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Purpose. To advance the implementation of consciousness-promoting therapies in patients with acute disorders of consciousness, the availability of potential therapeutic agents in formulations suitable for administration in hospitalized patients in the presence of complex comorbid conditions is paramount. The purpose of this study is to evaluate the long-term stability of extemporaneously prepared preservative-free methylphenidate hydrochloride (HCl) 5 mg/mL intravenous solution for experimental use.

Methods. A methylphenidate 5 mg/mL solution was prepared under proper aseptic techniques with Methylphenidate Hydrochloride, USP, powder mixed in sterile water for solution. Methylphenidate HCl 5 mg/mL solution was sterilized by filtration technique under USP <797>–compliant conditions. Samples were stored refrigerated (2-8°C) and analyzed at approximately days 1, 30, 60, 90, 180, and 365. At each time point, chemical and physical stability were evaluated by visual inspection, pH measurement, membrane filtration procedure, turbidometric or photometric technique, and high-performance liquid chromatography analysis.

Results. Over the 1-year study period, the samples retained 96.76% to 102.04% of the initial methylphenidate concentration. There was no significant change in the visual appearance, pH level, or particulate matter during the study period. The sterility of samples was maintained and endotoxin levels were undetectable throughout the 1-year stability period.

Conclusion. Extemporaneously prepared preservative-free methylphenidate 5 mg/mL intravenous solution was physically and chemically stable at 32, 61, 95, 186, and 365 days when stored in amber glass vials at refrigerated temperatures (2-8°C).

Keywords: coma, consciousness, drug stability, injection, methylphenidate, stimulants

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Methylphenidate hydrochloride (HCl) is classified as a Schedule II controlled substance by the US Drug Enforcement Administration and approved by the US Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.[1,2] Methylphenidate has been used off-label for the management of major depressive disorder, narcolepsy, and severe fatigue in the cancer or palliative care setting and is increasingly utilized as a neurostimulant to promote recovery after traumatic brain injury, cardiac arrest, and stroke in the acute and chronic recovery periods.[3-8] It is actively being explored as a therapeutic agent to promote emergence of consciousness after generalized anesthesia or in patients with severe traumatic brain injury.[9-11] With the launch of the Neurocritical Care Society's Curing Coma Campaign in 2019 to strategically advance the implementation of consciousness-promoting therapies in patients with disorders of consciousness, the availability of potential therapeutic agents in formulations suitable for administration to hospitalized patients in the presence

of complex comorbid conditions is paramount.[12]

Methylphenidate is currently available in the United States as immediate-release, sustained-release, and extended-release oral suspension, chewable and disintegrating tablets and/or capsules, a transdermal patch, and bulk powder.[13] Methylphenidate HCl is supplied as a racemic mixture *dl-threo*-methylphenidate subject to enantioselective first-pass metabolism.[2] Intravenous methylphenidate may have advantages over enteral administration due to its more predictable absorption profile.[13-15] Additionally, intravenous methylphenidate may be administered to hospitalized patients for whom enteral administration is contraindicated due to postoperative status, to patients with gastrointestinal dysfunction during hospitalization, or for acute treatment to promote recovery of consciousness in the research setting.[10,11] In the absence of stability and sterility data, the *United States Pharmacopeia* (USP) specifies that beyond-use dating of this nonsterile to sterile compounded solution be limited to 72 hours when refrigerated or 24 hours at room temperature.[16]

KEY POINTS

- Parenteral methylphenidate is a potential therapeutic option for patients with disorders of consciousness under experimental use conditions.
- Extemporaneously prepared methylphenidate 5 mg/mL intravenous solution was stable at approximately 1, 2, 3, 6, and 12 months post compounding when refrigerated in amber glass vials.
- Nonsterile to sterile compounding using bulk ingredients under USP <797>– and USP <71>–compliant conditions can be considered for experimental parenteral use.

The purpose of this study was to evaluate the long-term stability of extemporaneously prepared preservative-free methylphenidate 5 mg/mL intravenous solution in the absence of commercially available product for experimental use.

Materials and methods

Solution preparation. Compounded solution was prepared by the department of pharmacy at Massachusetts General Hospital in Boston, MA. An intravenous stock solution of methylphenidate 5 mg/mL was prepared in a glass beaker by dissolving 1,950 mg of Methylphenidate Hydrochloride, USP, powder in sterile water for injection to obtain a final volume of 390 mL. A stock solution of hydrochloric acid and/or a stock solution of sodium hydroxide was utilized to adjust the pH of solution to within a pH range of 3 to 4 (Table 1). Under a class II, type A2 biosafety cabinet in an ISO-7 buffer room under aseptic conditions specified in USP general chapter 797 (USP <797>), 390 mL of nonsterile methylphenidate 5 mg/mL solution was filtered into an empty polyvinyl chloride plastic container using a 0.22-µm filter (Millipore Sterivex-GP pressure filter unit; Merck KGaA, Darmstadt, Germany) to filter sterilize the solution.[17] Filtration procedures were performed within 180 minutes of compounding in accordance with USP <797> regulations (ie, within 6 hours, to minimize bacterial endotoxin growth). A bubble point

