Plan Overview

A Data Management Plan created using DMPTool

DMP ID: https://doi.org/10.48321/D1RH2Q

Title: Superiority of intestinal lipoproteins (chylomicrons) for oral drug delivery: a screening platform for formulation candidates

Creator: Vassili Kotlov - **ORCID:** 0009-0000-8162-0671

Affiliation: Impact@10

Funder: National Institutes of Health (nih.gov)

Funding opportunity number: PA-23-230

Template: NIH-FDP Pilot Template Alpha

Project abstract:

Oral drugs are often 70-90% metabolized during the first pass through the liver via the portal vein, rendering their tissue bioavailability correspondingly low. This results in many agents being administered intravenously or through inhalation. Mammals, including humans, have 2 distinct systems for absorbing nutrients into the blood after ingestion. Nutrients such as amino acids, sugars, salts, water and virtually all oral drugs are absorbed into the portal vein blood. The pathway through which fats (lipids) are exclusively absorbed is under-utilized for drug delivery.

Orally administered lipophilic drugs may be absorbed in conjunction with absorbed triglycerides in chylomicrons. Chylomicrons (CM) transit into the subclavian venous blood via the terminal lymphatics, thus avoiding first pass hepatic metabolism.

Systemic pharmacokinetics are the gold standard for quantitating exposure of a drug. However, differences in absorption during the first circuit through the body is not reflected in systemic PK. Up to a 10-fold increase in the arterial vs venous levels of inhaled nicotine which has a 2 hour plasma half-life, suggesting that “first circuit” removal is considerable. CM only have a 5-minute half-life and first circuit effects on the A/V ratio are likely much greater than observed with inhaled nicotine. Thus, drug absorbed via this route experience rapid delivery unreduced by metabolism. Because of the first circuit absorption effects, systemic pharmacokinetics are a poor measure of success. When we assessed the difference in CBD exposure in rats when comparing a formulation in medium chain triglycerides and one in long chain triglyceride (LCT) to 2 experimental formulations with a variety of LCT and surfactants added to promote solubility we observed a not statistically significant increase in AUC in the systemic circulation. In contrast, when portal blood and mesenteric lymph were collected, highly significant differences were seen with a 10x increase in portal blood levels and 100x

increase in mesenteric (chylomicron carried) levels over the control formulations.

The proposed research in Phase I will focus on (Aim 1) Showing that oral lipophilic drugs (API) carried as cargo in chylomicrons have improved tissue distribution, metabolism and exposure over API absorbed directly into portal blood and (Aim 2) testing whether the degree of API enrichment of chylomicrons isolated from systemic blood is predictive of a formulation's ability to partition API into chylomicrons in the enterocyte and can be used for screening formulation candidates. The data from these trials will form the basis for using the enrichment assay as a method for screening formulations to maximize chylomicron carriage of the API.

Start date: 04-01-2024

End date: 03-31-2025

Last modified: 01-19-2024

Copyright information:

Superiority of intestinal lipoproteins (chylomicrons) for oral drug delivery: a screening platform for formulation candidates

- New

Oral drugs are often 70-90% metabolized during the first pass through the liver via the portal vein, rendering their tissue bioavailability correspondingly low. This results in many agents being administered intravenously or through inhalation. Mammals, including humans, have 2 distinct systems for absorbing nutrients into the blood after ingestion. Nutrients such as amino acids, sugars, salts, water and virtually all oral drugs are absorbed into the portal vein blood. The pathway through which fats (lipids) are exclusively absorbed is under-utilized for drug delivery.

Orally administered lipophilic drugs may be absorbed in conjunction with absorbed triglycerides in chylomicrons. Chylomicrons (CM) transit into the subclavian venous blood via the terminal lymphatics, thus avoiding first pass hepatic metabolism.

Systemic pharmacokinetics are the gold standard for quantitating exposure of a drug. However, differences in absorption during the first circuit through the body is not reflected in systemic PK. Up to a 10-fold increase in the arterial vs venous levels of inhaled nicotine which has a 2 hour plasma half-life, suggesting that “first circuit” removal is considerable. CM only have a 5-minute half-life and first circuit effects on the A/V ratio are likely much greater than observed with inhaled nicotine. Thus, drug absorbed via this route experience rapid delivery unreduced by metabolism. Because of the first circuit absorption effects, systemic pharmacokinetics are a poor measure of success. When we assessed the difference in CBD exposure in rats when comparing a formulation in medium chain triglycerides and one in long chain triglyceride (LCT) to 2 experimental formulations with a variety of LCT and surfactants added to promote solubility we observed a not statistically significant increase in AUC in the systemic circulation. In contrast, when portal blood and mesenteric lymph were collected, highly significant differences were seen with a 10x increase in portal blood levels and 100x increase in mesenteric (chylomicron carried) levels over the control formulations.

The proposed research in Phase I will focus on (Aim 1) Showing that oral lipophilic drugs (API) carried as cargo in chylomicrons have improved tissue distribution, metabolism and exposure over API absorbed directly into portal blood and (Aim 2) testing whether the degree of API enrichment of chylomicrons isolated from systemic blood is predictive of a formulation’s ability to partition API into chylomicrons in the enterocyte and can be used for screening formulation candidates. The data from these trials will form the basis for using the enrichment assay as a method for screening formulations to maximize chylomicron carriage of the API.

1.0

09/05/2023

I-N-001

Superiority of intestinal lipoproteins (chylomicrons) for oral drug delivery: a screening platform for formulation candidates

Vassili Kotlov and Ramon Seva listed on the grant proposal will implement and monitor the policy and the plan.

- No

- No

We will make available our protocols at the end of our 1 year study. Relevant quality controlled datafiles will be made available in SAS formatted databases when the study is completed.

- No

- Yes

Data Type	Brief Description	Organism, Model or other Sources	Amount of Data	Standards	Shared Formats	Data Repository	Data Access Type

Data Repository	Expected number and frequency of submissions	Projected timeline for first submission to repository	Projected timeline for last submission to repository	Target timelines for release	Type of persistent IDs that will be used for data releases, to enable findability and citation of shared datasets	If you will be contributing data to a dataset that is already registered with a data repository, provide that ID

SAS or JMP software.

Available only from the research team.

Within 1 year after the conclusion of the study.

The data generated from these experiments will only be interpretable after QC and formatting into final databases.
