

Integrated Oral Drug Delivery

Ivan S. Coulter

CEO, Sigmoid BioTechnologies Ltd, Units 1&2, 70 Heather Road, Sandyford, Dublin 18, Ireland



Dr Coulter is Chief Executive Officer and co-founder of Sigmoid BioTechnologies Ltd. He has held research positions at University College Dublin, Institut Curie, Paris, and holds an MBA from Cornell University, New York. Research topics included anti-cancer agents, antisense oligonucleotides, embryology and gene therapy. Sigmoid is focused on proprietary integrative drug delivery technologies and developing novel cyclodextrin constructs.

Introduction

The need for an integrated oral drug delivery technology is apparent. While delivery technologies have made significant progress to enhance solubility, improve permeability and increase stability, these approaches remain, to date, largely mutually exclusive. There is a need to break down the silo mentality that exists within the pharmaceutical, biotech and drug delivery sectors and develop technologies to enable the synergies that exist between, or amongst, otherwise disparate but complementary technologies to be fully realised. Through technology integration or bundling, exploitation of the above synergies has the potential to enable oral peptide or protein delivery, controlled release of drugs that are optimally formulated as non-powders, as well as combining otherwise incompatible drug formulations, such as water-soluble and lipid-soluble, into a single pill format.

Formulation Strategies

Solubility

More than 40% of all pharmaceutical entities exhibit low solubility, therefore, significant effort and expense has been devoted to overcoming this issue. After all, if a drug remains insoluble, it will be rendered ineffective. The principal approaches to enhancing drug solubility include:

Lipid-based – lipid-based formulations, including, but not limited to, liposomes, emulsions, microemulsions, self-emulsifying lipid formulations (SELF) and variations thereof, rely upon various combinations of lipid excipients, including simple oils, non-ionic surfactants and co-surfactants. To facilitate oral administration, such formulations mostly are encapsulated within large soft-gel capsules.

While serving as a means to administer consistent doses, the soft-gel format is not suited to further processing and is not amenable to conventional controlled-release polymer coatings that have been successful for water-soluble solid pill formats. Thus, a controlled-release technology for drugs optimally formulated in liquid or emulsion format is highly desirable.

Nanotechnology – dissolution is a factor of the surface area to volume ratio. Therefore, in theory, increasing this ratio should serve to increase the dissolution of molecules from particulate surfaces. This theory serves the basis of drug nanoformulation and leads to increased aqueous solubility of otherwise insoluble agents. In general,

nanoformulation is either bottom up or top down, the former relying on solvent evaporation, the latter on grinding particles down to the nanoscale. In either case, to prevent flocculation and increase particle stability, the formed nanoparticle surfaces must be coated with various polymers.

Cyclodextrins may be included amongst the various nanoformulation approaches. Cyclodextrins are inclusion-complexing agents that are, in effect, water-soluble host molecules for inclusion of lipophilic guest molecules.

To be converted to controlled-release oral administration formats, most nanoformulations are first converted to a free-flowing powder form prior to compaction into convention solid pellet or pill formats which are then coated with conventional controlled-release polymers. Such conversion often results in a detrimental effect on the enhanced solubility. A controlled-release format suited to non-powder drug formulations would maintain the drug in its enhanced solubility formulation.

Permeability

Enhanced solubility is but one variable in the oral bioavailability equation, albeit an important one. Another variable is permeability. Regardless of how soluble a drug molecule is, if it does not permeate the epithelial cell barrier lining the gastrointestinal and colonic tract, bioavailability and thus efficacy will be sub-optimal. Up to 50% of all drugs, amongst them many biopharmaceutical agents, exhibit poor intestinal permeability. A number of approaches have been adopted to enhance drug permeability. These approaches include:

Bio-conjugation – non-covalent or covalent attachment of various polymers facilitates the transit of poorly permeable drugs through the intestinal wall. Conjugated entities include molecules with a lipid head group which then permeates through the lipid-rich cell membranes. These entities also include muco- or bio-adhesives which stabilise the molecule, manoeuvre it toward the intestinal lining and increase the residence time at the intestinal wall.

