Galenic Preparation of 40% Dextrose Gel: A New Approach to the Management of Neonatal Hypoglycemia

Melania Rivano, Maria Albrecht, Giorgia Longobardo and Cinzia Veneziano
IRCCS San Raffaele, Milano, Italy.

Dear Editor,

Neonatal hypoglycemia is a common condition that affects up to 15% of neonates in the first few days after birth.1 Transient low blood glucose levels are physiologic and occur during the establishment of postnatal glucose homeostasis. Despite that, severe prolonged hypoglycemia is associated with brain injury and poor neurodevelopmental outcome.2,3 Specific groups of infants as preterm babies, infants of diabetic mother, and high or low birthweight babies represent a high-risk population.4 Hypoglycemia is generally considered a serum glucose concentration <46 mg/dL (2.6 mmol/L), but the definition remains controversial.6 If blood glucose levels remain low, admission to Neonatal Intensive Care Unit (NICU) for IV glucose is usually required,7 separating mother and baby and delaying the establishment of breast feeding. Early feeding, often with supplemental formula milk, is one of the options available to prevent neonatal hypoglycemia. Harris et al8 demonstrated that the treatment of neonatal hypoglycemia with oral dextrose gel was more effective than feeding alone in reversing the hypoglycemia and also reduced the rate of NICU admission. Also, the use of dextrose gel reduces hospital costs for management of neonatal hypoglycemia, as it is showed in a cost analyses study.9

Dextrose gel contains dextrose, a simple carbohydrate, in concentrated aqueous solution, which can be administered by direct application to mucosal surfaces of the mouth, including buccal and lingual surfaces. Absorption from these sites may allow rapid access to the bloodstream.10 Oral dextrose gel is a noninvasive and inexpensive treatment option that can be administered on the neonatal wards to newborns. Dextrose gel can be manufactured by hospital pharmacies; indeed, commercial preparations are inexpensive, widely available, but they contain artificial preservatives and flavor additive, which makes them not always suitable for neonates. In addition, recent analyses demonstrate that glucose concentrations in commercial preparations were significantly different from the expected 40% of dextrose with variability in each tube.11 At our institution, neonatal care unit requested the implementation of 40% dextrose gel for the treatment of neonatal hypoglycemia and the pharmacy service developed a galenic formulation. The aim of this work is to describe the preparation procedure of the galenic formulation and test its stability. A systematic literature review concerning dextrose gel preparation was conducted. We carried out a PubMed search using the following key words: “dextrose gel,” “glucose gel,” and “neonatal hypoglycaemia” published within 10 years. The pharmacy service developed a procedure for the galenic formulation. The glucose gel was stored in different conditions at room temperature (Sample 1) and 2°C to 8°C (Sample 2) and tested for stability and physicochemical analysis at different times points (the day of fabrication, T0; day 7, T7; and day 30, T30). Microbiological stability was tested at 2 different time points (the day of fabrication, T0; day 30, T30) into different substrates for the detection of mycetes, as well as aerobic and anaerobic bacteria. Due to the nature of the study, no consent or ethical approval was required. The formulation was tested in triplicate, and each analysis was duplicated.

Materials: Glucose 50% was purchased from Fresenius Kabi (Germany), and carboxymethylcellulose (E466), glycerol, and parabens were purchased from Farmalabor (Italy).

Preparation of Glucose Gel
Glucose 50% solution is thickened to a gel using 2 g of carboxymethylcellulose. To extent the microbiologic stability of the formulation, the exact amount of sodium propylparaben (0.02 g) and methylparaben (0.16 g) was dispersed in water for injections (14 mL) and added to the glucose solution (80 mL). The carboxymethylcellulose was moistened with an adequate amount of glycerol (4 g) and then slowly mixed to the glucose solution with continuous stirring to avoid lump formation. The dispersion was kept at rest for 24 hours. The obtained gel was divided in sterile enteral
feeding syringes (Nutricair™ Enteral-Enfit®) with an Enfit cap. The reason of this choice is preventing the incorrect route of drug administration. For the administration, nurses used a device for sampling. The syringes were labeled.

Macroscopic Analysis of Formulation
The prepared glucose gel formulation was inspected visually for its color, homogeneity, and consistency. The clarity was determined by using the natural light and all the macroscopic analyses were realized comparing with carboxymethylcellulose and glycerol.

pH Analysis
The determination of the pH was performed on compounding day, after 7 days and 30 days (T0, T7, and T30) using a HI-1131 pH meter (Hanna instruments™, Tannerie, France). The measurement has been performed on the 2 batches (n = 2) and stored in different conditions, at room temperature (Sample 1), and at 2°C to 8°C (Sample 2). A variation of one unit in the pH value was considered significant enough to indicate a modification compared to the initial pH of prepared solution.

Microbiology Quality Testing of Nonsterile Products
This preparation is not produced by aseptic processes. Therefore, it is not expected to be totally free from microbial contaminations; 2 mL of samples were inoculated into 2 bottles of the same bottle type (SA [aerobic], SN [anaerobic] BacT/Alert 3D [BioMérieux Marcy l’Etoile, France]) for 5 days of incubation. For the detection of mycetes, BD Vacutainer® blood collection tubes were used for 8 days of incubation.

As it is reported in General Chapter 5.1.4 of Microbiological quality of pharmaceutical preparations, in Eur. Ph. 9, for aqueous oral formulations, enumeration of total aerobic microbial count (TAMC) was established and had to be less than 102 CFU/g. Moreover, the total combined yeasts/molds count (TYMC) should not exceed 101 CFU/g. Besides, no Escherichia coli was detected in any tube.

Dextrose gel formulation prepared by the pharmacy service responded to the need of the neonatal care unit. Dextrose gel formulation has several advantages: it is simple to produce, easy to use, and cost effective. The stability study demonstrated that dextrose gel was stable for 30 days, both stored in a refrigerator between 2°C and 8°C and at room temperature. However, further long-term stability studies should be required. Our findings show that the preparation of 40% dextrose gel is an effective, safe, and low-cost option for the management of hypoglycemia.

Author Contributions
GL was responsible for study conception and design; MR was responsible for data analysis and drafting; MA and GL were responsible for data quality assurance, revision of the manuscript and final approval of the version to be submitted.

ORCID iD
Melania Rivano https://orcid.org/0000-0002-8541-539X

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Table 1. Average of the pH values.

| CONDITION OF STORAGE | STORAGE DURATION (DAYS) |
|----------------------|-------------------------|
|                      | T0  | T7      | T30    |
| Sample 1            | Room temperature | 7.35 ± 0.1 | 7.41 ± 0.1 | 7.43 ± 0.1 |
| Sample 2            | 2°C-8°C       | 7.22 ± 0.1 | 7.21 ± 0.1 | 7.24 ± 0.1 |