Long Term Stability of PEG 3350 and Lactulose in Common Liquids

Allison B. Lardieri, PharmD, BCPPS; Jill A. Morgan, PharmD, BCPS, BCPPS; Soundarya Vaithianathan, PhD; Claire L. Carter, PhD; Maureen A. Kane, PhD, James E. Polli, PhD
University of Maryland School of Pharmacy

Background

- Constipation is a common problem in pediatric patients contributing to discomfort and parental concern[1,2]
- Polyethylene glycol (PEG 3350) and lactulose are the most common pharmacologic agents use to treat children with chronic constipation
- Children have difficulty adhering to constipation treatment, with an adherence rate of <40% in one parental survey[3]
- One way to increase adherence is by mixing PEG 3350 or lactulose with liquids a child may be more likely to drink
- Pediatricians most commonly instruct patients to mix PEG 3350 in water, apple juice, and orange juice[4]
- However, there is no published information available on stability of mixing PEG 3350 or lactulose with liquids other than water

Objectives

- Primary objective: Determine if lactulose (Kristalose®) and PEG 3350 (Miralax®) can be mixed with water, juices, soda, and milk and maintain stability for up to 72 hours.
- Hypothesis: Lactulose (Kristalose®) and PEG 3350 (Miralax®) will be stable at 72 hours in all liquids tested except milk.

Methods

- Three different lot numbers of commercially available lactulose and PEG 3350 were prepared with water according to their respective package insert directions, as well as prepared with 4 common liquids: soda (sprite), orange juice, apple juice, and 2% milk.
- Solutions were immediately placed in the refrigerator and physical characteristics of the solutions were evaluated at time of preparation (time 0) and at 24 hour intervals for 3 days.
- At each time point, the samples were examined for obvious changes in color and odor, and then stored at -80C until analysis.
- 2,5-dihydroxybenzoic acid was used as the MALDI matrix, in a solvent system of 70% methanol.
- Upon analysis samples were thawed at room temperature, mixed with the MALDI matrix, 2,5-dihydroxybenzoic acid, and spotted onto a stainless steel MALDI target plate.
- Analysis was carried out in positive ion mode on a Bruker UltrafleXtreme MALDI-TOF/TOF mass spectrometer (Bruker Daltonics, Massachusetts, USA).
- Stability of PEG 3350 and lactulose was assessed by monitoring for its sustained presence as well as formation of degradation products of interest.

Results

- PEG 3350 dissolved in all 5 liquids easily.
- Lactulose took more time to dissolve than PEG 3350.
- Lot #2 of Lactulose formed large clumps in soda (sprite) that would not dissolve at the 30 minute time point, despite vigorous shaking. Clumps were dissolved at the 24 hour time point.
- Lot #1 of lactulose formed clumps in water but eventually dissolved with vigorous shaking.
- There were no significant differences in the profiles for 0hr and 72hr in any of the common liquids, suggesting the stability of PEG 3350.
- The stability of lactulose could not be determined in milk, juices and soda due to naturally occurring sugars that interfered with detection.

Figure 1. Miralax® – Representative mass spectra from orange juice, milk and sprite