Nano- and micro-formulation – various particulate morphologies and sizes are recognised by, and absorbed through, specialised cells lining the intestine such as the Peyer's Patches and/or M cells. By tuning the drug particle size and morphology, nano- and micro-formulations target this pathway, thus enhancing drug bioavailability.

Lipid-based formulation – due to a combination of charge, size and stability characteristics, hydrophilic entities exhibit poor intestinal permeability. Formulating these polar organic compounds as various lipid-based formulations, including medium chain triglycerides, optimally presents the drug-absorption promoter formulation to the absorption site, thus enhancing drug absorption. These formulation approaches also apply to macromolecules which often exhibit poor permeability.

Permeability enhancers – several permeability enhancers, ranging from the various chitosan and modified variants thereof to sodium caprate, medium chain fatty acids and other adjuvants have been demonstrated to enhance permeability, either by trans- or para-cellular means.

Stability

While not exclusive, the third in this trinity of variables considered important to oral drug absorption is stability. Several drugs, both small molecule and biopharmaceutical are rendered unsuitable for oral administration due to inherent gastric acidic and intestinal enzymatic instability. Additionally, cellular metabolism and efflux further reduces drug bioavailability.

Controlled release – the use of enteric and controlled-release polymer coatings for drugs formulated as pellets or solid pills is a well-established approach. Oral controlled release permits temporal and spatial release of drug as the coated format passes along the gastrointestinal tract. Advantages range from protecting the drug from the harsh gastric environment to enabling constant or variable pulsatile release profiles as is clinically preferable.

Adhesion – muco- or bio-adhesive polymers allow for prolonged residence of drug molecules with the intestinal mucosa, leading to a high concentration gradient of drug to intestinal lining which drives passive absorption and thus bioavailability. Commonly utilised adhesives include chitosan, gums, carbomer and derivatives of all the aforementioned. In addition to prolonged residence time, some adhesives have also demonstrated permeability enhancing as well as enzyme inhibiting properties.

Enzymatic inhibition – intestinal as well as cellular enzymes result in the degradation and/or metabolism of biopharmaceuticals and small molecules. In most cases this results in drug inactivation. The addition of intestinal enzymatic inhibitors is employed to prevent peptide or protein degradation while cellular enzymatic inhibitors prevent drug metabolism.

Integrated Approaches

As many of the above drug-solubility and permeability-enhanced formulations are optimised as liquid, emulsion or suspension format and are administered as soft-gel capsules, they are neither suited to, nor have benefited from, conventional oral controlled-release technologies. Similarly, many of the adhesive and enzyme inhibitors, which when present in high localised intestinal concentrations exhibit irritant or toxic effects on the

intestinal epithelial cells, are not fully utilised. In order to overcome such limitations, a delivery system to harness advances in solubility and permeability through controlled release, while limiting the potential adverse irritant or toxic effects associated with localised high adhesive, enzyme inhibitor or permeability enhancer concentrations, is highly desirable. **Sigmoid** has developed a seamless, fully integrated bundling or aggregating technology, Liquid/Emulsion Drug Delivery System or LEDDS™.

LEDDS™ Approach

LEDDS™ is based on a modified minicapsule technology. Rather than encapsulate an optimised drug formulation as fragile large soft-gel capsules which dump the entire contents into the harsh gastric region, LEDDS™ encapsulates the formulation in a robust seamless minicapsule format (*Figure 1*) which is readily amenable to further processing, including multiple coatings. Each minicapsule is multi-compartmental with a core space, an outer shell with a buffer in between. All three compartments may be modified, the inner core may be comprised of drugs in liquid, semi-liquid or solid form; the shell may be coated with various polymers; while the buffer may be modulated to ensure compatibility between the core and shell. The result is a drug or combination of drugs, optimally formulated, which may be pre-programmed for released in the stomach, intestine or colon depending on where specific drug absorption or activity is maximised.

