ORAL DRUG DELIVERY:
PACKAGING TECHNOLOGY, DISPENSING DEVICES & ADVANCED FORMULATIONS

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"Oral Drug Delivery: Packaging Technology, Dispensing Devices & Advanced Formulations"

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Aug	CDMOs & CROs Offering Drug Delivery Solutions & Services
Sep	Drug Delivery in Diabetes
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THE GROWTH OF LIQUID-FILL ENCAPSULATION:

A FOCUS ON ITS BROAD VERSATILITY & APPLICATIONS IN ORAL DRUG DELIVERY

This article, from Joseph V Carey, PhD, Head of Contract Services & Business Development, Hansueli Schaub, Head of Tillotts Services, and Claudio Scialdone, Senior Manager, all of Tillotts Services (a business unit of Tillotts Pharma AG), presents an overview of the key benefits and recent developments in liquid-fill encapsulation with a focus on practical applications and case studies from the company's own product portfolio. The three variable components, coating technologies, capsule format and formulation design, are also discussed with respect to engineering a dosage form that can be targeted to a specific region of the gastro-intestinal tract and provide a specific drug delivery profile.

INTRODUCTION

Pioneering developments in manufacturing equipment, capsule design, excipients and coating technologies have propelled liquid-fill encapsulation up the list of oral drug delivery options for the formulation development scientist. Together with an increasing number of poorly water soluble drugs, highly potent APIs, probiotics and biologicals within drug company pipelines, the potential applications for liquid-fill encapsulation has grown substantially in recent years. These drivers have served to reduce costs such that liquid-fill encapsulation is able to compete economically with soft gelatine capsule manufacturing.

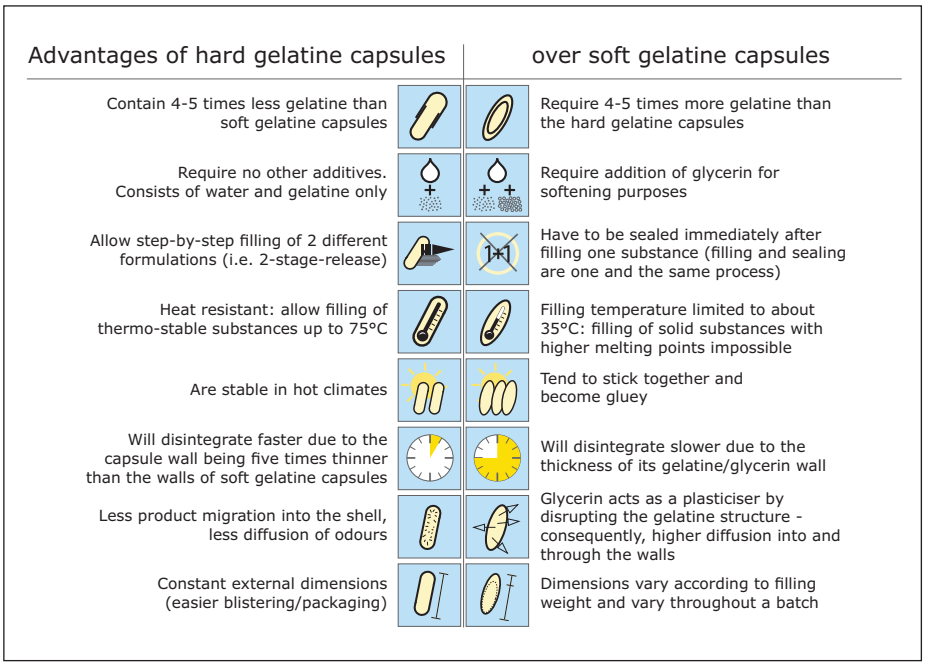

Figure 1: Advantages of liquid-filled, hard-shell capsules over soft gelatine capsules.

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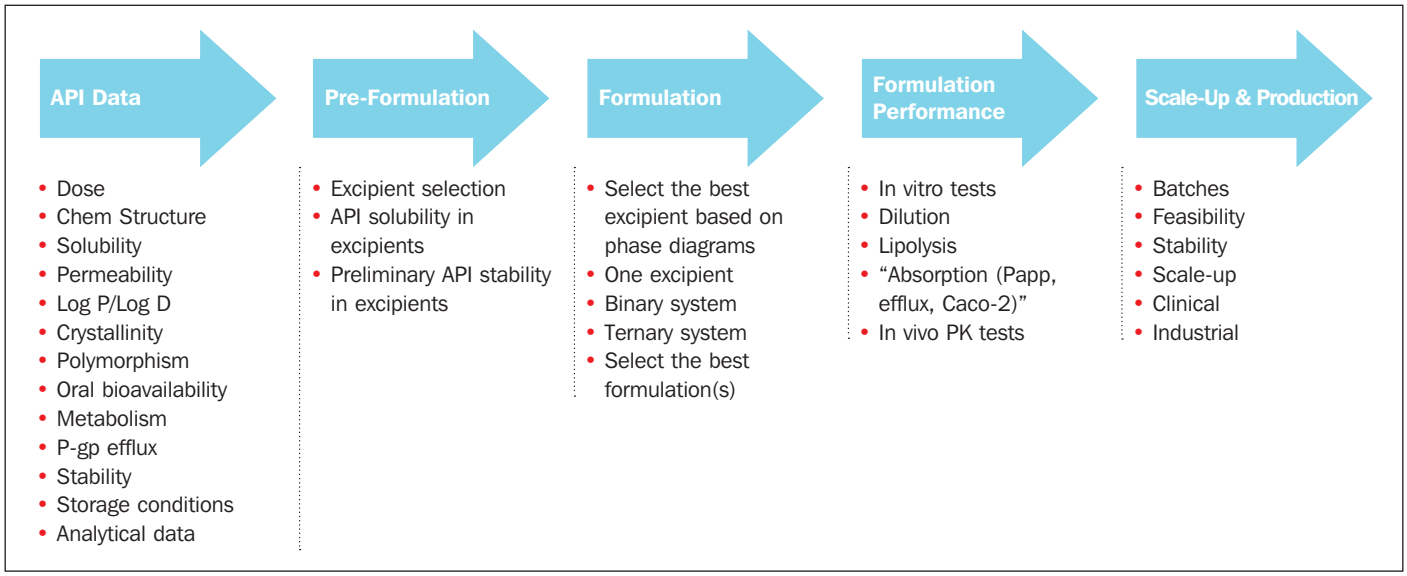

Figure 2: Tillotts Services' milestone-based approach to formulation design and scale-up.

UNIQUE BENEFITS

Two-piece hard-shell capsules offer formulators several unique benefits over soft gelatine capsules (Figure 1), particularly for more challenging APIs.

Capsules made from hydroxypropylmethylcellulose (HPMC) also provide a source of non-animal-derived alternatives to gelatine but with the added benefits of liquid-fill encapsulation.

INNOVATIONS IN TWO-PIECE, HARD-SHELL CAPSULES

During the last decade, an increasing number of suppliers of gelatine and HPMC capsules have emerged. This increased competition has served to drive down costs as economies of scale have also improved together with a shift in production to low-cost countries such as China and others within Eastern Europe. Capsugel (Morristown, NJ, US), Qualicaps (Irving, TX, US), ACG (Mumbai, India) and Suheung Capsule Co (Seoul, South Korea) are also developing modified capsule formats using new (GRAS listed) ingredients to provide broader end-user applications. For example, ACG has recently developed an enteric capsule that has the potential to remove the need for a final coating step and thereby reducing time and costs.

Two-piece, hard-shell capsules provide further advantages with respect to addressing other challenges currently facing the pharmaceutical industry such as the threat from counterfeit products. Barcode printing, hologram inclusion and the addition of markers in the coating or capsule shell can serve to provide additional anti-counterfeit barriers. In this way, individual capsule batches can potentially be uniquely tagged at the dosage form level and provide easy verification at key stages in the distribution chain.

A STARTING POINT IN FORMULATION DESIGN USING LIQUID-FILL ENCAPSULATION

Understanding the physicochemical properties of the drug substance is a key starting point with regards to pre-formulation design since molecules with poor solubility, hygroscopic, polymorphic, air/moisture sensitive or highly potent properties will need careful management with regards to their development and scale-up. However, liquid-fill encapsulation is highly applicable to such challenging molecules and commercial manufacturing can be effectively implemented with comparable cost economics to other technologies.

Tillotts Services' starting point is to review the available API data with our customer which allows the pre-formulation strategy to be defined and in doing so minimise development costs and time (Figure 2).

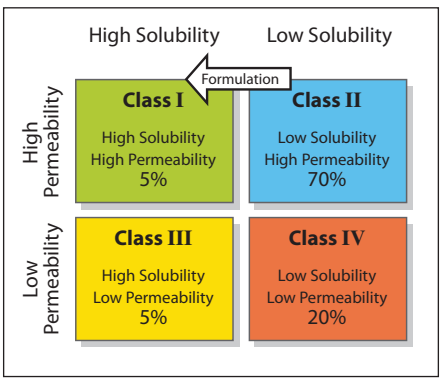

Figure 3: The Biopharmaceutical Classification System (BCS).

