Lipid-based delivery of peptide therapeutics

Julien Meissonnier of Catalent Pharma Solutions explains how the company’s Softgel Technology has been developed for lipid-based oral delivery of poorly soluble drugs and is now being applied to meet the challenge of improving the delivery of peptide therapeutics.

According to recently published data, the market for peptide drugs has grown significantly and sales for insulin alone reached $25 billion in 2013 (Source: IMS Health), with growth forecast to continue at a pace. Catalent, a leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products, has invested significantly in developing a broad range of complex oral drug delivery technologies, with OptiGel Bio™ technology being one of the most applicable for peptide drug delivery.

Due to permeability, stability, and delivery challenges, the dosing of macromolecules has traditionally been via injection. This invasive delivery form, while being able to provide an optimal pharmacokinetic therapeutic profile, may present challenges in patient compliance. Catalent’s proprietary OptiGel Bio technology may help overcome the traditional hurdles to oral dosing by enhancing permeability, and enabling targeted delivery in vivo through enteric coating.

The company’s research into the non-invasive delivery of macromolecules and peptides began in 2007. Over the past 20 years, its softgel technology has been successful in enabling poorly soluble drugs to reach the marketplace, with more than 50 NDAs approved. This technology employs lipid-based drug delivery systems (LBDDS) and has also helped overcome some permeability limitations of poorly soluble drugs. Catalent’s research on the oral delivery of macromolecules has also demonstrated the potential for LBDDS to take advantage of the intestinal permeability of a broad range of macromolecules.

OptiGel Bio technology is based upon the targeted co-delivery of permeation-enhancing formulations/systems with the macromolecule or peptide. This localised delivery allows for higher concentrations of permeation-enhancing excipients alongside the active pharmaceutical ingredient. These formulations are made up from ‘generally recognised as safe’ (GRAS) ingredients, so it is easier to create a safety package for their oral use.

Finally, the formulation offers some physical protection of the peptides against the harsh gastrointestinal (GI) environment (eg pH and proteases). Catalent has established evidence of the applicability of this technology to various classes of macromolecules, including oligosaccharides and peptides, and is conducting research to further expand its application to more complex delivery challenges on larger and/or less stable entities (ie oligonucleotides).

**Strategies for oral delivery of poorly soluble drugs**

The drug delivery strategy for a given drug depends on the unique properties of the drug substance, including physical properties such as the physical state (melting point); crystal form (polymorph); particle size distribution, extent of lyophilic surface area; and physical stability (hygroscopicity). Important chemical properties include salt form; molecular weight; solubility (aqueous, pH solubility profile, intrinsic dissolution); chemical stability; and compatibility with excipients. Significant biopharmaceutical properties include the mechanism of absorption (passive diffusion or active transport); site of absorption; first-pass metabolism; efflux; enterohepatic circulation; and drug dosing requirements.

As stated by Dr David Elder of GlaxoSmithKline, the solubility challenge can be split into two classes, the drugs exhibiting true intrinsic solubility limitations in biological fluids (DCS IIB) and those for which dissolution rate in biological fluids is the only limiting factor (DCS IIA). There are a number of ways in which drug substances can be modified to resolve each issue, including different types of salts; crystal forms (polymorphs); amorphous forms; hydrates or solvates; prodrugs; and cocrystals; leading to the development of a range of formulation strategies, including lipid-based drug delivery systems, the most successful solubility-enhancing technology applied to DCS IIB drugs; nanocrystals; solid solutions and dispersions; solid-lipid nanoparticles; and inclusion complexes (cyclodextrins). Catalent offers a variety of these technologies (Fig 1).

**Softgel technology for lipid-based drug delivery systems**

Lipidic excipients and resulting formulations are most often liquid or semi-solid in nature. This is a proven dosage form for lipid-based formulation with good developability (compatible with a wide range of excipients and formulations); good manufacturability (there are more than 50 NDA-approved products) and uncompromised in-vivo...
performance giving fast release of the fill formulation.

When developing a lipid-based drug delivery system, it is best to ‘begin with the end in mind’, thus achieving drug solubility in the formulation pre-administration; and maintaining drug solubility in the formulation (or the formulation’s digestion products) post-administration. Two critical factors influence the fate of lipid systems in vivo, formulation dispersion state and formulation digestibility. Therefore, lipid-based formulations have been ranked by Professor Colin Pouton in four classes encompassing a variety of systems (e.g. simple solution and dispersions in lipids, self-microemulsiifying systems…).

Some strategies specifically designed to leverage solubility and reduce variability comprise a typical self-microemulsiifying drug delivery system which would be a lipid-based ‘preconcentrate’ of solubilised drug composed of lipid excipients; surfactants (hydrophilic); co-surfactants (lipophilic); and co-solvents (e.g. ethanol). The desired characteristics of this formulation upon dilution with the gastrointestinal fluids are the spontaneous formation of a thermodynamically stable microemulsion, and that the drug stays in solution and does not precipitate.

