Low Temperature Vacuum Drying: Evaluation of Excipients in injectable Dosage Forms

K. P. Flora, A. Rahman and J. C. Cradock

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Low Temperature Vacuum Drying: Evaluation of Excipients in Injectable Dosage Forms

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ABSTRACT: Low temperature vacuum drying is an alternative to sterile dry filling as a formulation approach for certain ethanol soluble substances that are poorly soluble or unstable in aqueous media. To date this approach has been limited to formulations containing the drug per se. However, several substances appear suitable as excipients including urea, polyethylene glycol 4000, ascorbic acid, methylparaben, and propylparaben. Ascorbic acid appears to increase the stability of bruceantin, a novel plant product that exhibits antitumor activity.

Introduction
Drugs with limited stability in aqueous solution are usually formulated as sterile “dry fill” preparations or as lyophilized dosage forms that are constituted with a sterile aqueous vehicle before administration. Lyophilization has several advantages over the “dry fill” technique including lower incidence of contamination with insoluble particulate matter (1), more rapid dissolution after reconstitution, and more precise fill tolerances (2). In addition, there may be less risk to health of personnel involved in manufacturing since the material is in dilute solution rather than a concentrated solid. This aspect is of particular concern with locally irritating compounds including certain antitumor agents (3). Unfortunately, lyophilization is an expensive process and is limited to aqueous solutions. Conventional freeze drying of aqueous solutions containing volatile organic solvents (i.e., water-ethanol mixtures) is unacceptable since expulsion of the drug substance frequently occurs during the drying cycle.

Flamberg et al. (4) have described a low temperature vacuum drying technique for the preparation of sterile dry pharmaceuticals from ethanol. The process utilizes a conventional freeze dryer equipped with an external condenser (outside the drying chamber). The solvent does not freeze but slowly evaporates under low pressure and collects on chilled (—70 °C) condenser plates leaving the drug as a dry residue in vials. Depending on solubility the vial contents are dissolved directly in sterile water, dilute ethanol, or undiluted ethanol and then water before administration. The low temperature vacuum drying technique has been used to date in formulations containing only the drug substance. However, we have recently had to formulate several potent plant products that require addition of bulking agents, pH adjustment, antioxidants, etc., to optimize the product. This report evaluates several excipients that may be included in dosage forms processed by low temperature vacuum drying.

Methods

Materials
Ethanol, Sodium Chloride Injection and Sterile Water for Injection were USP grade.
Antitumor agents were provided by the Division of Cancer Treatment, National Cancer Institute. Solvents for chromatography were HPLC grade. All other chemicals were reagent grade and were used as received.

**Solubility Screen**

The solubility of a variety of organic substances was estimated in ethanol USP at room temperature. The solubility determinations were performed by mixing excess solute in ethanol for 24 hr, filtering the mixture through a 5-μm teflon membrane, adding a measured aliquot of filtrate to a tared vessel, evaporating the ethanol under nitrogen to constant weight, and determining drug gravimetrically. A minimum solubility of 10 mg/ml in ethanol was required for further evaluation by low temperature vacuum drying.

**Vacuum Drying**

Small batches of the individual excipients were prepared for initial evaluation by the low temperature vacuum drying technique. Afterwards, products containing selected excipients with either bruceantin or carmustine were prepared by low temperature vacuum drying to investigate their utility in practical formulations. The procedure involved:

1. Vials containing the fill solution were placed on the prechilled shelf of a Virtis 10-MRSA unit connected to a Freeze Mobile and cooled to —50 °C or less.
2. Ethanol was evaporated under vacuum with shelf and condenser temperatures below —50 °C for 24 hr.
3. When the product appeared dry, refrigeration input to the shelf was discontinued and the shelf and product were allowed to gradually reach room temperature over 24 hr.
4. The sample was removed after the shelf temperature was >15 °C for at least 4 hr.

**Estimation of Carmustine (BCNU)**

BCNU in reconstituted formulations was quantitated using the colorimetric method described by Loo and Dion (5).