Table 1. Materials List

Product	Manufacturer	Lot[a]
Institutional Compounding Materials[b]		
Methylphenidate Hydrochloride, USP	Mallinckrodt, Inc	1510000199
Sterile Water for Injection, USP	Baxter, Inc	c935445
Sterile Empty Amber Vials, 30 mL-20 mm	Allergy Labs, Inc	SEV 2021315, 2081816, 210415
DynaLabs, LLC HPLC Materials		
Gemini C18 HPLC Column	Phenomenex	NA
HPLC Grade Water	Millipore	NA
HPLC Grade Methanol	Honeywell	NA
Potassium Phosphate Monobasic	Fisher Scientific	NA
Hydrochloric Acid Solution 1M	Fischer Scientific	NA
Sodium Hydroxide 10M	Fischer Scientific	NA
35% H_2O_2, HPLC Grade	Spectrum Chemical	NA

Abbreviations: H_2O_2, hydrogen peroxide; HPLC, high-performance liquid chromatography; NA, not available.
[a]As chromatography studies were performed through a third-party contracting site, some specific lot numbers were not available to report.
[b]Compounded parenteral methylphenidate HCl 5 mg/mL solution was tested to have a pH of 3.5; as a result, the stock solution of hydrochloric acid and/or stock solution of sodium hydroxide did not require pH adjustment to be within the target pH range of 3 to 4.

filter integrity test was conducted on the filter to confirm appropriate filtration. Using a calibrated Multi-AD dispensing system (B. Braun Medical, Inc., Bethlehem, PA), 15.2 mL of the filtered solution was packaged into each 30-mL amber glass vial for the total volume of the solution. Amber glass vials were sealed using tamper-evident seals to preserve sterility and strength and labeled accordingly. Vials were stored under refrigerated conditions (2-8°C) and transported to a third-party laboratory for subsequent testing. Forty-six vials were transported for validation testing, followed by 25 vials for stability testing approximately 1 month later. Refrigerated samples were stored in a dark refrigerator and exposed to light only during sampling. These samples were allowed to warm at room temperature without application of external heat sources.

Physical and chemical stability of the 15-mL samples of methylphenidate 5 mg/mL solution were evaluated at approximately days 1, 30, 60, 90, 180, and 365. Physical and chemical stability testing was performed by DynaLabs LLC, St. Louis, MO. Chemical stability was evaluated using high-performance liquid chromatography (HPLC), as outlined in USP <621>, and was defined as at least 90% retention of the initial methylphenidate HCl concentration at each time point evaluated.[18] Microbial growth testing for bacteria and fungi was performed using membrane filtration procedures pursuant to USP <71>.[19] Particulate matter was examined using a light obscuration particle count test in accordance with USP <788>.[20] Visual inspection for clarity and color, as specified in USP <797>, was additionally performed at these time points.[17]

Chromatographic apparatus and conditions. Chromatographic studies were performed using a Phenomenex Gemini C18 HPLC column (Phenomenex Inc., Torrance, CA). The mobile phase was a 65:35 mixture of a 2.7-g/L solution of potassium phosphate monobasic in water buffer and methanol. The flow rate was 1.8 mL/min for 0.5 minute and 10 minutes for step 0 and step 1, respectively.

Validation of methylphenidate hydrochloride HPLC method. Calibration curves were developed using linear regression of the calculated areas versus theoretical concentration (µg/mL). The acceptance criterion was set a priori at a coefficient of determination (r^2) of >0.999. Accuracy was determined using a standard stock solution of 10 mg of Methylphenidate Hydrochloride, USP, standard powder diluted with a 2.7-g/L solution of potassium phosphate monobasic in water to a final concentration of 500 µg/mL. Samples were further diluted according to a dilution schedule to concentrations of 15 µg/mL (n = 3), 25 µg/mL (n = 3), and 35 µg/mL (n = 3). The acceptance criterion for accuracy of average percent recovery was set at a range of >97.5% and <102.5%. Precision was determined using the same standard stock solution formula as that subject to the accuracy methods. Samples were diluted according to a dilution schedule to 25 µg/mL (n = 9). Percent relative standard deviation (RSD) for retention time and area under the curve (AUC) was calculated, and the acceptance criteria were set at a value of <2% RSD. Precision analysis was repeated on a different day and with a different instrument to determine intermediate precision (ruggedness).