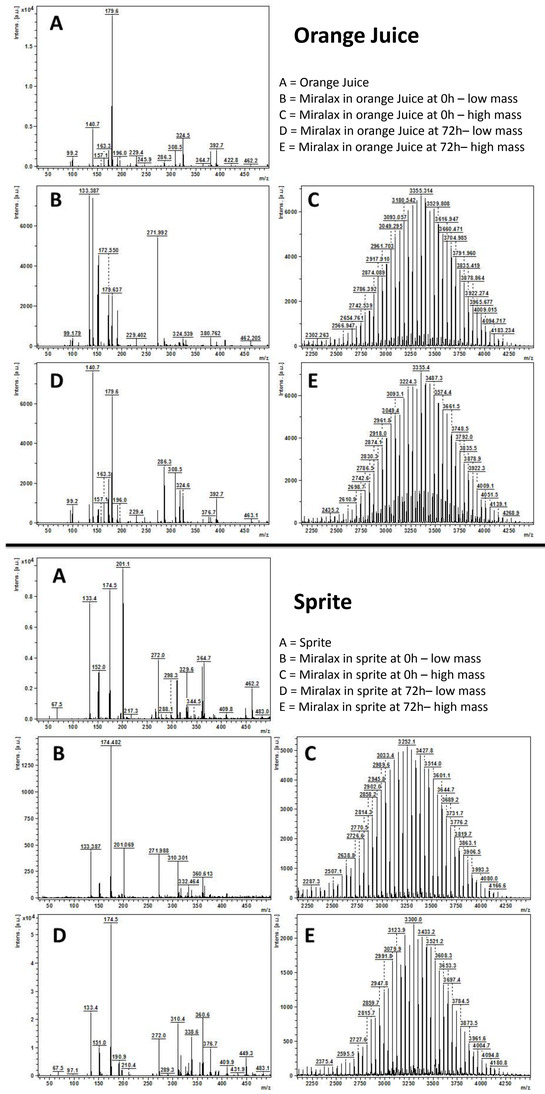


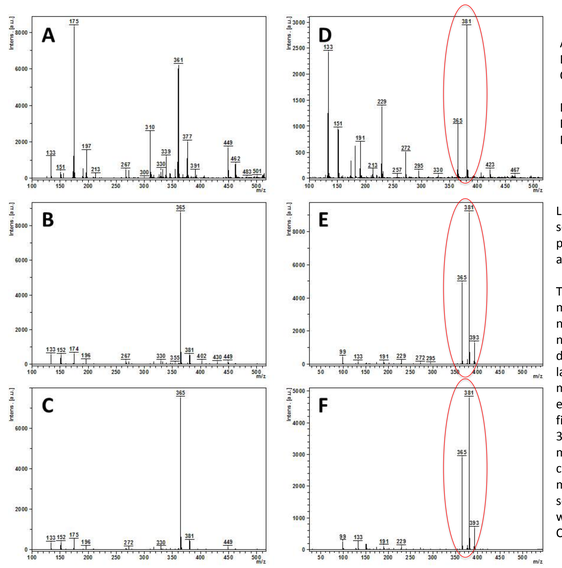
Table 1. List of potential degradation and metabolism products that can arise from PEG 3350.

Table 1			
LMW Species	**Abbreviation**	**Relationship / justification**	**Molecular Weight (MW)**
Diethylene glycol	DEG	Detected in PEG 3350 product by FDA	106.12 g/mol
2-hydroxyethoxyacetic acid	HEAA	Metabolite of DEG	120.10 g/mol
Diglycolic acid	DGA	Metabolite of DEG	134.09 g/mol
Ethylene glycol	EG	Detected in PEG 3350 product by FDA	62.07 g/mol
Glycolic acid	GA	Metabolite of EG	76.05 g/mol
Oxalic acid	OA	Metabolite of EG	90.03 g/mol
Polyethylene glycol 200	PEG 200	Low molecular weight PEG	~200
Polyethylene glycol 400	PEG 400	Low molecular weight PEG	~400

EG and DEG (low molecular weight (LMW) species) were detected in PEG 3350 by the FDA in 2008. The absorption and potential accumulation of these species and their metabolites may cause neurotoxicity and metabolic acidosis. No PEG degradation products, including EG or DEG, were detected in this study in any solutions.

Results

Figure 2. Lactulose – Representative mass spectra from water and milk



A = Water
B = Lactulose in water at 0 h
C = Lactulose in water at 72 h

D = Milk
E = Lactulose in milk at 0 h
F = Lactulose in milk at 72 h

Lactulose is observed in solution as a sodium or potassium adduct at *m/z* 365 and 381 respectively.

The stability of lactulose in milk, juices and soda could not be evaluated due to the naturally occurring disaccharides , sucrose and lactose that share the same mass as lactulose. An example of this is shown in figure 2D-F, which shows *m/z* 365 and 381 was detected in milk alone and in the milk containing lactulose. These masses were detected in all solutions except water, as would be expected, figure 2A-C.

Discussion

- Miralax appeared stable for 72 hours in all solutions. No degradation products were detected throughout the time course in any solutions.
- Clinicians can counsel families to mix PEG 3350 in common liquids, which may be more preferable to children, thus potentially increasing adherence.
- Families of children receiving a clean out regimen over several days with PEG 3350 can be instructed to pre-mix the PEG 3350 and keep refrigerated during the course of the clean out.
- Lactulose stability could not be evaluated in milk, juices and soda.

References

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4. Lardieri AB, Polli JE, Morgan JA. Polyethylene glycol 3350 and lactulose preparation in children. Poster, Pediatric Pharmacy Advocacy Group Annual Meeting. Minneapolis, MN. May 2015

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