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WHAT DO CUSTOMERS NEED IN ORAL DOSE DEVELOPMENT?

Here, Chris Halling, Senior Manager, Global Communications & European Marketing, Catalent Pharma Solutions, describes the translation of a drug design concept through to the development of an oral dosage form that satisfies the needs of the manufacturer, physicians and patients. This is achieved by applying a target therapeutic profile to give the best possible therapeutic performance of a drug product.

Oral dose development – in particular the inexpensive creation of a simple, once-daily small white pill with optimal therapeutic performance – is the goal of many drug developers. The translation of a drug design concept to the delivered oral dose can be complicated, and understanding the needs of pharmaceutical clients, as well as patients and doctors, is a vital part of the process.

The steps to reach this goal include:

- Creating the target therapeutic profile (TTP)
- Understanding the physicochemical properties of the molecule
- Getting to preclinical and clinical proof-of-concept
- Creating a viable solution for poorly soluble molecules
- Ensuring the stability and robustness of formulations
- Optimising delivery technology and dose forms to get to the TTP
- Meeting the TTP with lowest development cost, fastest development pathway and best therapeutic performance.

CREATING THE TTP

The TTP is the basic summary of all the required characteristics of a newly formulated drug. Developing this is the first step of the process. There are a number of considerations to bear in mind when creating the TTP,[1] including:

- Indication
- Patient group, e.g. children or adults
- Dosage form
- Size of dose
- Frequency of dose
- Duration of treatment
- Safety profile and adverse reactions
- Mechanism of action
- Clinical efficacy
- Stability at varying levels of temperature or humidity
- Dose profile, or the relationship between pharmacokinetics and pharmacodynamics
- Cost of goods sold (CoGS).

As with many steps in drug development, planning early will improve outcomes and make the process smoother and more cost-efficient. Creating a therapeutic target profile can also help with decision-making processes throughout dose and formulation development, including planning product development strategies, gaining partners and investors, and moving through the regulatory process. Ideally, the TPP should be formulated before initiating Phase I trials, so it can be used as part of the go/no-go decision process.

UNDERSTANDING THE PHYSICOCHEMICAL PROPERTIES OF THE MOLECULE

Understanding the properties of the molecule is critical to developing an ideal oral formulation. The key physicochemical factors are permeability and solubility, which impact the amount and rate of drug absorption, and therefore its bioavailability.[2]

Mr Chris Halling
Senior Manager, Global Communications & European Marketing
T: +44 1793 864 000
E: info@catalent.com

Catalent Pharma Solutions
Frankland Road, Blagrove
Swindon
Wiltshire
SN5 8YG
United Kingdom

www.catalent.com

Figure 1: A selection of Softgel capsules. Softgel can improve solubility for BCS Class II/IV compounds, improve solubility and permeability for BCS Class III/IV compounds, and improve dose uniformity and minimise interpatient variability.

The US FDA divides drugs into four classes of bioavailability, under its biopharmaceutics classification system[3,4]:

- Class I – high permeability, high solubility
- Class II – high permeability, low solubility
- Class III – low permeability, high solubility
- Class IV – low permeability, low solubility

The combination of these properties, and the requirements of the TPP, allow the next step of the process to begin, which is creating a formulation for preclinical and early clinical trials.

Catalent has created FormProRx™, a web-based tool that generates suggestions based on API characteristics to help drug developers select the best dose form of oral delivery to improve bioavailability.

GETTING TO PRECLINICAL AND CLINICAL PROOF-OF-CONCEPT

Drug development is a costly business, and getting drugs through studies and to the market as quickly as possible is important to ensure a rapid return on investment, as is ensuring that the drug remains on the market for as long a period as possible without generic competition. Creating an oral formulation can slow the process down, but it is possible to maintain speed by carrying out development steps in parallel.

Formulation steps do not need to be sequential. It is possible to begin preclinical and even clinical trials without a finished formulation by using a bridging study to show bioequivalence between tablets, liquids, or capsules. However, the FDA require 12 months of stability data for a given formulation, so this must be borne in mind when carrying out studies of the final formulation.

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Solubility is an important factor in oral drug development to ensure that drugs are absorbed through the gut wall, and it should be considered on a case-by-case basis along with the permeability of the drug (as per the previous section on "understanding the physicochemical properties of the molecule").

Measurements for solubility and bioavailability include assessing solubility in simulated gastric fluid, and crosschecking this with the drug's ability to penetrate the gut wall.

Other approaches to improving solubility include changing particle size to increase the surface area. This can be achieved with milling or micronisation, or by dissolving lipophilic drugs in lipids with a surfactant in a self-emulsifying drug delivery system (SEDDS), which creates a drug emulsion on contact with an aqueous environment.