Forced degradation study. A forced degradation study was performed to ensure the HPLC method was indicative of stability and capable of separation of degradation products from parent drugs. Forced-degradation stock solution was compounded using 4.5 mg of methylphenidate HCl diluted with a 2.7-g/L solution of potassium phosphate monobasic in water to a final methylphenidate concentration of 90 µg/mL. Triplicate samples were prepared in 2-dram amber vials for all test samples except for light testing samples, which were prepared in clear 2-dram vials and diluted to 30 µg/mL. Samples underwent acid hydrolysis, base hydrolysis, or oxidization using 1 mL of 0.1 M hydrochloric acid solution, 0.1 M sodium hydroxide, or 3.5% hydrogen peroxide, respectively. Light samples were placed 8 cm apart from a 365-nm UV lamp light and left static for 3 hours, after which 1 mL of water was added to the sample and placed into amber liquid chromatography (LC) vials. Heat samples were placed in a beaker filled with deionized water heated to 70°C on top of a heated stir plate for 3 hours, after which vials were removed and allowed to cool to room temperature, mixed with 1 mL of water, and placed into amber LC vials. LC sequencing was performed on all standard forced-degradation samples after an initial blank sample was run. The AUC for 3 standard injections was averaged to one value. For all other samples, the percentage recovery was determined by dividing the sample AUC by the average AUC for the standard and multiplying by 100. Purity values were analyzed according to peak apex and similarity algorithm for 5 distinct portions. Values of >900 were considered to indicate purity, while values

Table 2. Stability of Methylphenidate Hydrochloride 5 mg/mL Intravenous Solution Stored at 2-8°C

Day	Concentration, mg/mL	Initial Concentration Remaining, %
1	5.10	102.04
32	4.96	99.14
61	5.06	101.15
95	5.03	100.52
186	4.84	96.76
365	4.93	98.68

Table 3. Physical Tests of Methylphenidate Hydrochloride 5 mg/mL Intravenous Solution Stored at 2-8°C

Test	Reference	Day 1	Day 32	Day 61	Day 95	Day 186	Day 365
pH	NA	3.57	3.52	3.67	3.43	3.59	3.58
Sterility (bacteria/fungi)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Visual inspection	NA	Clear, colorless	Clear, colorless	Clear, colorless	Clear, colorless	Clear, colorless	Clear, colorless
	Reference	**Day 4**	**Day 33**	**Day 68**	**Day 95**	**Day 182**	**Day 375**
Particulate matter ≥10 µm	≤6,000 parts/ container	102.0	47.0	70.0	52.0	28.0	155.9
Particulate matter ≥25 µm	≤600 parts/ container	0.0	0.0	4.0	2.0	2.0	6.0
	Reference	**Day 4**	**Day 32**	**NA**	**NA**	**Day 181**	**Day 368**
Endotoxin	≤3,500.00 EU/mL	<0.05 EU/mL	<0.05 EU/mL	NA	NA	<0.05 EU/mL	<0.05 EU/mL

Abbreviations: NA, not applicable;

of <900 were considered to indicate purity only if within 10% of the standard values.

Results and discussion

Extemporaneously compounded methylphenidate prepared from bulk ingredients maintained product stability and sterility throughout the 1-year follow-up assessment period. At least 95% of the initial concentration of methylphenidate was retained throughout the 1-year study period (Table 2), well over the generally recognized labeled minimum potency threshold of 90%. Upon visual inspection, no detectable changes in color or clarity were observed (Table 3). Furthermore, no microbial growth was detected at any point during the 1-year study period, and endotoxins were nondetectable (<0.05 EU/mL). No appreciable change in pH (range, 3.43-3.67) over the 1-year study period was observed. Parenteral methylphenidate was compounded to a target pH of 3 to 4; if utilized for experimental patient use, administration via a large-bore intravenous line or central venous catheter is preferred to minimize the risk of phlebitis.[21] Particulate matter under light obscuration was maintained within the reference range for particles throughout the 1-year study period, further supporting product stability in solution (Table 3). Individual chromatograms were performed for each test to verify product contents at each stage.

Limitations. The data were obtained using a single stock solution for stability testing. Compounding procedures tested a single manufacturer of Methylphenidate HCl, USP (Table 1). Sterility testing conducted for the purposes of this study may not be extrapolated to other compounders in different environments per USP <797> regulations, with beyond-use dating carefully considered in the context of a compounded sterile product from nonsterile bulk active ingredients.[17] Beyond-use dating based on appropriate testing per USP <71> standards according to batch size is advised for patient use. Intravenous methylphenidate is an off-label formulation developed for experimental use.[9-11,19]

Conclusion

Extemporaneously prepared preservative-free methylphenidate 5 mg/mL intravenous solution was stable at 32, 61, 95, 186, and 365 days when stored refrigerated in 30-mL amber glass bottles.

Disclosures

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