Tillotts Services has recently established a co-operation agreement with Solid Form Solutions (Penicuik, Scotland, UK), a world-leading CRO providing the pharmaceutical industry with chemical development services covering:

- Salt Screening
- Co-Crystal Screening
- Crystallisation Screening
- Polymorph Screening
- Batch Process Development (API)
- Physical Properties and Developability Testing

It is well established that there is an increasing number of highly potent molecules within drug development pipelines that require a high containment strategy.[1] Defining the Occupational Exposure Level (OEL) at the pre-clinical stage can sometimes be challenging where minimal toxicity data may be available. In such cases it is possible to utilise external experts (SafeBridge Consultants, for example) in toxicology and occupational hygiene who are able to use comparative structural or compound class data in order to assess such risk.

Additional challenges include poor solubility where currently around 70% of new chemical entities entering drug discovery and development programmes exhibit inferior aqueous solubility and consequently have poor or variable bioavailability. These BCS Class II drugs (see Figure 3) can now be formulated through the utilisation of an increasing number of lipid-based systems such as self micro-emulsifying drug delivery systems (SMEDDS) where a range of excipients with different hydrophobic lipophilic balance (HLB) values can be screened and subsequently optimised to maximise solubility.

Lipid-based formulations range from simple oily solutions to complex mixtures of oils, surfactants, co-surfactants and co-solvents, classi-

fied as lipid self-emulsifying (SEDDS) or SMEDDS. Due to their ability to maintain the active molecule dissolved and/or to prevent precipitation *in vivo*, self-dispersing lipid formulations are of high pharmaceutical interest for improving the biopharmaceutical properties of active molecules.

An additional and important testing programme involves the performance of the drug product in bio-relevant *in vitro* tests which are now increasingly able to predict the *in vivo* behaviour and fate of the drug product more accurately. Within Tillotts Services, we have established state-of-the-art instruments and equipment for both development projects and up to large-scale industrial manufacturing.

Excipient choice and formulation approach is also critical in terms of controlling polymorphism where subtle solvent changes can cause polymorphic transformation and thereby present substantial difficulties in process control and compliance, again undertaking the appropriate solid state API screens are important.

A good understanding of these and other physico-chemical properties (see Figure 2, left column) place the formulator in a strong position with respect to developing a liquid-fill capsule dosage form for further optimisation. In some cases a formulation will consist of two or more excipients and compatibility experiments will be undertaken in order to support the provision of regulatory data.

Following excipient selection, phase diagrams will be used to demonstrate the effectiveness of the chosen formulation. Liquid-fill encapsulation is also applicable to high melting point excipients such as beeswax and polyethylene glycols since capsules can be filled up to 75°C (Figure 1).

FAST INTO MAN APPLICATIONS

Given the above benefits, liquid-fill encapsulation using two-piece, hard-shell capsules is now being more widely utilised within clinical development where drug product can be quickly produced in small batches and validated for first in man studies. Within Tillotts, we have over 26 years' experience in the development of gastro-intestinal (GI) therapies and can modify the capsule coating for delivery to specific areas of the GI tract as well as modify the formulation for a tailored release profile. Such optimised and tailored targeting and release profiles can be easily optimised during early development in order to identify the optimal drug product characteristics.

Figure 4: One of two Tillotts Services Bosch GKF 1500 and Shionogi S100 production lines.

SCALE-UP ADVANTAGES

Liquid-fill encapsulation is also amenable to expedient scale-up once key process parameters are defined during the development phase. Within Tillotts Services, we have successfully scaled-up from laboratory scale to commercial scale within one day and achieved un-optimised filling speeds of 30,000 capsules/hour. Further optimisation of the production process can quickly achieve the maximum filling speed of 50,000 capsules/hour using our one of our two Bosch GKF 1500 commercial liquid-filling machines (Figure 4) that is configured in a linear fashion with a Shionogi S100 banding and drying machine.

The key parameter for liquid-fill encapsulation is the formulation viscosity and for it is important to define and fix the range of this parameter very early in the development process. Viscosity is also monitored at key stages prior to capsule filling through in-process controls (IPCs). Hygroscopic and sensitive APIs can also be handled within production and an increasing number of biological, probiotic and sensitive materials are being produced using this technology.

COLPERMIN® CASE STUDY

Twenty six years ago, Colpermin®, a pioneering liquid-fill product was launched by Tillotts Pharma AG as a health-food supplement and is now sold throughout most of Europe as an OTC therapy for Irritable Bowel Syndrome (IBS). Colpermin® consists of 0.2 ml of Peppermint Oil (PO) formulated as a semi-solid oleo gel and contained within an enteric coated, two-piece, hard-shell gelatine capsule. The formulation and manufacturing process for Colpermin® was developed by Tillotts Services and we currently produce the finished and packaged product exclusively within our state-of-the-art liquid-fill encapsulation facility in Ziefen, near Basel, Switzerland.

The GI clinical pharmacology of PO has been reviewed in an article by Grigoleit et al who have qualified its benefits in treating the severe symptoms of IBS.[2] Their conclusion confirmed the adverse effects of PO, such as heartburn, which occur if it is released in the upper GI tract. They further conclude the importance of a sustained-release PO formulation, as used in Colpermin®, having an optimal peak release at about four hours after ingestion with a release time of PO of up to 24 hours.

Peppermint oil (*Menthae piperitae aetheroleum*) is obtained from the fresh leaves of peppermint, *Mentha piperita L*, by steam distillation. The plant, indigenous to Europe, is now widespread in cultivation throughout all regions of the world. The major constituents of the oil

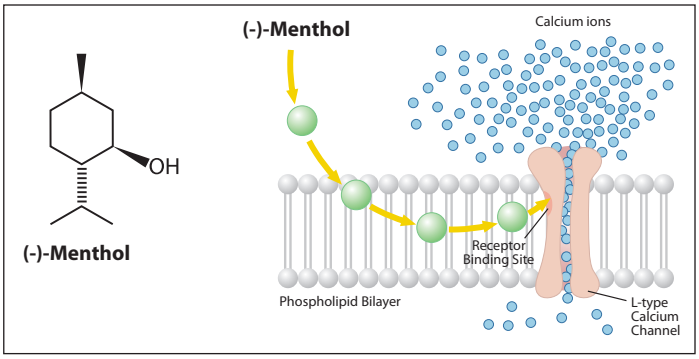

Figure 5: Mechanism of action for (-)-menthol.

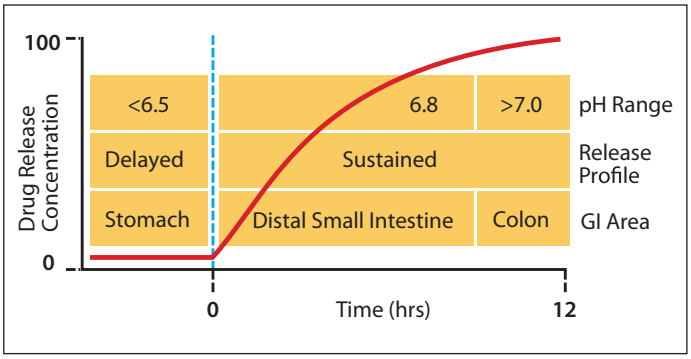

Figure 6: Pharmacokinetic profile for Colpermin® capsules.

include the terpenes (-)-menthol (30-55%), (-)-menthone (14-32%), (+)-isomenthone (1.5-10%), (-)-menthyl acetate (2.8-10%), (+)-menthofuran (1.0-9.0%), 1,8-cineole (3.5-14%) and limonene (1-3.5%).

Hawthorn *et al* have attributed the calcium antagonistic properties of (-)-menthol to the anti-spasmodic effects of PO (Figure 5).[3] However it is likely that the additional terpene components of PO also positively contribute to, or enhance its clinical effects in treating IBS.

The pharmacokinetics of Colpermin® have been optimised to provide a sustained release of PO over 12 hours along the distal small intestine and colon (Figure 6). The enteric coating of the capsule enables survival in the acid environment of the stomach. However on reaching a pH of 6.8 the coating begins to disintegrate along with the capsule shell to release the oleo gel formulation containing PO. The sustained-release profile provides active over 12 hours within the region of the distal small intestine and colon.

COLPERMIN® MANUFACTURING PROCESS

Tillotts have manufactured Colpermin® capsules for over 26 years and is a pioneer in the development and commercialisation of this technology. Tillotts Services' SwissMedic- approved GMP facility is dedicated to liquid-fill development and manufacturing such that all the necessary development, analytical and production equipment is housed under one roof along with a highly experienced team of scientists, project managers, engineers and production staff. During the next year we plan to begin production of products for the US market and expect to be the subject of a US FDA inspection in the near future.

A. Preparation of the filling mixture

The first step is mixing Arachis oil and Beeswax from a mixing vessel and PO from a second vessel, colloidal silica is also added during the mixing and blending process. The viscosity of the homogenised mixture is tested and is a key IPC (Figure 7, Stages 1-4).

B. Filling Process

A precise quantity of the blended formulation mixture is injected into one half of an empty, two-piece, hard-shell capsule of size 0. The filling nozzles can be temperature adjusted and the diameter modified according to specific needs, this enables filling of high viscosity mixtures to be used which is a key benefit over soft gel technology (see Figure 1). After the filling, the capsule is closed and forwarded to a conveyor belt for cooling and transfer to the banding station (Figure 7, Stages 5 & 6).