**High-Pressure Liquid Chromatographic Determination of Bruceantin**

A modular high pressure liquid chromatograph (Model 3500B, Spectra-Physics, Santa Clara, CA), including a reciprocating piston pump with flow feedback control, delivered mobile phase at a constant rate (1 ml/min) to a stainless steel column (3.9 X 300 mm) packed with 10-μm porous silica chemically bonded to C₁₈ groups (μ-Bondapak 10 μm, Waters Associates, Milford, MA). A fixed wavelength (312 nm) ultraviolet detector (Model 8200, Spectra-Physics, Santa Clara, CA) with a sensitivity setting of 0.08 absorbance units full scale detected the eluted compounds. The detector output signal was recorded with a strip chart recorder equipped with variable chart speed controls (Model A5211-1, Omniscribe, Houston Inst., Austin, TX). Samples were introduced onto the column with a manual injection valve equipped with a 10-μl sample loop (Model CV-6-UHPa-N60, Valco Inst. Co., Houston, TX). The mobile phase consisted of 55 volumes of methanol, 10 volumes of isopropanol, and 35 volumes of distilled water. All solvents were filtered through solvent resistant membranes (0.5 or 0.8 μm pore size) before use. Samples of bruceantin were assayed after dissolving the contents of a vacuum-dried vial in 4 ml of mobile phase containing internal standard (0.4 mg/ml benzophenone). An injection volume of 10 μl was used in all cases. Quantitation was accomplished using an internal standard method employing peak height ratios of bruceantin to benzophenone.

**High-Pressure Liquid Chromatographic Determination of Parabens**

Methylparaben and propylparaben were quantitated alone and in products containing bruceantin and BCNU by an HPLC system similar to that described above for bruceantin. The following modifications were necessary: the mobile phase was methanol:water (63:37) delivered at 1.2 ml/min; detection was at 254 nm. Samples were prepared for analysis by reconstituting the vacuum-dried product with 5 ml of ethanol. An aliquot (0.125 ml) of the
sample was placed in a 10-ml volumetric flask along with 0.2 ml of internal standard solution (benzophenone, 0.8 mg/ml). The contents were diluted to 10 ml with the mobile phase. Samples (10 µl) of this solution were injected directly.

Gas-Solid Chromatographic Estimation of Ethanol and Water

Residual ethanol and water were determined in several vacuum-dried products by gas-solid chromatography. The solid residue was dissolved in 0.1 to 0.5 ml of methyl ethyl ketone containing the internal standard (1% isopropanol, v/v) by injecting the appropriate volume through the butyl rubber stopper into the vial with a gas-tight syringe. A 2-µl sample was withdrawn through the stopper with a microliter syringe and was injected into a Hewlett-Packard Model 5750 gas chromatograph equipped with a thermal conductivity detector and 0.3 cm x 1.8 m (1/8 in. x 6 ft) stainless steel column packed with 80-100 mesh Porapak Q. Operating conditions were: carrier gas (helium) flow rate 50 ml/min; temperatures (°C), column 185; injector 215; detector 225; bridge current 165 mamp; and attenuation x 2. Ethanol and water were quantitated using an internal standard method employing peak height ratios.

Results and Discussion

Solubility Aspects

A variety of pharmaceutical excipients were evaluated regarding applicability to the low temperature vacuum drying process. Agents were included from the following functional classes: bulking agents, pH modifiers, bacteriostats, and antioxidants. The initial evaluation included a determination of solubility in ethanol. Solubility ≥10 mg/ml was required for further evaluation. The largest number of compounds were in the "bulking agent" category. In addition to standard excipients such as lactose, mannitol and povidone, a large number of relatively nontoxic, endogenous substances were tested, including amino acids, sugars, and nucleosides.

Several compounds demonstrated adequate ethanol solubility (≥10 mg/ml). Potential bulking agents meeting this criterion and their approximate ethanol solubilities (mg/ml) were: urea (89), D-ribose (>100), D-xylene (57), D-deoxyribose (133), proline (133), fructose (>50), povidone 10,000 mol. wt. (>50), thymidine (17), polyethylene glycol 4000 (>50), and polyethylene glycol 1500 (>50).

Other substances with good solubility in ethanol (≥10 mg/ml) and acceptable drying characteristics include the antioxidants, ascorbic acid and cysteine HCl; the cationic surfactant, sodium deoxycholate; and the antibacterial preservatives, methyl- and propylparaben.

Vacuum Drying

Vacuum-dried formulations usually differ substantially in appearance from those prepared by conventional freeze drying techniques. The freeze-dried product generally appears as a "cake or plug" that has the same dimensions as the frozen solution. In contrast, the vacuum dried product appears as a film or collapsed amorphous residue on inside vial wall and bottom. Bulking agents are added to freeze dried products to: (a) improve appearance of the lyophilized product, (b) provide sufficient strength to prevent crumbling during storage (6), and (c) add mass to permit estimation of uniformity of fill using conventional balances. Bulking agents may also be used as a major component in placebo formulations when the drug product is to be evaluated in "blinded" studies. Addition of bulking agents to vacuum dried products would be applicable in all instances but (b).