**Lipid-based formulations for permeability and bioavailability enhancement**

Lipid systems (unlike polymer based systems) not only leverage solubility but also provides incremental properties to the formulation. Permeability enhancement results in passive transport through enterocytes, passive transport around enterocytes (tight junctions), and enterocyte-based active transport and metabolic processes (P-gp, CYP3A4, lipoproteins). Bioavailability enhancement can also be achieved through alternate absorption routes such as lymphatic transport. All these strategies are enabled by the proper selection of functional lipid ingredients.

Softgel technology has a number of advantages as a delivery tool for NCE candidates, in that it is highly suited for the delivery of BCS class II and IV drugs; highly potent, low dose APIs; oxygen-sensitive and light-sensitive drugs; and liquid or low melting point APIs.

Other advantages are that it is a proven technology that provides a robust dosage form (no brittleness or leaking); and is appropriate for low- to high-viscosity formulations (up to ~15,000 cps) with fill formulation temperature up to ~40°C. There are minimal to no scale-up issues with the technology.

**Future approaches**

Softgel systems that are becoming increasingly adopted include modified-release formulations using OptiShell® capsule technology. This system employs a semi-solid/solid lipid fill matrix for modified drug release of poorly soluble and water-soluble drugs and is also suitable for compounds that exhibit a short half-life and require frequent dosing or that have high peak blood levels and unacceptable side effects.

The OptiShell capsule shell polymer system undergoes thermal transitions at higher temperatures than traditional gelatin-shell systems. This allows encapsulation of lipid fills at high temperatures that are semi-solid or solid-like at room temperature. An example of the use of OptiShell capsule technology for modified drug release would be a fill formulation comprised of active ingredient, mineral oil, paraffin wax, lipophilic emulsifier and hydrophobic emulsifier.

This technology also enables encapsulation of lipid based formulations at temperatures up to ~80°C. This enables by analogy with hot-melt extrusion (OptiMelt™) the development of solid dispersions of poorly soluble drugs in lipid ingredients and the overcoming of drug load limits (over 200 mg/g) of conventional lipid-based formulations.

Therefore RP Scherer Softgel combined with OptiShell enables the conversion of any lipid-based formulation designed to overcome complex biopharmaceutical limitations into a concrete dosage form (e.g. pure caprylo/caprylic macrogol glycerides based formulations).

Other formulations that have been developed recently are film-coated softgels for the targeted delivery of poorly soluble, poorly permeable drugs, employing post-gastric (targeted) drug delivery. This gives protection of acid-labile drugs from gastric fluids; reduces local gastric side effects; and has the potential for enhanced drug absorption through rapid release of fill contents at the targeted site of delivery following dissolution of the film coat and high local concentrations of API and permeation enhancers.

A typical targeted drug release example is a fill formulation comprised of active ingredient, mono- and diglycerides of medium-chain lipids; medium-chain fatty acid macrogol glycerides; and surfactants. The film coat formulation comprises polymethacrylate dispersion; macrogol; talc; simethicone emulsion; and purified water.

Catalent has undertaken a number of projects on the delivery of macromolecules and proprietary peptides and in addition to those works, the company has created some standard pre-formulation and formulation screening models in order to quickly (ie in a few weeks) evaluate whether OptiGel Bio technology can assist in the delivery of candidate macromolecules including peptides. Also, these models have enabled the determination of potential structural changes to the peptides which would maximise the ability to cross the enterocyte along with the permeation-enhancing system when formulated.

Catalent currently has strong partnerships with several universities and the Catalent Applied Drug Delivery Institute’s leaders are actively engaged in expanding academic and industry partnerships by launching a global Non-invasive Macromolecule Consortium with academic and industry experts, conducting clinical roundtable research and creating tools for future life science leaders such as the Oral Drug Delivery Reference Guide. The Non-invasive Macromolecule Drug Delivery Consortium was launched in San Diego on June 23 this year, just prior to the annual BIO International Convention.

**To summarise**

The bioavailability of poorly soluble and permeable drugs including macromolecules and peptides can often be enhanced from lipid-based formulations. With more than 50 US-NDAs approved, Rp Scherer Softgel and OptiShell are the most reliable dosage forms to reliably translate those delivery systems into approvable drug products.

Self-microemulsiifying lipid-based formulations can not only enhance bioavailability but also minimise absorption variability while mitigating potential ‘food effect’. Lipid-based solution or suspension formulations also provide unique features influencing membrane permeability which can be achieved by enzyme and/or efflux inhibition, or by modification of the absorption route (lymphatic transport). Future approaches include modified delivery for improved safety and/or efficacy.

**Further information**

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