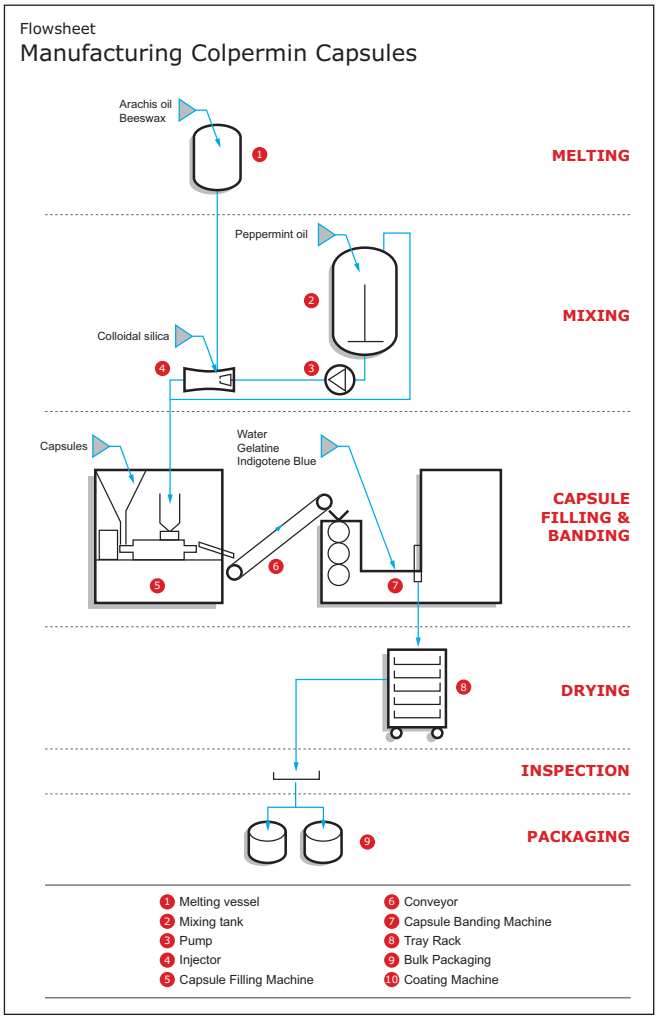

Figure 7: Colpermin® manufacturing process.

C. Banding and Drying Process

Rectification rollers rotate the capsules into the correct orientation and transfer them onto a stainless steel belt with embedding for size 0 capsules; formats are also available for other capsule sizes. Gelatine is applied by using two spinning discs that are in contact with a gelatine bath, and then the capsules are fed into the drying chamber and placed afterwards onto drying trays. It is also possible to modify the drying chamber to decrease the drying time if this is required. The last step of the process is the visual inspection of the capsules for any defects or leaks (Figure 7, Stages 7-9).

D. Coating Process

A proprietary coating mixture is evenly applied using a pan coater which provides a gastro-resistant barrier. The enteric coat is resistant to low pH and only starts to dissolve around pH 6.8 (Figure 6). For confidentiality reasons, we are unable to disclose the exact nature of the coating mixture. Tillotts Services' capabilities include the development of new coatings for our customers who may require targeted delivery to the lower digestive tract or colon (Figure 8).

This step is followed by a final drying stage and the capsules are sent for blistering and final packaging (Figure 9).

COLPERMIN® CAPSULE FEATURES

- Each Colpermin® capsule contains 187 mg (0.2 ml) of peppermint oil.
- Oleo-gel formulation – ensures sustained delivery (>12 hrs).

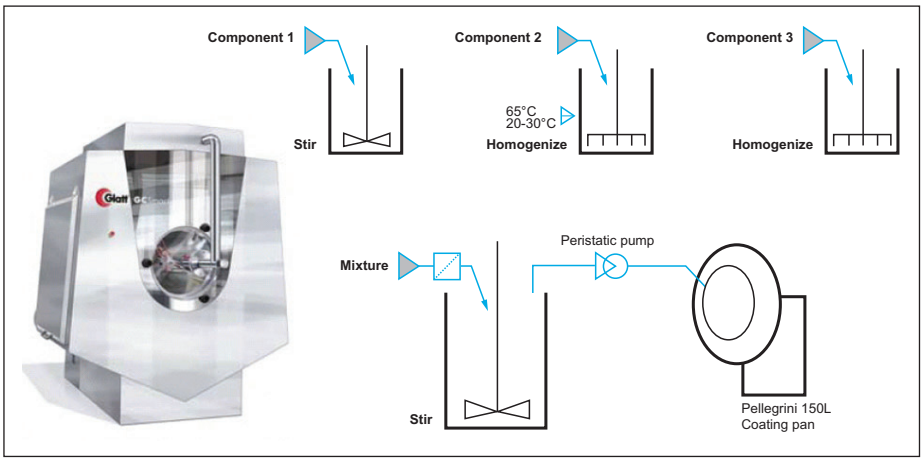

Figure 8: Colpermin® Coating Process.

Figure 9. The inspection, blistering and packaging of Colpermin®.

- Gastro-resistant, hard-shell capsule – avoids release in the stomach.
- Optimal delivery profile for prolonged & effective relief of symptoms.
- Global liquid-fill GMP manufacturing production process.

CONCLUSIONS

Liquid-fill encapsulation using two-piece hard-shell capsules has matured considerably during the last decade as witnessed by the increasing number of commercial products and development stage projects that utilise this technology. The primary drivers have been a decrease in the cost of capsules, innovation in their design and performance together with the introduction of new excipients and coating technologies.

A continued increase in the number of poorly water soluble drugs, probiotics and biological molecules within drug development pipelines means that this technology will have an increasing number of applications.

ACKNOWLEDGEMENT

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ONdrugDelivery EDITORIAL CALENDAR

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October 2012	Prefilled Syringes	September 3rd
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May 2013	Injectable Drug Delivery 2013: Formulations Focus	April 2nd
June 2013	Injectable Drug Delivery 2013: Devices Focus	May 6th

Balda MEDICAL

takes care

SMART TABLET DISPENSERS FOR DYNAMIC TREATMENT & PATIENT COMPLIANCE

Here, Rolf Eilers, PhD, Managing Director, Balda Medical, outlines the rationale for different oral tablet dispensing device designs, including electronic devices, and provides two case studies.

Oral medicines represent the most common dosage form for pharmaceutical products for a variety of reasons and as such, processing, storage and application are to a large extent standardised. The packaging of many oral medicines is also widely standardised.

Packaging can be divided into primary and secondary packaging. Primary packaging material for medicinal products is for the storage of the medicine and provides adequate protection from external influences such as, for example, light, humidity, temperature and mechanical stress. It guarantees the stability of the product and its effectiveness under changing conditions during transport, storage and if necessary also during application.

Primary packaging can exhibit further auxiliary functions like a child-proofed closure or an originality closure. Primary packaging usually consists of relatively simple and, to a large extent, standardised packing such as blisters, cans or bottles.

Secondary packing serves to protect and facilitate transportability of the primary packaging material, and functions predominantly as a storage medium. In the case of oral medicines the secondary packaging consists very frequently of a simple folding box with enclosed patient information leaflet lying inside.

The effectiveness of a medicine depends not only on the nature of the active pharmaceutical substance, but also on its correct and timely dosage and delivery. The relatively simple standard packaging common for oral medicines traditionally plays only a very minor role in supporting the patient in terms of compliance. In 2003, the WHO estimated that only half of the patients adhere to the instructions from their doctor, pharmacist and the patient information leaflet enclosed with the pharmaceutical product, and therefore potentially half of all medicines are not achieving their full effect.

Thus, intelligent drug packaging and drug delivery systems, which provide significant added value through additional functions for the patient in terms of medical compliance, have a role to play in improving this situation. Drug delivery devices can allow for safe dispensing of an accurate dose. Integrated counting and alarm functions support the patient in medical compliance.

In addition to the growing need for intelligent packaging for promoting compliance, increasingly applications arise which require a variable or dynamic intake pattern. In the field of paediatrics, for example, physicians often have to use medicines which were originally conceived for use in adults. For babies and infants such medicines are unsuitable due to the active substance content and physical dimension. Tools for mechanically splitting tablets are available. However, their application is connected with difficulties (source: *World Pharmaceutical Frontiers*, Vol.1, 2011).

The dosing of liquid medicines for babies and infants is no less critical. In January 2007, the EU issued a special regulation on paediatric medicines, EC No. 1901/2006. New drugs may only be applied to the market, if the applicability has been successfully proven in children.

Other therapies, analgesics or psychotropic drugs for example, require an individual and dynamic intake regimen in order to adapt the dose to the symptoms.

The solid oral dosage form – a tablet or a melt-film for example – offers fundamental advantages compared with liquid formulations (syrups, drops, suspensions and emulsions), since they are easier to handle and safer. Liquid medicines have the added disadvantage of a limited shelf-life once the bottle is open. Hygiene risks and inaccurate dosages also give rise to problems. These difficulties become particularly apparent with drug delivery systems which are intended for repetitive use.

From the perspectives production, pharmacology and application, the suitability of the tablet as the preferred dosage form is clear. A strong argument with regard to the technical requirements is that tablets can be manufactured inexpensively in mass quantities. Likewise they are good to pack and transport. From a pharmaceutical point of view the tablet ensures a high stability of the active substance, and a reliable dose is provided to patients via a convenient delivery route.