After an excipient met the minimum solubility criterion it was evaluated individually by the low temperature vacuum drying technique. Vials containing urea, polyethylene glycol 4000, and polyethylene glycol 1500 exhibited a white, amorphous appearance. In spite of the appreciable solubility of certain monosaccharides and povidone in ethanol, these substances were not suitable as bulking agents. The residue from povidone, D-ribose, or D-deoxyribose was a clear syrup or transparent
band. Since it is difficult to determine if complete dissolution has occurred upon reconstitution, such a transparent product is not acceptable.

Several organic salts or acids for potential use as pH modifiers are reasonably soluble in ethanol (≥10 mg/ml) including citric acid, tromethamine, and sodium acetate. Pilot vacuum drying studies indicated that a dry amorphous product resulted that could be readily reconstituted with an amount of ethanol equal to the fill volume. Also, the powder did not sublime during the drying process.

Most ethanol soluble antibacterial preservatives, benzyl alcohol, chlorobutanol, phenol, etc., are volatile and thus not suitable for freeze dried products (2). However, methylparaben and propylparaben are very soluble in ethanol and may be suitable as bacteriostats for products processed by low temperature vacuum drying. Methyl- and propylparaben were lost during low temperature vacuum drying when dried alone or in the presence of BCNU. However, methyl- and propylparaben were retained when dried with bruceantin (Table I). Similar studies utilizing conventional freeze drying have shown that parabens will be lost unless drug substances which are capable of significant hydrophobic and electrostatic interaction with parabens are present.

TABLE I. Retention of Parabens in Low Temperature Vacuum-Dried Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Remaining</th>
<th>MP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruceantin, 5 mg;</td>
<td>94.2</td>
<td>97.4</td>
<td></td>
</tr>
<tr>
<td>MP, 4 mg;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP, 1 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCNU, 5 mg;</td>
<td>48.1</td>
<td>62.4</td>
<td></td>
</tr>
<tr>
<td>MP, 4 mg;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP, 1 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP, 4 mg;</td>
<td>64.1</td>
<td>64.6</td>
<td></td>
</tr>
<tr>
<td>PP, 1 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ ^a \text{MP} = \text{methylparaben}; \text{PP} = \text{propylparaben.} \]

The carcinostatic agent carmustine is formulated by low temperature vacuum drying (4) and supplied as a sterile 100-mg dry residue. At time of use the drug is dissolved in sterile ethanol and diluted with nine volumes of Sterile Water for Injection, USP. Since carmustine is very unstable in aqueous media, the reconstituted solution must be administered within one hour after reconstitution. Carmustine solutions in 10% ethanol exhibit an apparent pH of about 5.6-6.0, which is outside the optimum range (pH 4.0-4.4) for stability (5). The effect of pH on the stability of carmustine was evaluated using citric acid to adjust to ~pH 4.0. The influence of several bulking agents and antibacterial preservatives was also monitored. The composition of the low temperature vacuum-dried formulations are detailed in Table II. Stability was monitored after reconstitution and storage at 50, 37, and 25 °C. Data from the 25 and 37 °C storage samples are described in Table III. The solution of carmustine alone was unstable and reached 10% decomposition within 2 hr at 25 °C, but was more stable in all formulations containing citric acid. In these preparations the time for 10% decomposition of carmustine

Application to Formulation Problems

The carcinostatic agent carmustine is formulated by low temperature vacuum drying (4) and supplied as a sterile 100-mg dry residue. At time of use the drug is dissolved in sterile ethanol and diluted with nine volumes of Sterile Water for Injection, USP. Since carmustine is very unstable in aqueous media, the reconstituted solution must be administered within one hour after reconstitution. Carmustine solutions in 10% ethanol exhibit an apparent pH of about 5.6-6.0, which is outside the optimum range (pH 4.0-4.4) for stability (5). The effect of pH on the stability of carmustine was evaluated using citric acid to adjust to ~pH 4.0. The influence of several bulking agents and antibacterial preservatives was also monitored. The composition of the low temperature vacuum-dried formulations are detailed in Table II. Stability was monitored after reconstitution and storage at 50, 37, and 25 °C. Data from the 25 and 37 °C storage samples are described in Table III. The solution of carmustine alone was unstable and reached 10% decomposition within 2 hr at 25 °C, but was more stable in all formulations containing citric acid. In these preparations the time for 10% decomposition of carmustine
TABLE II. Composition of Carmustine (BCNU) Formulations Prepared by Low Temperature Vacuum Drying

