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Gitanjali Kerkar

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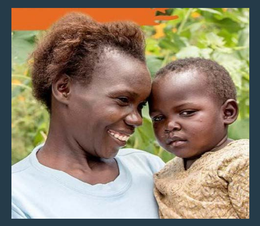
Pediatric Milk-based Efavirenz Freeze-dried Nanoemulsion: Formulation and Characterization

Author: Gitanjali Kerkar Research co-advisors: Dr. Qinfeng (Sarah) Liu & Dr. Mali Gupta Research committee: Mr. Paul Johnson
Campbell University College of Pharmacy & Health Sciences, Buies Creek, NC 27506



www.pedaids.org

Introduction

- Approximately 1.8 million children under 15 years of age are living with HIV (c.2017)
- Pediatric patients with HIV have been lagging behind adults in receiving anti-retroviral therapy (ART) due to numerous barriers, one of which being the lack of appropriate pediatric anti-retroviral (ARV) drug formulations
- Efavirenz (EFV) is an HIV-1 specific and a first choice anti-retroviral in adults and pediatric pharmacotherapy
- The available efavirenz formulations for pediatric patients older than 3 months are Sustiva tablet (600 mg) and capsule (50 mg, 200 mg)
- These formulations are “Pediatric” not necessarily “Pediatric friendly”
- Therefore, there is a need to formulate a product that is easy to administer to pediatric patients and contains natural and minimum excipients
- The freeze-dried efavirenz o/w nanoemulsion contains milk as the aqueous phase, medium chain triglyceride as the oil phase and span 80 was added to improve the homogeneity of the nanoemulsion
- The efavirenz freeze-dried powder will be suitable to administer by dissolving in water or milk-based drinks or sprinkled on food for oral administration in pediatric patients three months of age or older.

Objective

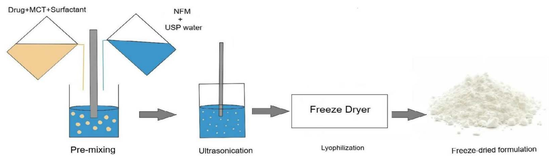
- To formulate a freeze-dried nanoemulsion with particle size less than 1000 nm
- To assess drug yield of the freeze-dried powder
- To determine stability of freeze-dried powder
- To characterize powder flow property for the freeze-dried formulation
- To characterize crystallinity of the freeze-dried formulation
- To determine the moisture content of the freeze-dried formulation

Hypothesis

A milk based freeze-dried nanoemulsion of efavirenz with a stable drug content and a z-average of less than 1000 nm can be prepared

Methods

Pre-mixing using a homogenizer	• Aqueous phase: non-fat milk + water • Oil phase: Efavirenz + MCT + span 80 • An oil/water emulsion was formed
Ultrasonication	• The particle size of the emulsion was reduced to form a nanoemulsion
Freeze-drying	• The nanoemulsion was freeze-dried for ~ 40 hours to form the final formualtion



Characterization of freeze-dried formulation

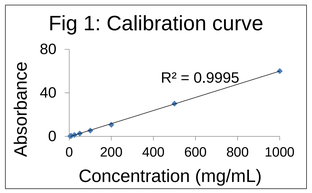
- Drug Content
- Particle Size Determination
- Powder X-ray Diffraction
- Thermogravimetric Analysis
- Powder Flow Study
- Accelerated Stability Study

Results

Drug yield

Table: 1 Drug content

Batch 1	Batch 2	Batch 3	Average
98.4%	96.7%	105.3%	100.2%



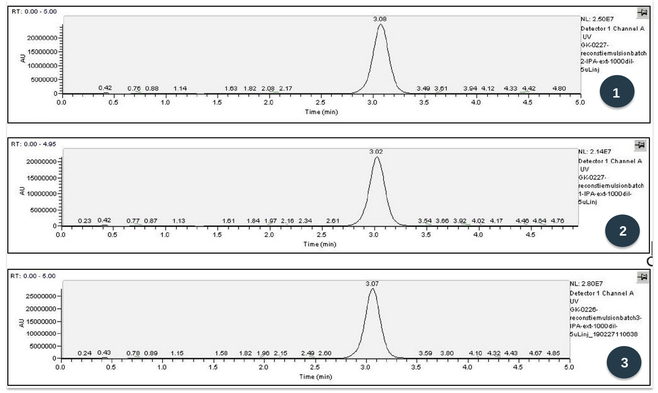


Fig 2: HPLC analysis of freeze-dried powder

Particle size

Table: 2 Particle size distribution of EFV freeze-dried reconstituted nanoemulsion (d.nm)

Sample name	Z-Ave	PDI	D(n)10	D(n)50	D(n)90
Batch 1	663.5	0.605	294	381	505
Batch 2	618.6	0.490	281	364	478
Batch 3	526.8	0.562	69.6	89.4	244

Thermogravimetric Analysis

The 3 batches of freeze-dried powder showed an average of 1.16% desolvation mass loss below 150 °C

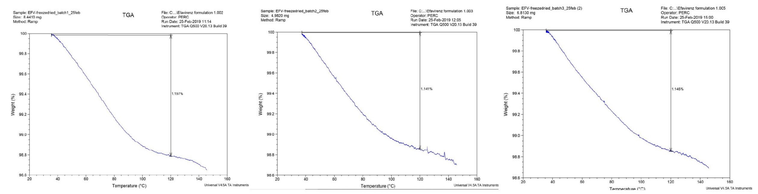


Fig 3: Thermogravimetric analysis of 3 batches of freeze-dried powder

Powder X-Ray Diffraction

Fig 3(a) shows that the drug is crystalline in nature whereas 3(b) shows that the freeze-dried formulation is amorphous

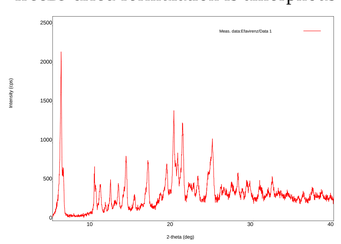


Fig 4 (a): Pure efavirenz drug

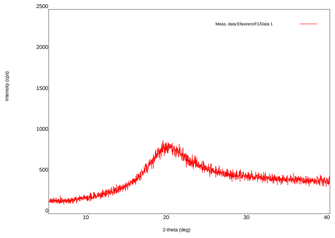


Fig 4 (b): Freeze-dried powder

Powder flow studies

The angle of repose was determined to understand the flow of the freeze-dried powder. It was calculated using the following USP formula:
tan(α)=height/0.5 base
= 62.5 degrees

Fig 5: Angle of repose experiment

Accelerated Stability Study

Table: 3 Accelerated Drug Stability

Batch 1	Batch 2	Batch 3	Average
Drug yield: 6 days			
97.8%	90.8%	94.9%	94.5%
Drug yield: 17 days			
89.5%	104.9%	95.6%	96.7%
Particle size (Z-average): 6 days			
604.9	561.8	576.1	580.93
Particle size (Z-average): 17 days			
597.1	442.6	502.0	513.9

Conclusion

- An amorphous final powder formulation was obtained by freeze-drying the nanoemulsion
- Drug yield obtained was within the FDA limit of 90-110%
- The powder could be reconstituted with water to give a nanoemulsion with mean hydrodynamic diameter less than 1000 nm
- The freeze-dried powder showed an average of 1.16% mass loss below 150°C
- There was no significant difference in the drug content from day 0 to day 17; p-value was 0.4983 > 0.05
- The stability testing results showed that the particle size was less than 1000 nm
- According to the USP <1174>, the powder flow was ‘very poor’

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