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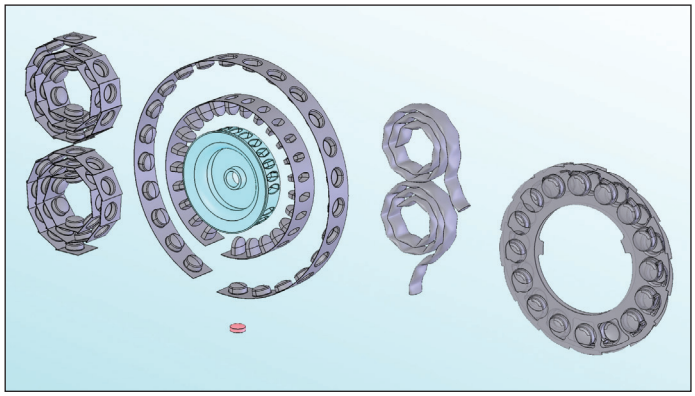


Figure 1: Size comparison of different individual protected film tablets (24 pieces rolled up).

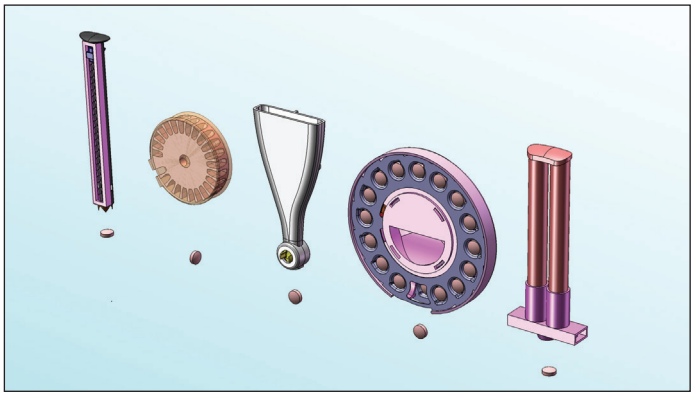


Figure 2: Stacking of the tablets (left) and comparison of different tablet orders for exact separation (as basis for cartridges).

Balda Medical has therefore developed several devices which dispense tablets and also melt-films in a safe and patient-friendly manner. In the context of a first concept design, the main functions of the device were defined and in each case different solutions were identified.

Storage of the tablets in a manner which allows them to be ejected (either individually or in multiples) was identified as one primary function. In one approach, storage is in a roll blister (see Figure 1). Here, each individual tablet is protected against environmental influences right until the point of use. Conventional blister designs can be used, for which filling and processing is standard, so that existing filling lines can be used. However, a major disadvantage of the roll blisters is their large volume, potentially meaning that a large and unmanageable device is required.

Another approach was tablet stacking, design examples of which are shown in Figure 2. The advantage of this solution is the small volume. Enclosing the tablet pile in a blister ensures the tablets are protected against possible environmental influences at least up to the use of the first tablet. Thereafter, the drug delivery device must take over the role of protecting the tablets. The disadvantage is that the tablets cannot be filled with standard filling machines.

Another primary function was dispensing the correct dosage. A dose can be prepared in principle by accumulation or separation of dosage units. Examples of different ways in which different dosage forms might be separated or accumulated are outlined in Figure 3.

In the case of the tablets, separation requires manual separating of tablets into the number of whole tablets required, and/or dividing tablets if fractions of one tablet are required. Also required are appropriate levels of dexterity, visual acuity and an intellectual competence, in order to understand and count out the dose.

The division of a tablet can be supported by break notches in the tablet structure and by pill-splitting devices. However, it remains a difficult and unreliable manual process, which only allows the tablet to be halved or at most quarterd, and always destroys the tablet's protective coating, potentially impairing active substance delivery and leaving the remaining fragments exposed without protection from the environment. Thus, from the perspective of medical compliance and device-related implementation, pill splitting should ideally be avoided.

The logical alternative to dividing large tablets into fractions is to use smaller dosage units as the starting point. These so-called microtablets allow finer adjustment of the required dosage for different age and weight classes, a feature which would be welcome, according to a market study conducted by Balda Medical. Microtablets, being smaller, have the added advantage that they are easier to swallow.

For both separation and accumulation of dosage units into the required dose, the use of a drug delivery/dispensing device ensures the correct specific dosage and safe withdrawal of the drug.

In addition to the basic requirements of a tablet dispenser, additional product requirements and regulatory standards can be implemented and customised.

Basic requirements:

- Storage of the tablets - protection from environmental influences
- Device must not interact with the tablet
- No mechanical damage to the tablets
- Dosing accuracy (regulatory requirement; European Pharmacopoeia 5,0 point 4.00/2.09.27.00 "*Uniformity of mass of delivered doses from multidose containers*")

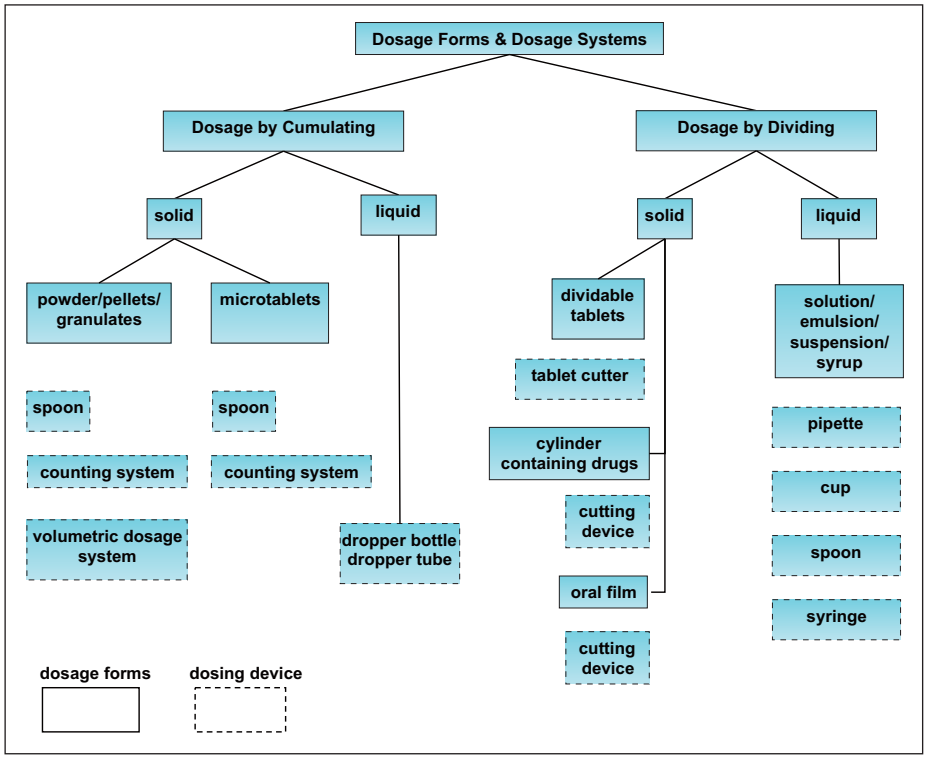


Figure 3: Classification of oral dosage forms and dosage possibilities for individual therapy (*Thesis Klaus Wening, "Entwicklung eines Dosiersystems für die Individuelle Therapie mit Neuen Festen Arzneiträgern", 2011*).

Figure 4: The Clyk™ dispenser.

- Reliability (with various tablet types)
- Usability, child safety catch, suitability for seniors
- Provision of an instruction manual (regulatory)

Additional requirements:

- Variable dosage (usually up to 15 tablets, in individual cases up to 90 tablets)
- Alarm and reminder functions
- Data logger functions (e.g. for use in clinical studies)

Regulatory requirements:

- GMP
- MDD 93/42/EWG (Medical Device Directive)
- DIN EN ISO 13485 (medical devices, quality management systems)
- DIN EN 60601-1-11 (medical electrical equipment, Part 1-11: "General requirements for basic safety and essential performance", collateral standard: "Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment"
- (EC) No. 1901/2006 – "Medicinal products for paediatric use"; EU PIP (Paediatric Investigation Plan)
- FDA 21 CFR 820.30 – "Design Control Guidance for Medical Device Manufacturers."

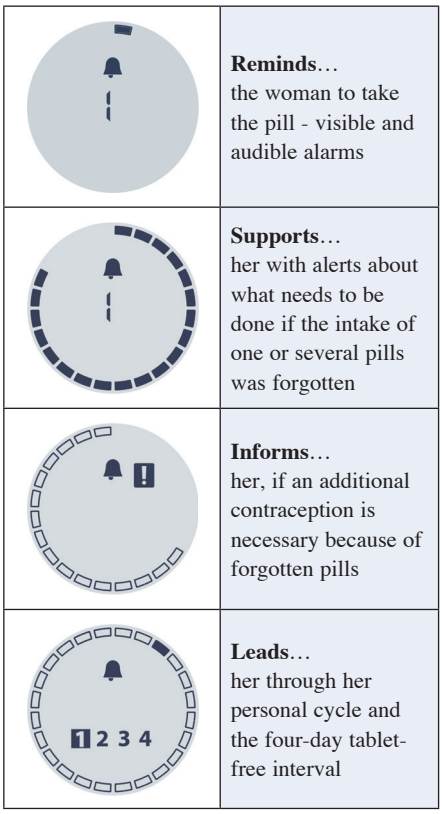
Within the additional requirements listed above, the alarm and data logging functions necessitate an electronic/digital device. Monitoring and managing compliance using digitised solutions is gaining increasing acceptance in the market (e.g. Sensidose). With the use of electronic devices the patient receives direct feedback and the regimen of the tablets can be adapted accordingly. The functional reliability can be examined in usability tests and clinical studies and the increase in value concerning security and also user acceptance can be guaranteed.