<table>
<thead>
<tr>
<th>Mg/Vial</th>
<th>BCNU</th>
<th>Citric Acid</th>
<th>Methylparaben</th>
<th>Propylparaben</th>
<th>Bulking Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation A</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Formulation B</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>40 (Urea)</td>
</tr>
<tr>
<td>Formulation C</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>40 (PEG 1500)</td>
</tr>
<tr>
<td>Formulation D</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>40 (Povidone)</td>
</tr>
</tbody>
</table>

* PEG 1500 = polyethylene glycol 1500.

...solutions is extended beyond 6 hr. The presence of bulking agents (urea, povidone, polyethylene glycol 4000) did not appear to affect the rate of degradation of carmustine.

Bruceantin is a recently isolated plant product (8, 9) that is in Phase I and II clinical trials. The drug is reasonably soluble in ethanol and exhibits acceptable solubility and short range stability in hydroalcoholic solutions. Two formulation approaches were considered: a glass ampul containing a sterile solution of bruceantin in absolute ethanol that would be aseptically diluted with at least nine volumes of Sodium Chloride Injection USP before intravenous administration, or a vial containing 3 mg of vacuum-dried bruceantin. The latter-mentioned product would be reconstituted with 1.5 ml of sterile absolute ethanol and diluted with 13.5 ml of Sodium Chloride Injection USP. The Phase I evaluation is a clinical dose finding study that requires administration of several dosage levels until the clinical toxicity and maximum tolerated dosage are established. The vacuum-dried formulation approach was selected since the mixing could be done aseptically in a previously sterile container and the appropriate dose withdrawn into a syringe. Although this approach was suitable for clinical use, the product exhibited satisfactory shelf life (less than 10% decomposition for a period of 1 year or more) only when stored in the deep freeze at -10 °C. Several approaches to improve the stability of the bruceantin dosage form were monitored.

TABLE III. Stability of Reconstituted BCNU Formulations

<table>
<thead>
<tr>
<th>Hours</th>
<th>Formulation A</th>
<th>Formulation B</th>
<th>Formulation C</th>
<th>Formulation D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent of Initial Assay</td>
<td>Percent of Initial Assay</td>
<td>Percent of Initial Assay</td>
<td>Percent of Initial Assay</td>
</tr>
<tr>
<td></td>
<td>37 °C</td>
<td>25 °C</td>
<td>37 °C</td>
<td>25 °C</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>78.2</td>
<td>91.0</td>
<td>91.8</td>
<td>92.5</td>
</tr>
<tr>
<td>4</td>
<td>41.6</td>
<td>75.4</td>
<td>78.0</td>
<td>74.7</td>
</tr>
<tr>
<td>6</td>
<td>27.8</td>
<td>64.1</td>
<td>66.0</td>
<td>64.9</td>
</tr>
<tr>
<td>1</td>
<td>94.3</td>
<td>96</td>
<td>97.4</td>
<td>97.0</td>
</tr>
<tr>
<td>2</td>
<td>91.4</td>
<td>96.2</td>
<td>96.3</td>
<td>96.7</td>
</tr>
<tr>
<td>4</td>
<td>79.5</td>
<td>96.2</td>
<td>96.1</td>
<td>97.0</td>
</tr>
<tr>
<td>6</td>
<td>71.5</td>
<td>93.5</td>
<td>92.2</td>
<td>92.7</td>
</tr>
<tr>
<td>24</td>
<td>26.5</td>
<td>72.0</td>
<td>74.2</td>
<td>72.7</td>
</tr>
</tbody>
</table>
using the high-pressure liquid chromatographic method. A chromatogram of a sample containing bruceantin, ascorbic acid, and internal standard is presented in Figure 1. Preliminary studies using ultraviolet spectroscopy indicated that polyethylene glycol and urea did not substantially reduce the rate of loss of bruceantin. Data comparing the stability of this agent with various concentrations of ascorbic acid are presented in Table IV. At room temperature substantial losses in potency were evident within 2 months in the preparation containing only bruceantin. Formulations containing ascorbic acid were more stable, particularly the product containing 5.7 mg (3:1 molar ratio of ascorbic acid to bruceantin). Addition of polyethylene glycol 4000, 25 mg, did not affect rate of disappearance of

Figure 1—High-pressure liquid chromatogram of a sample containing ascorbic acid, 1; bruceantin, 2; and benzophenone (internal standard), 3.