Softgel technologies (Figure 1), such as those developed by RP Scherer, may improve solubility for BCS Class II/IV compounds, and improve solubility and permeability for BCS Class III/IV com-

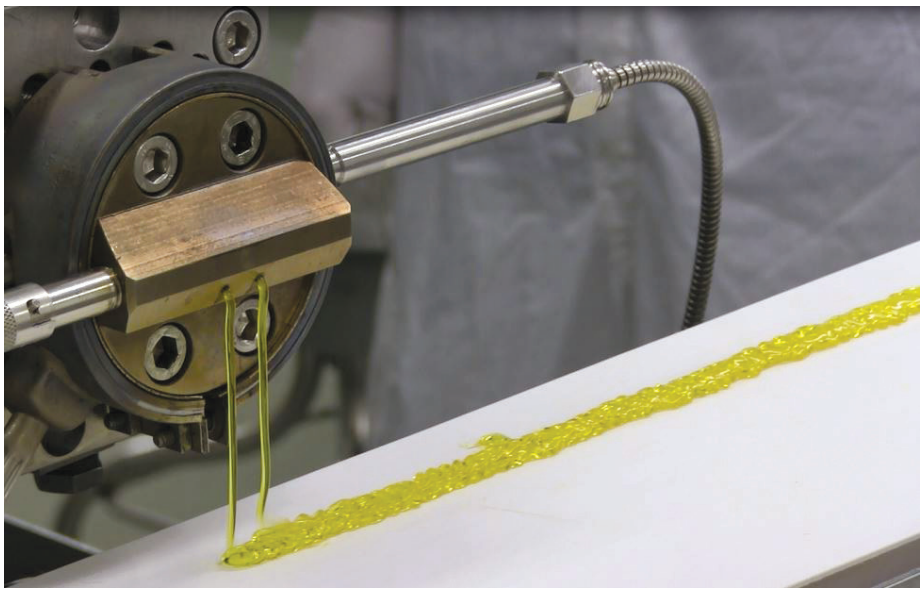

Figure 2: Hot-melt extrusion creates extrudates – solvent-free solids that can be milled and formulated into a variety of different dosage forms, including controlled delivery and taste-masked tablets.

pounds. The technology can also improve dose uniformity and minimise variability between patients.

Hot melt extrusion, where drugs are mixed with a polymer and then heated to create a solid solution, improves drug solubility and bioavailability. It creates a solvent-free solid (Figure 2) that can be milled and formulated into a variety of different dosage forms, including controlled delivery and taste-masked tablets. Catalent's OptiMelt™ hot melt extrusion technology optimises safety and efficacy, and helps speed drugs to market.

ENSURING STABILITY & ROBUSTNESS

The finished oral formulation needs to be physically robust enough to survive packaging, transport and storage. It also needs to be stable, to ensure that the drug's activity and performance is consistent, whether it is used one month or one year or more after manufacturing. To achieve this, it should have a minimum shelf-life of 18-24 months, with an ideal shelf-life of up to five years. The length of shelf-life is particularly critical for products that have to be shipped over long distances, or that have been developed for rare diseases, where pharmacies may have to stock them for long periods.

The manufacturing process also needs to be robust, and here, simple really is better, both for quality and reliability. The process must be reproducible, so the manufacturer will not face the risk that the finished drug lacks the correct specifications.

As with solubility, the processes to improve drug stability will vary on a case-to-case basis. For example, coatings can help to increase the physical stability and robustness of oral tablets and capsules, especially when they are particularly fragile. Coatings applied to tablet or capsule formulations can also control drug release by protecting against degradation as the drug passes through the gut.

OPTIMISING DELIVERY TO GET TO THE TTP

The next step in the process is to optimise the delivery technology and the dose forms, in order to meet the requirements of the TTP. Options include:

- Solution/syrup/elixir
- Suspension
- Powders for reconstitution as suspension
- Dispersible/effervescent tablets
- Chewable tablets
- Orally disintegrating tablets
- Tablets
- Sprinkles, oral powders and granules
- Capsules.

Ideally, the manufacturer will not need to enhance the drug or change its properties to produce the dose form. However, many promising compounds encounter formulation issues. The drug developer or formulation partner must identify the problem in preclinical or early clinical trials and find the right oral formulation solution while meeting as many of the requirements of the TTP as possible.

The following are some examples of the use of the TTP as a development guideline.

Indication

The indication makes a difference in patient-centric dose form choice, particularly in over-the-counter medications. For example, the majority of adult patients prefer pills for indications such as pain, but will ask for liquid medications for coughs and colds.

Whether the disease is common or rare is also significant. For example, if the indication is for a severe and rare disease for which there is no other therapeutic product, the frequency of the dose and the cost per dose may not be as critical as it would be for an antihypertensive, where there is a lot of competition. However, because the drug for the rare disease is not in high demand, the shelf-life may need to be longer.