Balda Medical has recently become increasingly engaged in the development, industrialisation and approval of drug delivery systems for solid medications following numerous requests from the market for such devices. The basic requirements of the projects were frequently alike. However, they have differed with respect to the form and size of the tablet, the complexity of the dosage, and specifications of additional functions such as electronics. From our project portfolio, two representative projects are described here in more detail.

CASE STUDY 1: CLYK™ - INTELLIGENT, INNOVATIVE, USEFUL

Only approximately 50% of the women taking oral contraceptives adhere to the dosing regimen, and the remaining users forget to take it several times per month. An intelligent tablet dispenser for an oral contraceptive with a matching cartridge for up to 30 tablets was thererore developed. The aim was to create packaging for the tablet which should be delivered with the help of a mechanical drug dispenser.

The tablet dispenser is a medical device of the class Im in accordance with MDD 93/42/EWG. The medical device is appropriate for multiple uses, whereby the emptied cartridges must be replaced regularly with new prefilled cartridges. The tablets are in an already presorted condition and thus do not have to be sorted by the system, in order to be able to be dispensed suitably.



Reminds… the woman to take the pill - visible and audible alarms

Supports… her with alerts about what needs to be done if the intake of one or several pills was forgotten

Informs… her, if an additional contraception is necessary because of forgotten pills

Leads… her through her personal cycle and the four-day tablet-free interval

Figure 5: Functions of the Clyk™ dispenser for the female contraceptive pill.

The Clyk™ dispenser (shown in Figure 4) is a refillable electronic tablet dispenser with an LCD display. It is designed to be used for two years. The dispenser was specifically designed to help women comply with a new oral contraceptive within a unique flexible extended intake regimen, to provide a woman with reliable contraception and the option to plan her period personally.

The intuitive and user-friendly dispenser is discrete, visually appealing and can be used globally due to its use of symbols. The dispenser not only provides a daily reminder through its visual and audible alarm, but it also guides the woman if pills are missed and advises her if back-up contraception is needed. The dispenser guides the woman through her cycle and the four-day tablet free interval.

The tablet dispenser supervises the pill intake, by storing the exact time of the last dispense. Thus the equipment "knows" always, whether the woman is still in her rhythm as shown in Figure 5.

The tablet dispenser which is currently in market launch, was, next to the classic requirements for primary packaging, also developed taking into account the Medical Product Act (MPG/MDD), DIN EN ISO 13485, and the "Design Control Guidance for Medical Device Manufacturer" (FDA 21 CFR 820.30), which has become an important issue for the development of pharmaceuticals (ICH Q8, Q9 and Q10).

Also the DIN EN 60601-1-11 "Medical electrical equipment, Part 1-11: General requirement for basic safety and essential performance. Collateral standard: Requirements for medical electrical equipment and medical electrical system used into the home healthcare environment", was considered in the development of the tablet dispenser. Medical-electrical devices (ME devices) and their accompanying documents such as the operating instruction must be examined according to the standard. The usability of the operating instruction, the hygiene requirements as well as the electrical interference with other devices and the safety of the user are very important issues.

Not only safety, but also the applicability and efficiency were key to the development. With the help of user studies the usability of the tablet dispenser was proven and Balda Medical has already received its EU CE certification.

CASE STUDY 2: MICROTABLET DISPENSER

The EU's PIP regulation (EC No. 1901/2006) requires that during new approvals of medicines for children that their usability is proven. This

Figure 6: The phenomenon of arching which blocks the device's exit channel.

Figure 7: Microtablet dispenser.

also includes the user-friendly and safe dosing of the medicine.

A device which can adjust the dose by dispensing the appropriate quantity of tablets is effective for use in the paediatric population which comprises patients of differing and changing body sizes and variable disease courses.

The starting point for this project was that the medicine would be presented in microtablets with a diameter of 2 mm, which were conventionally pressed. Furthermore the microtablets should be easy to dose in a wide range. In a market study, a requirement for up to 15 tablets per administration was determined, in individual cases even far beyond that.

Another condition was that standard packaging should be used for storage of the microtablets. Standard packaging materials can be used as an integrated component (disposable) of the tablet dispenser or as replaceable unit. Advantages here are the proven storage protection, as well as the use of the existing filling lines.

Depending on the mechanical exposure, microtablets with a diameter of about 2 mm can be quite challenging in terms of tolerances, friction, breaking, splitting, powdery abrasion and their weight relative to electrostatic forces. These characteristics can change during storage and exposure to moisture, and can lead to blocking phenomena (bridges) within a container.

A reliable separation of the single dose from a total volume, at the same being a gentle process for the tablets, was essential. The separation and handling are made more difficult by the problem of "arching", where the tablets form an arch across the exit channel, which blocks it (see Figure 6). This phenomenon can lead to substantial malfunctioning.

One design iteration used integrated electronics, which provide the means to supply and count the tablets. Inside the device is a rotating dosing disc with cavities. Tablets fall unsystematically into the individual cavities, since the cavities are slightly larger than the tablets. Under a partial area of the dosing disk is an outlet channel, through which the tablets can fall out.

So that tablets cannot escape uncontrolled, a stripper brush is attached above this area on the dosing disk. So tablets can only be dispensed by a rotation of the disk. Since it cannot be guaranteed that each cavity contains a tablet, a photocell counts the tablets in the outlet channel.

A second product execution is solved purely mechanically (Figure 7). After adjustment of the mechanism to the desired number of tablets, the tablet fall from a special piling device into the predetermined number of cavities. The final operation of a key leads to the automatic ejection of the desired number of tablets. The mechanical solution is limited to dispensing a maximum of 16 single tablets, but clearly simpler and cheaper than the electronic variant.

With the two product executions, function tests were accomplished. For the mechanical device, dosing accuracy (a dosage corresponds to 16 tablets) and user dependence were examined. During slower operation and assumed user operation there were good results. In each case 16 tablets were dispensed. During very rapid operation, which does not reflect typical use, hooking and wedging occurred. Here an average of only 14 tablets was dispensed because the tablets did not have the time to fall into a cavity. The system was modified by inclusion of a damping element, so that operation at a rapid rate that impacts on dosing accuracy is no longer possible.

With the electronic device, doses of between one and 99 tablets were entered and these were dispensed accurately in every case.

Both product executions represent a platform technology for dosing microtablets, on whose basis further user-specific solutions can be generated. In both cases the proof of a safe and exact dosage could be confirmed.

TREND-SETTING DELIVERY SYSTEMS

The advent of personalised medicines and more efficient treatment regimens are substantial drivers for intelligent oral drug delivery and dispensing devices. They improve medical compliance and guarantee a patient-specific, dynamic dosage.

Monitoring of the intake of medicines with the help of Bluetooth is inevitable in the future in an increasingly mobile world. Data can be sent from the delivery device to mobile telephones, PDAs or laptops. Thus, remote supervision and an optimal therapy routine could be guaranteed, in order to increase the medical compliance further.

An intelligent drug delivery system, good usability and economic considerations are all decisive factors during the development and the implementation of a therapeutic product. The success of a product depends not only on the implementation and the costs, but finally on the acceptance of the end user – the patient.

Clyk™ is a trademark of Bayer AG.

ABOUT BALDA MEDICAL

Balda Medical GmbH & Co KG was founded in 2002 by the Balda Group, and is focused on the development, industrialisation and the production of complex systems made of plastic – a leading OEM partner in healthcare.

The systematically structured development process as well as the manufacturing-oriented product development and the comprehensive expertise in the production sector are essential prerequisites in the fields pharmaceutics, diagnostic and medical devices. Particularly within the field pharmaceutics Balda manufactures customised solutions in the context of the packaging and drug delivery devices. Balda develops and produces innovative systems with consideration of the market requirement and appropriate regulatory requirements, which deliver the medicines in defined doses to the patients and thus improve the effectiveness and reliability of the medicine.

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Honeywell

BLISTER PACKAGING OF ORAL SOLIDS – CHALLENGES FOR THE PHARMA INDUSTRY AND PATIENT IMPLICATIONS

In this paper, Thomas Dries, PhD, Market Development Manager Europe, Healthcare & Packaging, Honeywell Specialty Materials, considers the challenges facing the pharmaceutical industry in implementing a blister packaging strategy that: protects advanced solid oral drug delivery systems from physical or chemical degradation; creates market advantage through product globalisation; and enhances the effectiveness of therapy for patients. Dr Dries looks at how companies are leveraging production and marketing value through ultra high barrier films within thermoform solutions. High barrier blister packaging technology offers opportunities for process rationalisation. This technology also provides a pathway to market oral solid drug therapies that are more effective, and the ability to package emerging solid dosage forms that are moisture, oxygen and/or even light sensitive.

INTRODUCTION

Over the past 40 years, blister packs have been adopted globally by the pharmaceutical industry because of the flexibility in design and high productivity that the process delivers for the packaging of oral solids.

The inherent unit-dose concept provides visual and haptical evidence of the number of doses taken, making it easy for patients to follow their therapy by swallowing an oral dosage. It is a comfortable and a familiar means of taking medication – and is one of the main reasons why the majority of marketed medicines have been presented as tablets and capsules over many decades.

