# ACCOUNT OF EXPERIENCE

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## Stability of vinblastine sulphate containing infusions

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The stability of vinblastine sulphate containing normal saline solution for infusion has been studied at various temperatures. The difference in stability during storage at room temperature and 2–8 °C was observed based on an HPLC assay. Stored in refrigerator, the decomposition of the active agent was less than 2% at the seventh day, and remained under 4% on the 21st day. Under room temperature the decomposition exceeded 2% on the seventh day and was more than 4% at the 21st day.

### 1. Introduction

Vinblastine sulphate steril powder, vinblastine sulphate injection, and solutions of the drug are light-sensitive and must be protected from light. Vinblastine sulphate sterile powder and injection should be refrigerated at 2–8 °C. Following reconstitution of the sterile powder with bacteriostatic sodium chloride injection which contains benzyl alcohol as a preservative, solutions of the drug have a pH of 3.5–5 and are stable for 28 days when refrigerated at 2–8° [1].

Heating an aqueous solution of vinblastine sulphate at 50 °C for 16 h at pH 2 causes 80% to 90% degradation, the primary hydrolytic degradation product was desacetylvinblastine. Maximum stability of vinblastine in aqueous solution occurred between ph 2.0 and 4.0. At pH 3.0, 90% of the initial concentration of vinblastine remained after storage for 39 days at 20 °C. The degradation process was unaffected by either the addition of phosphate buffer (0.005 to 0.05 M) or an increase in ionic strength from 0.1 to 0.4 by the addition of sodium chloride [2].

Aqueous solutions of vinblastine sulphate (1 mg/ml, pH 4.5 to 5.0) were sealed into glass ampoules, protected from light, and maintained at one of six different temperatures (55 °C, 37 °C, 25 °C, 5 °C, −5 °C, or −25 °C) for 84 days. Data obtained by HPLC led to the detection of eight different degradation products. The two major products of early heat degradation were tentatively identified by mass spectrometry as a C 19′-oxidation product (19′-oxovinblastine) and an isomer of vinblastine. Later degradation products were thought to include 19′-hydroxy-3′,4′-dehydrovinblastine or 3′,4′-dehydrovinblastine-6′-N-oxide [3].

Decomposition of vinblastine sulphate was observed after 8 days and after 14 days when solutions (1.197 mg/ml, pH 5.0) were exposed to direct intermittent light (25 °C) and to direct continuous incandescent light (30 °C), respectively, an amber tint developed by the end of the 70 days study period. Samples exposed to indirect incandescent light (shielded samples) remained stable, optically clear and colorless over 70 days. Samples subjected to direct, continuous incandescent light, at 30 °C, lost 10% of their initial vinblastine sulphate concentration after slightly more than one day [4].

### 2. Investigations, results and discussion

The HPLC retention time of vinblastine sulphate under the experimental conditions described is 17.2–17.5 min and decomposition products appeared at 7.8, 13.2, and 14.9 min on the chromatogram. On the seventh day, 98.82 ± 0.88%, and 97.24 ± 1.52% of the original compound could be measured in the infusion mixture when stored in a refrigerator and at room temperature, respectively. The stability of vinblastine was maintained (less than 5% decomposition) when stored in a refrigerator and at room temperature for 3 weeks protected from light (0.05 mg/ml) in sodium chloride 0.9% intravenous solution in a glass container (Table).

The degradation kinetics of vinblastine sulphate were studied at 80 °C over a wide pH range using a stability-indicating HPLC assay. The degradation pathway was complex, the major degradation product, desacetylvinblastine, was formed at pH values below 1.5 and above 10.5. Between pH 2.5 and 7.5, the amount formed was negligible and several other (unidentified) products were detected. The decomposition reaction followed pseudo-first-order kinetics at constant pH [1].

The stability of vinblastine was maintained (less than 5% decomposition) when stored at 4 °C and 25 °C for 3 weeks in the dark in sealed polypropylene test-tubes at a concentration of 20 μg/ml in either glucose 5% injection, sodium chloride 0.9% injection, or compound sodium lactate injection [5].

Reconstituted injections of vinblastine sulphate (1 mg/ml) were chemically stable for at least 30 days when stored in polypropylenes syringes at either room temperature (21 °C) in the dark or in a refrigerator (6 to 9 °C) [6].

**Table: Stability of vinblastine sulphate in sodium chloride 0.9% intravenous solution**

| Time* (d) | Content in % ± SD of the initial concentration** | |
|---|---|---|
| | 22–25 °C | 2–8 °C |
| 0 | 100 | 100 |
| 1 | 99.30 ± 0.46 | 99.89 ± 0.67 |
| 2 | 99.12 ± 1.23 | 99.85 ± 0.89 |
| 3 | 97.99 ± 1.46 | 99.67 ± 1.77 |
| 4 | 98.09 ± 0.96 | 99.54 ± 0.72 |
| 5 | 98.01 ± 1.44 | 99.32 ± 0.58 |
| 6 | 97.56 ± 0.66 | 99.14 ± 1.89 |
| 7 | 97.24 ± 1.52 | 98.82 ± 0.88 |
| 14 | 96.11 ± 1.98 | 97.95 ± 1.44 |
| 21 | 95.42 ± 1.06 | 96.98 ± 1.38 |

* after dilution
** each value represents the mean of 6 determinations

In contrast, no significant loss of vinblastine sulphate (40 μg/ml) was observed during simulated infusions in either glucose 5% or sodium chloride 0.9% injections for 2 hours, at ambient temperatures, using polyvinyl chloride infusion bags and administration sets. Vinblastine sulphate (100 μg/ml) was also found to be stable either in glucose 5% or sodium chloride 0.9% injections, when stored in polyvinyl chloride infusion bags for 7 days at 4 °C, protected from light [7].

## 3. Experimental

### *3.1. Materials*

Vinblastin 5 mg vinblastine sulphate powder for injection (Richter Gedeon PLC), 0.9% NaCl infusion solution used for diluting vinblastine is the product of Human RT (Human Serum production and Research PLC), (Salsol a 100 ml).

### *3.2. Preparation of solution*

The compound (vinblastine sulphate 5 mg) was dissolved in 0.9 NaCl infusion solution. The examined concentration was 0.05 mg/ml. The infusion mixture, prepared under aseptic conditions in a laminar box using protective clothing, was stored in a refrigerator (2–8 °C) and at room temperature (21–25 °C) in a glass container pH = 4, protected from light for 3 weeks. The values measured after the preparation of the right away infusion mixture are regarded as zero values. 6 samples of vinblastine solution were measured every 24 h for 21 days. The chemical analysis of vinblastine was carried out by HPLC according to a literature procedure [8].

### *3.3. Equipment used*

Merck Hitachi HPLC system, supplemented by pump (L-6200 A model), injector (Rheodyne 7161 model), detector (L-4250 UV-vis model) and D 6000 A interface.

### *3.4. Conditions of chromatography*

Column Ultrasphere ODS BST 250 × 4 mm, 5 μm, mobil phase: methanol/acetonitril (4 : 1), flow rate: 1.5 ml/min, UV detector = 262 nm, Injection volume: 20 μl. Degradation products did not interfere with the determination of vinblastine.

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