Sigmoid recognised the unique potential of minicapsules to enable incompatible drug delivery technology bundling (*Figure 2*). The minicapsules are comprised of three layers:

- **Core** – containing the drug in a potential myriad of formulations, ranging from liquid, semi-liquid to solid, solubility or permeability enhancing and/or enzyme inhibiting;
- **Buffer** – generally an oil to prevent interaction of the core with the shell;
- **Shell** – encapsulates core and buffer.

The variable shell coatings control:

- where and at what time the core contents are released,
- adherence to intestinal cells to: protect drug, increase absorption and reduce uptake variability.



Figure 1 – Fragile soft-gel capsule vs robust LEDDS™ minicapsules.

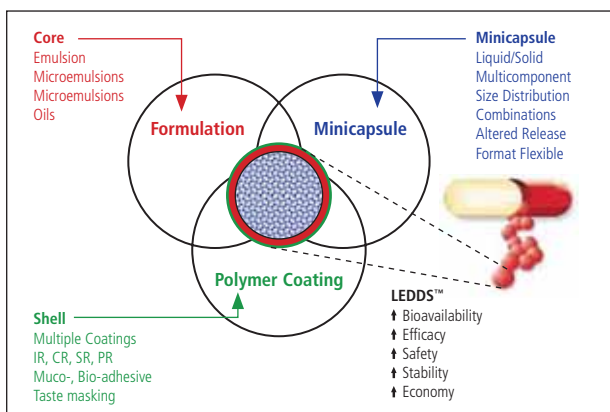


Figure 2 – Minicapsule-enabled LEDDS™ bundling.

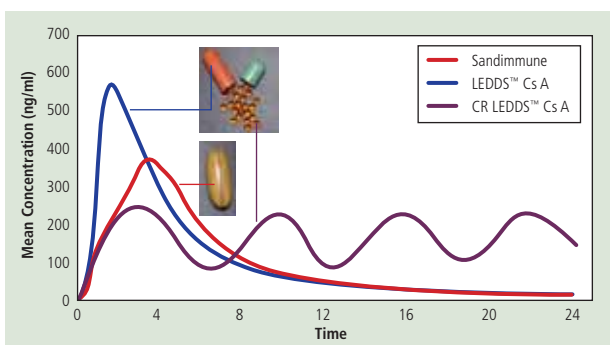


Figure 3 – LEDDS™ Cyclosporin A (IR and CR) vs Sandimmune.

LEDDS™ Clinical Results

Human pharmacokinetic studies demonstrated that, for cyclosporine A, the LEDDS™ formulated drug enters the blood stream up to four times as fast as its conventional equivalent. Also, using LEDDS™ technology, 50% more drug enters the bloodstream. The increased rate of uptake and enhanced absorption will bring significant benefit to a number of drugs, both small molecules and biopharmaceuticals, which exhibit low solubility, poor permeability and instability. The added benefit of qd or b.i.d. rather than t.i.d. or q.i.d. cannot be underestimated from a patient compliance or safety perspective as well as from an economic viewpoint.

Potential applications:

- convert 2-4 times daily administration to once-daily;
- oral Peptides and Proteins, including insulin;
- pain management – quick onset and sustained effectiveness/tamper-proofing;
- combination products, e.g. for cardiovascular/heart conditions or cancer;
- paediatric/geriatric formulations – easy to swallow minicapsules in soft food or drink;
- enhanced Over-The-Counter (OTC) products;
- oral vaccines;
- veterinary/aquaculture applications.

Conclusion

The need for a seamless drug delivery technology that will permit disparate delivery technologies to be aggregated or bundled is evident. In theory, drawing on the synergies enabled through integration, the power of combined solubility, permeability, stability or mucoadhesive technologies is greater than when either is applied individually. In practice, Sigmoid has demonstrated that LEDDS™ technology has the potential to aggregate or bundle disparate delivery technologies. The LEDDS™ advantages are multiple and broadly applicable, not only in partnership with pharmaceutical and biotech companies, but also in collaboration with other drug delivery companies.