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.

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.

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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 quartered, 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 4.002.09.27.00 “Uniformity of mass of delivered doses from multidose containers”)

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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).

**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).
tion 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 therefore 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 1m 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 pre-sorted condition and thus do not have to be sorted by the system, in order to be able to be dispensed suitably.

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 systems used in the home healthcare environment”, (EC) No. 1901/2006 – “Medicinal products for paediatric use”; EU PIP (Paediatric Investigation Plan)

**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)
- (EC) No. 1901/2006 – “Medicinal products for paediatric use”; EU PIP (Paediatric Investigation Plan)

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 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
The phenomenon of arching which blocks the device’s exit channel.

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 (dispensable) 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.
Balda MEDICAL takes care

Your product idea perfectly realized.

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