Looking at companies' drug development pipelines, it can be noted that the absolute number and the percentage of oral solids in those pipelines versus other dosage forms is declining. At the same time, the number of oral solid drugs requiring high to ultra-high barrier protection to maintain stability and achieve shelf life targets is growing substantially. Today it is harder than ever before to develop a solid oral formulation that can be marketed in blister packs without having a sufficiently high level of barrier protection.

"PRIMARY PACKAGING CHOICES AND PACK DESIGN HAVE SIGNIFICANT IMPLICATIONS ON PHARMACEUTICAL STAKEHOLDERS AND PATIENTS, AND SUPPLEMENT EFFORTS IN DRUG FORMULATION"

As demonstrated here, primary packaging choices and pack design have significant implications on pharmaceutical stakeholders and patients, and supplement efforts in drug formulation.

TRENDS IN ORAL DELIVERY

More sophisticated drug formulation technology

For drug substances to work they need to be absorbed within the body, otherwise they pass through the gastro-intestinal tract and are excreted without causing any pharmacological effect. For the growing number of poorly soluble drug substances it is a challenge to arrive at a viable formulation. Reducing drug particle size down to submicron level is the first and most critical step to enhancing dissolution rate.

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Efforts to enhance solubility include changing the physical form by either adopting a less stable polymorph or the amorphous phase of a given API.

Most often, the drug-release profile is controlled with the aid of hydrophilic polymers. For example, third-generation solid dispersions consist of finely dispersed drug particles that are embedded in polymeric carriers aided by surfactants. Obviously, from a packaging perspective, without moisture barrier protection the hydrophilic polymers may absorb water during storage and become prematurely plasticised. This affects the physical stability and, in turn, the performance of the entire formulation.

With the decrease of drug particle size, the affective surface of all drug particles in the dosage is greatly enhanced. Therefore, if the drug molecule exhibits a moisture- or oxygen-sensitive chemical group the likelihood for chemical degradation is increased. As a result, both pharma and drug delivery companies are increasingly looking to blister packaging made from high or ultra-high barrier films because they enable a consistent performance of the drug product and maintain product integrity during the targeted shelf-life.

Growing Number of LCM projects

Numerous lifecycle-management (LCM) projects focus on reducing the frequency of drug administration with an anticipated gain in patient compliance and improved treatment outcomes. Modified-release (MR) formulations such as controlled release (CR) or extended release (ER), fixed-dose combinations (FDCs) and oral dispersible tablets (ODTs) are the most prominent categories. It is observed that nearly every drug product launched in these LCM categories was in blister packs made from some level of high or ultra-high moisture barrier films.

Bigger Dosages Sizes Resulting in Bigger Packs

Tailoring the drug-release profile quite often results in bigger dosage sizes due to the elevated amounts of high-performance excipients and API required for a viable formulation. The same holds for any efforts to enhance drug dissolution rate by creating sub-micron drug particles, as this involves a greater increase in the overall drug surface requiring higher amounts of excipients to be matched. Similar arguments apply for FDCs and low potency APIs. Dosages are getting significantly bigger pack sizes, too. It is well known that most people with a chronic condition prefer small packs as they enable discretion, portability and convenience. Ironically, packs that are too bulky may even compromise patient compliance efforts in drug delivery.

"NEARLY EVERY DRUG PRODUCT LAUNCHED IN THESE LCM CATEGORIES WAS IN BLISTER PACKS MADE FROM SOME LEVEL OF HIGH OR ULTRA-HIGH MOISTURE BARRIER FILMS"

Beyond Moisture Sensitivities

Quite a few formulations consist of APIs that are not only moisture sensitive but also exhibit sensitivities to oxygen and/or light. Drug products containing vitamins are often found in blister packages made with multi-layer films that provide either a combination of moisture and oxygen barrier or even moisture, oxygen, and light barrier.

BLISTER PACKAGING CRITERIA – THE INDUSTRY DRIVERS

Globalisation

A growing number of drug products are now marketed globally. In many cases the barrier protection of primary packaging used in moderate climatic zones is not sufficient in the hot and dry or hot and humid regions. Consequently, high and ultra-high moisture barrier films such as Aclar® films are growing in adoption and are outperforming the mid and low barrier categories in terms of number of oral solids launches.

Complexity Reduction

Establishing a limited number of agreed "first intent" primary packaging standards has become common practice within many pharmaceutical companies. Key selection criteria for primary packaging materials include the capability to offer stability in all climatic zones and to meet the needs of both marketing and packaging operations stakeholders. Additionally, there are ongoing efforts to reduce complexity by limiting the number of agreed variants down to a select few in order to drive both a reduction in cycle time and in the analytical costs inherent in parallel stability testing. The downstream benefits for packaging operations are gains in operational equipment efficiency (OEE) via faster changeovers, easier site transfer projects, and overall economies of scale.

Reduction of Cost of Goods

Moreover, the productivity targets for packaging operations are getting more ambitious year by year. Increasing output with existing manufacturing facilities or meeting production budgets with lower capital expenditure are key drivers. As a result, packaging processes and equipment are selected with regards to achieving significant reductions of cost of goods (CoGs).

Gains in Pack Sustainability

A growing number of pharmaceuticals companies have defined a sustainability strategy that achieves demonstrable reductions of consumed energy and waste, particularly with regard to packaging. This results in a concerted effort to introduce smaller and slimmer packs.

Prevention of Medication Errors

Many oral solid brands are available in more than one tablet or capsule strength. Proper colour coding of the outer carton and /or potential colour differences in the dosage itself combined with clear blister packaging films has proven to be helpful in the effort to prevent medication errors.

Child Resistance

Designing packages that are difficult for a child to open while also being easy for the user to open, in particular the elderly, remains a challenge. Although there are now numerous blister packaging solutions available that are both child resistant (US 16 CFR 1700-F=1 standard) and "senior-friendly", companies continue to dedicate time and effort to creating a package that meets all requirements.

BLISTER PACKAGING CRITERIA – THE PATIENT BENEFITS

A high percentage of prescribed drug therapies do not achieve optimum outcomes for simple reasons like patient forgetfulness. To compensate, pharmaceutical companies are looking to maximise the benefits of oral therapies to better match users' lifestyles.

In addition, there is a high likelihood that a patient who experiences packaging-related issues during his/her therapy will not adhere to it and consequently will not enjoy optimum treatment outcomes. This greatly affects longer-term therapies as the physician may not be inclined to refill the prescription, resulting in a lost patient from a brand owner's perspective. In the meantime there is a growing acknowledgement among brand managers of prescription medicines that the pack design itself can add to more successful therapies resulting in better treatment outcomes and higher revenues. A highly successful and well known example of this is Pfizer's Z-Pak® wallet, which is an antibiotic packaged in a pre-regimented unit-dose format.

HIGH-BARRIER PACKAGING CHOICES

There are various pack presentations available that meet the functional requirement of providing high moisture, oxygen and light barrier protection. This includes amber glass bottles with metal-screw caps; multi-layer HDPE bottles; cold formed foil (CFF) blisters; and blister-packs made from high-barrier thermoforming films.

High-barrier thermoforming and cold forming are the most dominant packaging technologies for moisture-sensitive oral solids outside the US.

CFF will continue to be an option for the stability testing of formulations that are highly sensitive to moisture, oxygen and light.

Aclar® films laminated with PVC as well as PVdC-coated PVC are the most prevalent polymeric films used in thermoformed blister application. Aclar films exhibit the highest moisture barrier at any given thickness of the barrier film layer. If oxygen barrier is needed there are solutions available that include an additional polymer such as EVOH or even PVdC. The high and ultra-high barrier film ranges start at Aclar film thicknesses of 51 micron and PVdC-coating weights of 120g.

The benefits common to all polymer-based thermoforming films are summarised as follows:

- Small blister footprint compared with CFF – even at big tablet and capsule sizes. For very large tablets and capsules, a reduction of blister footprint up to 65% can be achieved – the average is about 55%.
- Gains in user acceptance as they enable patient's discretion, portability and ease of dose extraction.
- Reduction in material use, from forming film to lid-stock and carton board – up to 60%
- Reduction in energy use and carbon footprint – up to 25%
- Gains in productivity on blister packaging lines – up to 200%

"HIGH AND ULTRA-HIGH MOISTURE BARRIER FILMS SUCH AS ACLAR® FILMS ARE GROWING IN ADOPTION AND ARE OUTPERFORMING THE MID AND LOW BARRIER CATEGORIES IN TERMS OF NUMBER OF ORAL SOLIDS LAUNCHES"

CONCLUSION

Value creation in drug delivery has traditionally focused on developing advanced solutions that meet the unmet needs of patients. Achieving better treatment outcomes has an impact on society as a whole: patients and their families live longer together and enjoy a better quality of life; social systems can plan for lower costs for acute care and assisted living; employers benefit from lower absenteeism rates; and physicians can provide better care and support for patients. There are growing efforts of pharmaceutical companies to enhance treatment effectiveness and improve outcomes under real-life conditions of patients – outside of controlled clinical trial settings.

Blister packaging has become a more important piece in this equation than ever before. Thermoforming films are enablers for optimising blister pack designs more holistically, with decisions based on understanding and meeting patient needs, while at the same time offering opportunities for significant productivity gains in packaging operations. The success story of polymer-based films for blister packaging will continue, particularly as a result of the new-generation films that provide global packaging solutions for advanced drug delivery systems.