> "Shelf-life is particularly critical for products that have to be shipped over long distances, or that have been developed for rare diseases, where pharmacies may have to stock them for long periods"

Patient Group

Different patient groups have different needs. Very young children may be best dosed with liquids, whereas older children may prefer chewables. Middle-aged people may be comfortable with pills, whereas very elderly people may find disintegrating pills easier. There is a wide variety of dose forms designed for the paediatric market, and many of these dose forms can be useful in older people and patients with chronic disorders, who may have issues with taking common oral dose forms such as tablets or capsules. About a third of patients in long-term care, for example, have difficulties swallowing (dysphagia).[5]

Formulation provides a number of "workarounds". Parents and caregivers for younger children or frail elderly people may find dosing easier with liquids and fast-dispersing dosage forms (FDDFs), or granules, powders, and sprinkles that can be mixed into foods or drinks. Dosing aids and devices, such as spoons, cups, and calibrated oral syringes, can also help in the administering of drugs to the elderly and children.[6] In contrast, adolescents, adults and the active elderly are more likely to prefer capsules and tablets as these are more convenient and discrete.[7]

Because paediatric dosing covers such a wide range of ages and sizes, from birth to 18 years of age, formulations for children need to be flexible, so that doses can be titrated according to age and weight. They must also take into account differences in metabolism that may require higher or lower doses. The dose difference between young babies and adolescents could be as much as 50-fold.[7]

Children under two years old also have differences in gastric pH and gastrointestinal motility, which can affect the rate of delivery of controlled-release medications.[6]

Minitablets or capsules at 1-2 mm are also a good option for children, as their size allows them to be swallowed easily. Liquid drugs are only practical in certain dose sizes, particularly in children, and tablets must be the right size to be swallowed easily. Because the dose is split, this allows titration.[8] In a study of children aged six months to six years, 2 mm uncoated tablets were accepted equally as well as sweetened syrups.[9]

Capsules loaded with pellets or minitablets can also be manufactured at a wider range of dose strengths, or administered using a tablet dispenser. This kind of detailed dose manipulation opens up additional potential indications for oral drugs.

Crushing tablets is not advisable, and tablets to be subdivided must be able to be split in two equal parts.[6] Where possible, children's medications should need to be

administered no more than twice daily.

Taste and smell, and even texture, are all important, particularly for oral drugs for children. Gelatin capsules were introduced in 1834 to mask the taste of drugs, and current approaches include adding flavours, aromas or sweeteners, coating tablets with polymers, liquids or sugars, encapsulation and microencapsulation, granulation, or using taste suppressants and potentiators.[10]

Dosing Profile

For some drugs, variability in the pharmacokinetics and pharmacodynamics has a significant effect on efficacy, safety, and side effects. This can be managed by changing absorption rates, or muting peaks and troughs. Two formulations of a multi-cored tablet, for instance, could allow the same drug to be released at different rates, or in different parts of the body. Gastro-resistant coatings on tablets or capsules will ensure that drugs are carried through the stomach and released in the gut, where absorption rates are often higher.

THE LOWEST COST OUTCOME FOR THE TPP

The simplest and least expensive option—and the preferred form for manufacturers—is the plain white pill at a single-dose strength. However, plain white pills may not be particularly patient-centric, especially for those who are taking a number of different medications at different times during the day. A plethora of similar small, white pills could make tablet-taking a complex and confusing process.[6]

FDA guidelines encourage manufacturers to develop formulations that make it easier for consumers to distinguish one drug from another by colour, shape, or size. Printing or embossing on the surface of the pill may also help.

Different shapes and colours can also improve acceptability and brand recognition, and create a clear differentiation between different brands, or between brands and generics. Nexium® (esomeprazole) is known as a purple pill, for example, and Viagra® (sildenafil citrate) as a blue triangular pill. Companies can submit images of shapes, colours, and designs to the FDA as part of the approval process.

THE IMPACT OF COST

The cost of drug manufacturing needs to be taken into account in the TTP. For higher-value drugs, where the API is expensive, and for indications where there is little competition, the cost impact of oral dose development is not significant. However, for generic drugs, where costs must be controlled to preserve profit margins, any increase in manufacturing expense is significant, making a plain white pill the most desirable target.

> "A well-designed oral drug can improve compliance, as well as therapeutic performance, and this impact for payers and patients also needs to be part of the health economics assessment"

A well-designed oral drug can improve compliance, as well as therapeutic performance, and this impact for payers and patients also needs to be part of the health economics assessment.

CREATING THE OPTIMISED DRUG PRODUCT

When developing an optimal dose form, it is important to focus on the science, creating the best possible therapeutic approach, while taking a practical and pragmatic approach. This will ensure a cost-effective, safe and efficacious patient-centered drug with broad-based applications that is convenient and easy to take, thereby improving compliance and outcomes.

ABOUT THE AUTHOR

Chris Halling is Senior Manager, Global Communications and European Marketing at Catalent Pharma Solutions. He joined the company in 2010 as a Product Manager before being made responsible for first European and then, in 2013, global communications. Prior to joining Catalent, Mr Halling held marketing roles for several leading medical device and surgical instrumentation companies. He is a member of the Chartered Institute of Marketing and a Chartered Marketer.

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