Figure 2—Gas-solid chromatographic separation of water, 1; ethanol, 2; isopropanol (internal standard), 3; and methyl ethyl ketone (solvent), 4.
TABLE IV. Stability of Bruceantin Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>16 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Room Temperature (21–23 °C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruceantin, 2 mg</td>
<td>98.6</td>
<td>85.1</td>
<td>54.8</td>
<td>44.7</td>
</tr>
<tr>
<td>Bruceantin, 2 mg; ascorbic acid, 1.9 mg</td>
<td>98.4</td>
<td>94.6</td>
<td>88.2</td>
<td>78.5</td>
</tr>
<tr>
<td>Bruceantin, 2 mg; ascorbic acid, 5.7 mg</td>
<td>102.7</td>
<td>99.5</td>
<td>95.3</td>
<td>83.5</td>
</tr>
<tr>
<td>Bruceantin, 2 mg; PEG 4000, 25 mg; ascorbic acid, 1.9 mg</td>
<td>99.6</td>
<td>98.5</td>
<td>90.8</td>
<td>—</td>
</tr>
</tbody>
</table>

| **Refrigeration Temperature (4–8 °C)**       |         |         |          |          |
| Bruceantin, 2 mg                             | 98.4    | 95.6    | 94.0     |          |
| Bruceantin, 2 mg; ascorbic acid, 1.9 mg      | 101.4   | 100.7   | 99.4     |          |
| Bruceantin, 2 mg; ascorbic acid, 5.7 mg      | 103.3   | 99.4    | 99.4     |          |
| Bruceantin, 2 mg; PEG 4000, 25 mg; ascorbic acid, 1.9 mg | 102.2   | 98.7    | 97.1     |          |

* All values are expressed as percent of initial assay.

bruceantin. However, the additional mass attributed by polyethylene glycol increases the net content weight ten fold and within the sensitivity of most balances used in the USP net content weight determination.

Although the presence of ascorbic acid did enhance the stability of bruceantin, the product still was not optimized for long-term storage. A more successful approach (Table V) was to seal the bruceantin formulations under vacuum. Decomposition of bruceantin was minor after 3 months at 50 °C. The same formulation sealed under room air was 60 to 70% decomposed after 3 months at 50 °C.

**Residual Ethanol and Water**

In the course of these investigations it was deemed desirable to know what amounts of residual ethanol and water might be present in products low temperature vacuum dried from ethanol USP. Therefore, a gas-solid chromatographic assay was developed to quantitate small amounts of ethanol and water in the bruceantin formulations. A typical chromatogram of a sample containing water, ethanol, and methyl ethyl ketone as a solvent and isopropanol as an internal standard is shown in Figure 2. Residual ethanol and water in low temperature vacuum-dried bruceantin formulations were 3.45 ± 1.44% and 2.72 ± 0.91% (mean ± standard deviation), respectively, of the total material present (2.0–7.7 mg). Addition of a shelf heating cycle (24 hr at 35–40 °C) at the end of the vacuum drying cycle did not significantly effect the levels of ethanol and water remaining.

**Summary**

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vacuum drying. Acceptable excipients included the bulking agents, urea and polyethylene glycol; the antioxidant ascorbic acid; and the pH modifiers, tromethamine and citric acid. Inclusion of several excipients resulted in improvements in two formulations of antitumor agents.

**Acknowledgment**

The authors thank Mrs. Shirley Swindell for her assistance in the preparation of this manuscript.

**References**


**Discussion of Paper**

SOL MOTOLA (Schering Corporation): Relative to the retention of methyl- and propylparaben, do you have any information concerning the pH of your system, and its effect, plus the drying cycle time and its effect?

K. P. FLORA: We have not looked at the pH effect, however since the paraben were studied in ethanol USP, a pH effect, if any, would be negligible.

SOL MOTOLA: I would imagine you would lose more in the acid than alkaline range since it would be tied up as the salt at high pH. Can you tell me why you selected ascorbic acid as an antioxidant and have you tried any others?

K. P. FLORA: Ascorbic acid met our criteria for solubility. We did try cysteine hydrochloride and it was unsatisfactory.

SOL MOTOLA: Have you tried acetone sodium bisulfite?

K. P. FLORA: No.
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