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A POSSIBLE APPROACH FOR THE DESIRE TO INNOVATE

Here, Hunsik (Brian) Wang, Chief Executive Officer, and Junsang Park, PhD, Chief Scientific Officer, both of GL PharmTech, introduce GLARS, a novel concept extended-release triple-layered tablet delivery technology for delivery to the intestine and colon.

How did you feel when you heard your brand product was easily copied by a generic company after the expiration of its new chemical entity patent? And what about the case when someone from sales & marketing came and complained of setbacks in developing a pre-defined reformulation product?...

For various reasons, with which readers will already be familiar, individuals working in pharmaceutical product development and formulation have been under significant pressure for some time. This pressure may have made possible various kinds of open-innovation by prompting the adoption of technologies or products from outside.

The drug delivery industry has been working as an innovator and excellent partner over the past 30 years, providing technologies that have enabled brand pharmaceutical companies to take new steps. This is surely one reason why the number of reformulated products reached about triple that of new chemical entities (NCEs) in 2009 (75 *versus* 26).[1] As a player in the oral drug delivery field, we at GL PharmTech were pleased to note that oral drug delivery products captured about 10% of the top 200 product sales, which reportedly reached US$14.5 billion.

"HOW DID YOU FEEL WHEN YOU HEARD YOUR BRAND PRODUCT WAS EASILY COPIED BY A GENERIC COMPANY AFTER THE EXPIRATION OF ITS NEW CHEMICAL ENTITY PATENT?"

UNDER PRESSURE FOR REFORMULATION

As product developers using oral drug delivery technology, GL PharmTech is constantly considering what gaps innovators want to fill in their currently marketed products. What should be the factor to drive reformulation?

There are many reasons why currently marketed products could be reformulated. These can originate from aspects of marketing, manufacturing, regulation, generic competition, and even sometimes a purely scientific basis. These various reasons can come alone, together, or complicatedly combined.

Therefore, a single outside technology or reformulated product could not fill all the gaps or cover possible voids the innovator did not feel compelled to address at one time. This might be the driving force for why innovative pharma companies have their departments of development review outside technology as often as possible and compile it in their databases.

Whenever we imagine someone at an innovator company trying to align all the variables to find a fit for their molecules or products with outside drug delivery technologies, the picture gives a strong feeling that a new drug delivery player might be what is required to make every thing click together.

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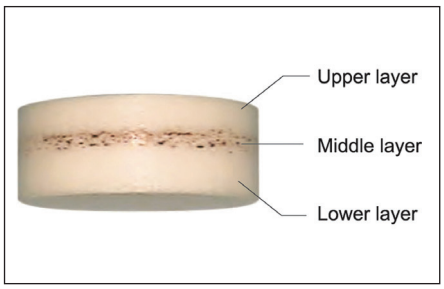


Figure 1: Triple-layered structure of GLARS

NEEDS FOR MEETING A NEW CONCEPT IN ORAL EXTENDED RELEASE

This situation could be particularly true in the field of oral extended-release dosage forms. The first big successes – OROS® from Alza (now Johnson & Johnson, New Brunswick, NJ, US) and Geomatrix® from Skyepharma (London, UK) – had a large impact in the field of oral extended-release drug delivery technology. However, there has not since been a other strong player showing a comparable, remarkable success, and the platform patents of both technologies have expired. In addition, the relatively short gastro-intestinal transit time cannot expectedly or unexpectedly give a new start to blockbuster products, even by applying the already-existing technologies. In other words, the molecule candidates on the market or under development must have a suitable half-life for those technologies to be applied.

Recently, a novel oral extended release technology was presented. Astellas Pharma (Tokyo, Japan; formerly Yamanouchi Pharma) suggested a possible cause for limited absorption in the colon and developed a new dosage form capable of dragging and retaining gastro-intestinal fluid into the dosage form itself, which could, in turn, act as drug-releasing media in the colon.[3, 4]

They found another main reason for malabsorption in the colon to be that there was no additional surrounding fluid present for active substance in dosage form to be released from, and described how this limitation could be overcome to some degree by incorporating highly water-retaining polymers into the dosage form. They named this technology OCAS (Oral Controlled Absorption System).

Up until now, Astellas has applied this technology to at least two products, according to the literature, including tamsulosin, a global leading drug for anti-benign prostatic hyperplasia (BPH), and mirabegron, an anti-incontinence drug. The reformulated tamsulosin product has been on sale in European regions under various local brand names such as Alna OCAS®, Omnic OCAS®, Flomaxtra XL®, Urolosin OCAS® and Praf T®. Mirabegron has been in Phase III clinical trials in various countries.

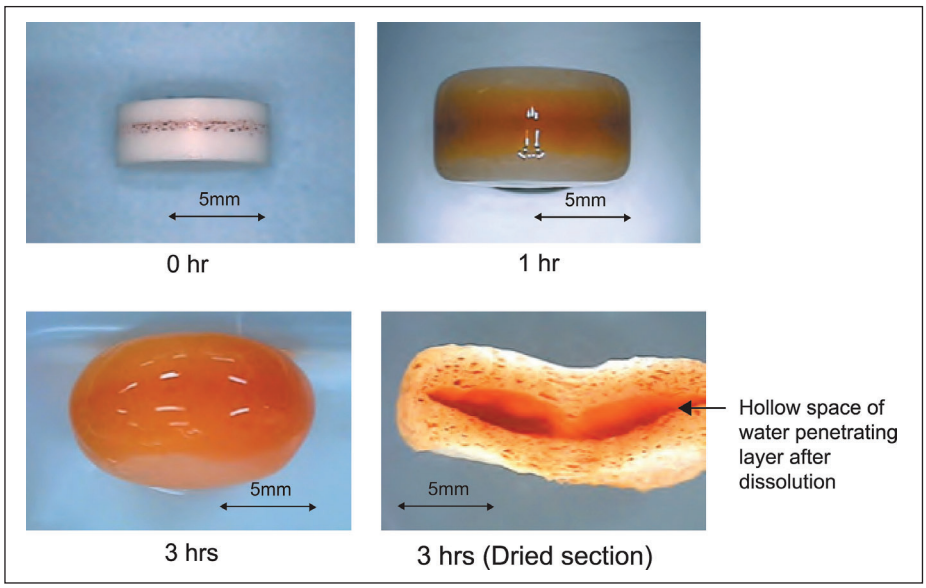


Figure 2: Morphological changes in GLARS upon water contact

The reformulated OCAS tamsulosin product was reported to show not only higher night-time maintenance of plasma concentrations during but also no food effects upon its pharmacokinetic profiles.[5, 6]

GLARS: A NOVEL INTESTINAL AND COLONIC EXTENDEND-RELEASE TECHNOLOGY

The focus of GL PharmTech over the past ten years has been on developing a technology named GLARS (Geometrically Long Absorption Regulated System). The system entraps more gastro-intestinal fluid into the dosage form at early dissolution time to give further extended absorption in the colon.

We have now reached a remarkable milestone. During the course of our work, we fabricated a triple-layered tablet, where the drug and very hydrophilic excipients are incorporated into the middle layer while highly water-retaining and swellable materials are embedded in the upper and lower layers (see Figure 1).

After oral administration, the surrounding GI fluid can penetrate very quickly into the middle layer, thus the upper and lower layers concurrently swell rapidly. These rapidly swollen upper and lower layers enclose the lateral side of the middle layer in quick-time (as shown in Figure 2).

The amount of water drawn into the tablet reaches about 3-5 times the weight of the tablet itself and it can function, in turn, as additional media which enables further later drug release out of the dosage form when it passes into the colon.[7]

The key feature of GLARS is the middle layer, where it horizontally divides the tablet structure. As long as the surrounding water penetrates into the tablet core, it can perform its role to diffuse outward from the core. During the diffusion process the water can also move upwards and downwards, and this additional diffusion, together with the diffusion of GI fluid present outside the tablet, allows the upper and lower layers to be quickly swollen and gelled, at the same time.

As is already recognised in the field, a conventional matrix sustained-release tablet has its own erosion, diffusion, swelling front, and un-swollen intact core. Achieving complete swelling of a tablet without an intact core before considerable erosion during normal gastro-intestinal transit time has appeared to be challenging. From this standpoint the insertion of a highly water-penetrating middle layer into GLARS was a radical approach.

Another feature of this system is rapid enclosing of the tablet's lateral side with the upper and lower layers in a relatively short time. As shown in Figure 3, after closing, drug release is mainly demonstrated through the enclosed lateral side, where the orange colour (from the incorporated colourant) in the middle layer is much thicker than on the other sides.

PROOF OF CONCEPT

Tamsulosin

The first target for determining whether this system could actually operate was the blockbuster molecule, tamsulosin.[8] Marketed under the name Harnal®, as well as Flomax®, this product was originally formulated into enteric-matrix granules in a hard gelatin capsule. In Asia, including Japan and Korea, a normal dose is 0.2 mg, compared with 0.4 mg in the Americas and Europe.

