

Introduction

Access's Cobalamin™ oral drug delivery system has the potential to improve the oral bioavailability of many drugs, including siRNA, proteins and antibodies, which currently have to be administered by other routes.

Oral administration of pharmaceutically active compounds usually requires that the active ingredient remains largely unaltered during transit through the gastrointestinal tract and that the drug possesses the requisite physico-chemical features (typically, low molecular weight, uncharged, and at least somewhat lipophilic) that allow it to pass readily across the wall of the intestine and be delivered into the bloodstream. For many active materials, particularly siRNA, peptides, proteins and other macromolecules, oral administration is currently not an option. Poor absorption and degradation in the gastrointestinal tract typically restricts oral bioavailability of proteins to less than one percent of the administered dose.

There are many oral drug delivery technologies that are intended to improve the pharmacokinetic profile of active ingredients. These can be classified as either:

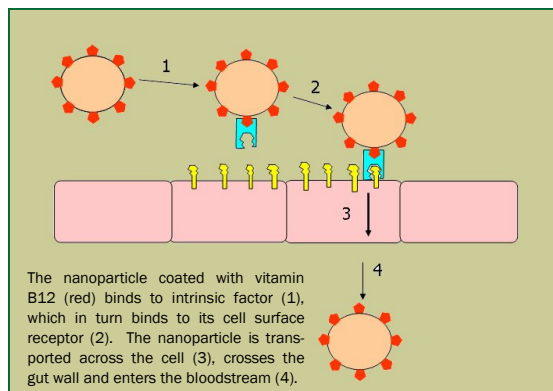
(1) protection systems (e.g. enteric-coated tablets), (2) release modification systems (to control the rate/site of drug release in the intestine), (3) mucoadhesives (to slow transit through the intestines), and (4) absorption enhancement systems.

The vast majority of of these systems provide either (1) or (2) or (3), but these give little or no tangible benefit unless the drug being delivered can cross the intestinal epithelium and enter the bloodstream.

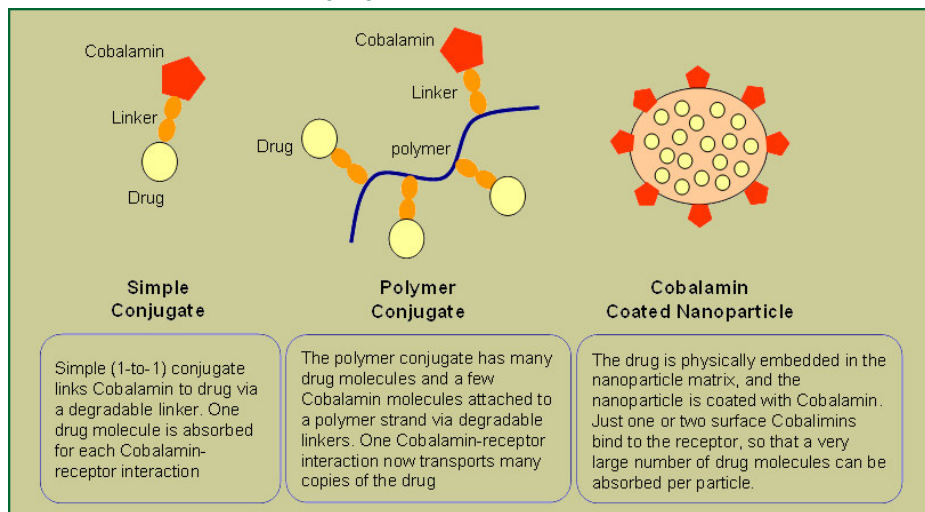
The Access Pharmaceuticals' Cobalamin™-mediated oral delivery technology is primarily an absorption enhancement system, with potential to provide oral bioavailability to any active compound which would otherwise not be orally available. Embodied in the technology are release modifying and protective effects which would likely enable the Cobalamin technology to be used without assistance from other proprietary technologies to provide effective oral drug delivery formulations

Mechanism of Absorption

The Access oral drug delivery technology addresses the problem of poor intestinal absorption of many drugs by utilizing the body's natural transport system for vitamin B12 (VB12). This receptor-mediated process actively transports VB12 from the gut to the blood stream. Our scientists have developed several different delivery options which use the natural uptake pathway of VB12.

