility values obtained by processing the data at three different wavelengths was 7.84 for 5,5-diphenyl hydantoin, and 2.70 for 3,3′-diindolylmethane, respectively. This indicates that there is no significant difference in the solubility values when the data is analyzed at different wavelengths. Hence, no practical difference was observed between the conventional method and direct injection method, when the direct injection method was used along with sample dilution prior to injection or by data analysis at multiple wavelengths. Therefore, the new direct injection method may be employed for solubility determination of compounds with both high and low solubility.

5. Conclusions

A new method for determining the solubility of compounds in pressurized MDI formulations was compared with a conventional method. This was accomplished by evaluating the solubility of BDP in different combinations of HFA-134a and ethanol, and solubility

of 5,5-diphenyl hydantoin and 3,3′-diindolylmethane in HFA-134a. The two methods were found to be in excellent agreement with each other, with the data for the new direct injection method less variable than for the conventional method.

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