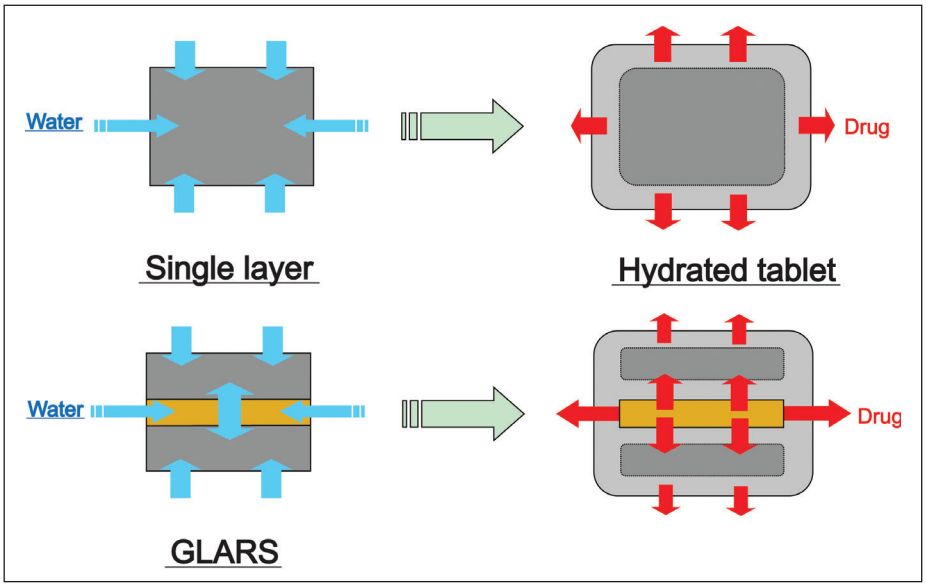


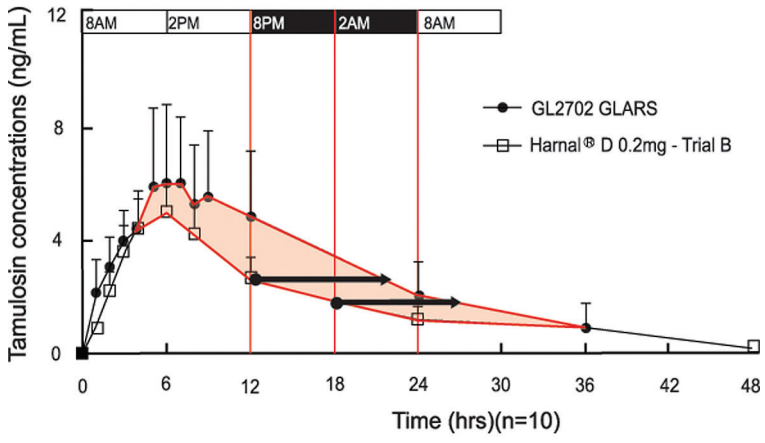
Figure 3: Schematic representation of rapid water penetration through middle layer as well as swelling and enclosing of upper and lower layers

As presented in Figure 4, Tamsulosin GLARS, including a double amount of the API (0.4mg), showed a nearly similar peak concentration to Harnal® containing only 0.2 mg of the API. Nonetheless, the extent of absorption, AUC, was not reduced but, instead, nearly doubled.

When considering normal cases of most types of drug product with dose proportionality – the greater the dose administered, the proportionally higher the pharmacokinetic parameters C_{max} and AUC. However, the GLARS system demonstrated a proportionally higher extent of absorption without a remarkable increase in the rate of absorption. This result suggests that the system can be applied to types of drugs with the very close relationship of peak concentration versus adverse effects, for which extended release dosage forms are desired.

Another finding in the application was that the therapeutic concentration was persistent even during the night. Considering reports that nocturia is a key worry frequently raised by BPH patients, longer duration of action at night could be a very meaningful step for meeting patients' ongoing needs.[9]

The relatively rigid swollen matrix structure of GLARS formulations allows drug release to be unaffected by surrounding mechanical flux, which can provide relatively consistent *in vivo* drug release irrespective of the degree of gastrointestinal motility.



Product	Cmax (ng/mL)	AUCt (hr ng/mL
Harnal® (0.2mg; qd)	5.16±0.97	69.6±22.3
GLPT's GLARS (0.4mg; qd	6.60±2.70	114.34±39.9

Figure 4: Pharmacokinetic profiles of Tamsulosin GLARS, which shows doubled extent of absorption without a dose-proportional increase of peak concentration

Tianeptine

Another proof on concept study was carried out with tianeptine, an anti-depressant, developed and marketed under the name Stablon® by Servier (Neuilly-sur-Seine, France). The purpose of the application was to determine whether the system could reduce the number of daily administrations for better patient compliance.

Figure 5 represents the results of the pharmacokinetic study, where the total amount of the API was the same, 37.5 mg. In terms of the pharmacokinetic parameters, no large difference was shown between Tianeptine GLARS (GX-2903) once daily, and three-times-daily administration of the immediate-release dosage form.

Of course, this should be further evaluated to determine whether this kind of plasma profile is clinically effective and comparable with the performance of existing immediate-release dosage forms.

CREATING EARLY PARTNERSHIPS

Several oral drug delivery technologies have come and gone, and new systems still emerge even today. However, their fates appear to be very similar to those of NCEs. Approximately five years is needed to demonstrate any pharmaceutical or clinical evidence of one technology. In addition, reformulated products must be exclusively marketed for at least ten years.

Then, we, as drug delivery industry workers, have only five years between showing evidence and launching a product into market.

Another aspect to be considered is that there comes a time when additional innovative pharmaceutical applications are needed over the previously much-used simple matrix-type sustained release form. When exclusivity expires, there is the likely tendency of copying by generic companies in a very short time.

Considering both aspects in combination, the marriage of the NCE with the drug delivery system, through a partnership between pharma company and drug delivery company, should be created as early as possible.

Early partnering would represent a great step towards securing more valuable next-generation reformulated products.

Based on the article which appeared in ONdrugDelivery, Issue 25 (2011), pp 10-13.

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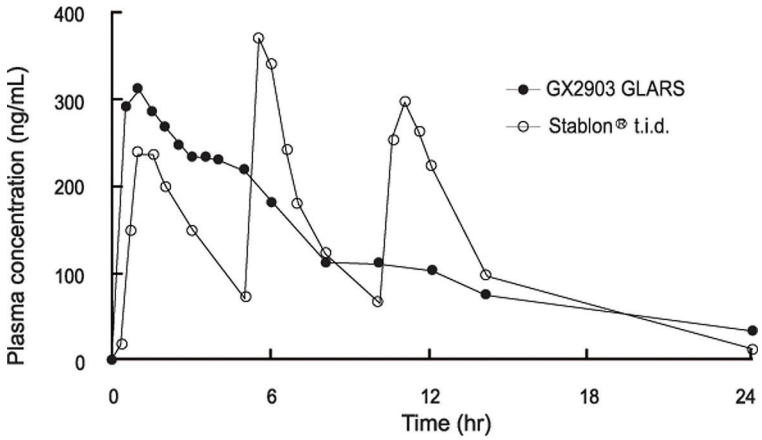

Product	Cmax (ng/mL)	AUCt (hr ng/mL
Stablon® (12.5mg x tid)	335±107.6	2705.3±601.8
GLPT's GLARS (37.5mg qd	359.2±74.2	2849.7±622.9

Figure 5: Pharmacokinetic profiles of Tianeptine GLARS, which shows the possibility of once daily administration

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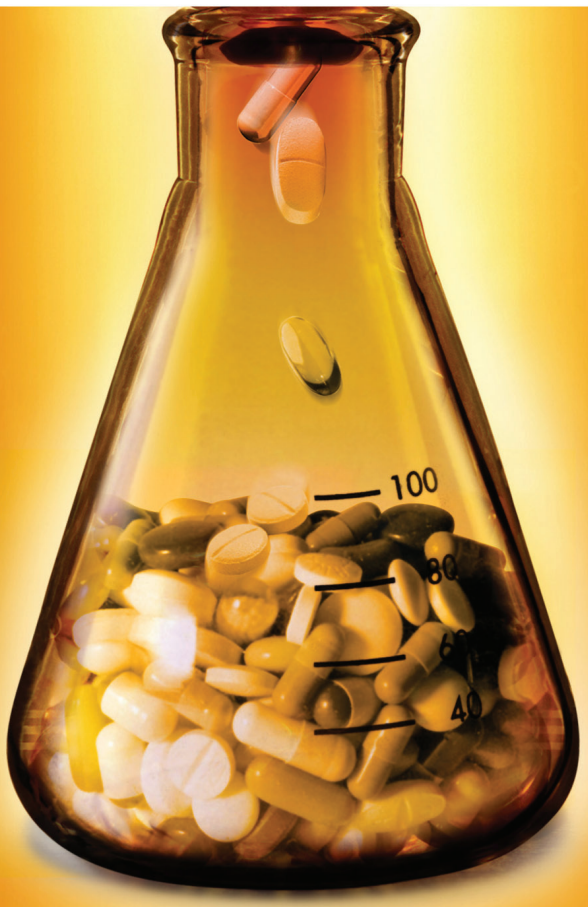

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GL2903	Tianeptin GLARS	Depression
GL2904	Bosentan SR	PAH
GL2907	Oxycodone SR	Pain
GLA2DLT	Tamsulosin 0.2mg + Dutasteride 0.5mg FDC	BPH
GLA3FT	Tamsulosin 0.4mg GLARS + Finasteride 5mg FDC	BPH
GLA5PR	Pregabalin SR	Pain

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