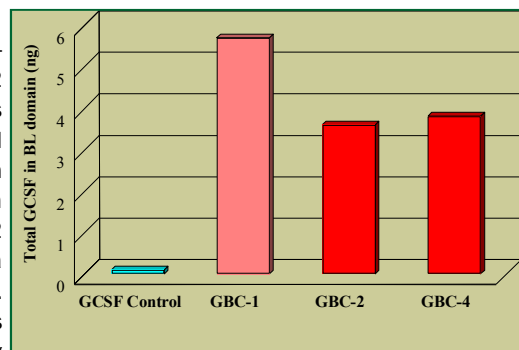


• Cobalamin™ Delivery Systems

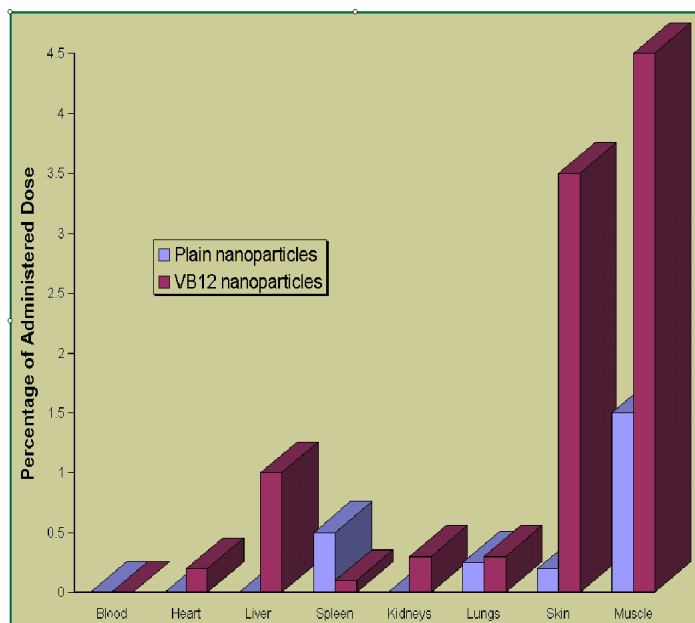


Receptor-Mediated Uptake

Initial proof-of-principle of this technology was provided using the Caco-2 cell monolayer technique. This monolayer method is well-established in drug development, and it has been shown that there is good correlation between results in the Caco-2 monolayer method and the ability of a drug to cross the cells lining the gut. Using the protein GCSF as a model; as shown in the bar chart (right), hardly any unmodified GCSF crosses the monolayer (blue bar), but relatively large amounts of three different Cobalamin-GCSF conjugates (pink/red bars) can cross the cells by VB12 receptor-mediated uptake.

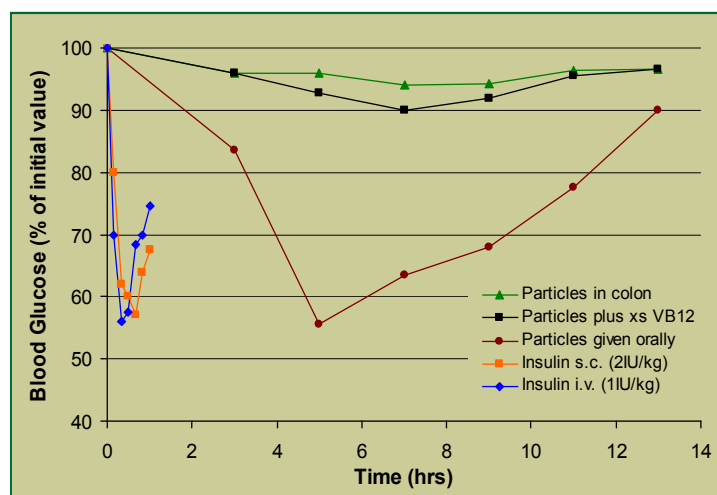


Cobalamin-coated nanoparticles



By radiolabeling, it is possible to follow the biodistribution of an active material following oral administration. The bar chart on the left shows results of such a study of the oral administration of Cobalamin-coated nanoparticles compared to uncoated nanoparticles in rodents. These particles were not carrying an active agent except for the radiotracer which is chemically bound to the nanoparticle. The distribution data shows that much larger amounts of radio-labeled nanoparticles were seen in the body following oral administration when the nanoparticles were coated with Cobalamin compared to uncoated nanoparticles, providing proof that the VB12 uptake mechanism has the capacity to transport nanoparticles, and that drug uptake is significantly enhanced by utilization of this mechanism.

The effectiveness of oral drug delivery using VB12-coated nanoparticles is demonstrated in the graph on the right which displays serum glucose levels following oral administration of insulin containing Cobalamin-dextran nanoparticles compared to injected insulin. Nanoparticles containing insulin and Cobalamin-coated insulin-loaded nanoparticles given orally provide a glucose lowering effect which is slower in onset and longer in duration than i.v. insulin. When these particles are injected directly into the colon, (green plot) there is a minimal pharmacological effect as the particles are "downstream" of the IF receptors in the ileum.



Summary

- Access's Cobalamin™ system has the potential to provide an oral delivery option to all molecules, small or large, with poor intrinsic oral bioavailability.
- Access' proprietary Cobalamin™ technology utilizes the body's natural vitamin B12 transport system to facilitate the oral absorption of drugs.
- Vitamin B12 can be transported across the gut with drugs, polymers or particles attached.
- Transportation of drugs is amplified by using nanoparticles or polymers
- Proof-of-principle has been demonstrated with LHRH, GCSF, EPO, Calcitonin, Interferon, insulin, and GHRP-6 (growth hormone)



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