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Review

Oral drug delivery in personalized medicine: Unmet needs and novel approaches

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ABSTRACT

Increasing knowledge into personalized medicine has demonstrated the need for individual dosing. Drug dosage forms are urgently needed enabling an individual therapy, especially for oral drug delivery. This review is focusing on approaches for solid and liquid oral dosage forms for individual dosing. The proposed dosage forms and devices may be distinguished into assembling and partition concepts and have been categorized regarding their applicability, costs, dose flexibility and potential benefits. Opportunities, challenges and further unmet needs are elaborated and critically discussed.

Liquid dosage forms can be accurately dosed by novel dropping tubes or oral syringes, but less precisely by dosing spoons and cups. Breaking scored tablets into fragments show major risks such as inaccurate dosing, formation of potent dust and stability issues of the residual segments. Novel approaches are proposed for solid dosage forms enabling a flexible and appropriate therapy such as various dispensers for multiparticulate drug formulations. However, most of the proposals still have to prove their applicability in practice. Promising concepts are the Solid Dosage Pen and drug-loaded oral films which can be cut in individual sections enabling freely selectable doses. Further research and development are required for novel dosage forms and medical devices appropriate for individualized therapy.

Contents

1. Introduction

Personalized medicine is a current and challenging research area. Numerous papers have been recently published focusing on metabolizing enzymes, biomarkers, screening tests for metabolizing capacities in ethnic subgroups or different external influencing factors on drug metabolism. It could be shown that due to the effects of poor but also rapid metabolizing capacities, adapted drug doses are required to ensure a safe and correct therapy. Paediatric and geriatric drug delivery also need individualized dosing, patient-adapted drug formulations and delivery devices (Breitkreutz and Boos, 2007). Further, some drugs with small therapeutic windows, such as digoxin and phenprocoumon, need precise dose adaptation, particularly in phases of initial dose titration. It is obvious that suitable dosage forms are urgently needed enabling the selection and application of individual doses to transfer fundamental knowledge on personalized medicine into daily medical practice. In the best

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case these dosage forms should be suitable for the complete patient population, starting from young children to the elderly (Standing and Tuleu, 2005; Kearns et al., 2003; Stegemann et al., 2010). Individual therapy has been often linked to parenteral application of a liquid drug formulation in a hospital setting. In pharmaceutical homecare only few applications for individual therapy have reached the market. Examples are the treatment of diabetes by insulin dosage pens and pump systems or growth hormone supplementation using child-appropriate dosing devices. However, parenteral drug formulations do not completely fill the gap as they are restricted to certain conditions and poorly accepted by many patients. Oral drug delivery is still the most important and most frequently used application route. Therefore, suitable oral dosage forms with the option for individualized dosing are urgently needed. This review is focusing on solid and liquid drug dosage forms enabling individual dosing for oral administration. We report on the delivery devices for individual oral therapy which have already reached the market or which have been published in patent or scientific literature so far. Opportunities, challenges and further unmet needs will be elaborated and critically discussed. The different approaches are categorized and evaluated according to applicability, cost of production or treatment costs, the potential of dose variation, handling, stability and suitability.

2. Classification of individualized dosing approaches

General classifications can be made between solid and liquid dosage forms and also between partitioning and accumulating dosing approaches (Fig. 1). In the partitioning approach subdivided doses are obtained from a bigger volume of a drug carrier and in the accumulating approach several small-sized drug carriers are collected for the total dose. The first strategy for individual dosing was applied to children by dropping liquid formulations from a multi-dose container. Hence, the age-dependent or body mass based dosing of a wide range of young children became possible. Later dosing devices such as dosing cups, spoons, dropping pipettes and recently oral syringes have been introduced into the market. However, liquid medications exhibit some major disadvantages in comparison to solid dosage forms such as poor stability of the active ingredient, unpleasant taste, toxicity of certain excipients and higher logistic costs (Breitkreutz et al., 1999). Therefore, the World Health Organization has recently released a concept paper demanding multiparticulate dosage forms for global paediatric drug therapy (WHO, 2009). In the paper there is however no proposal how to achieve and to secure correct dosing of these multiparticulate formulations according to the children's needs.

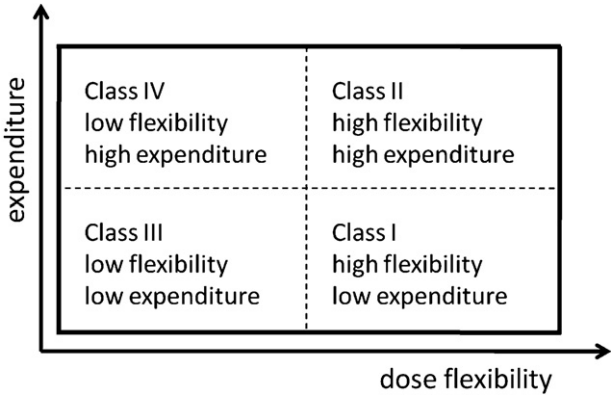

Fig. 2. Classification of different concepts for individual therapy with oral dosage forms considering dose flexibility and production/development costs.

Essential factors for market success of the different approaches for individualized therapy are the cost of goods due to varying development, production and transport expenses, the added value for drug therapy in general and the benefit for each individual patient. We propose a simple classification system to distinguish the different approaches to individualized dosing into four basic categories (Fig. 2). In the best case an individual dosing system belongs to Class I (high dose flexibility, low costs), in the worst case to Class IV (low dose flexibility, high costs). Some approaches might come along with more expenditure in development and/or production, but this may be acceptable if the system is highly flexible and solves a major problem in drug therapy (Class II). Others may be easy to produce, but offer minor dose flexibility (Class III)

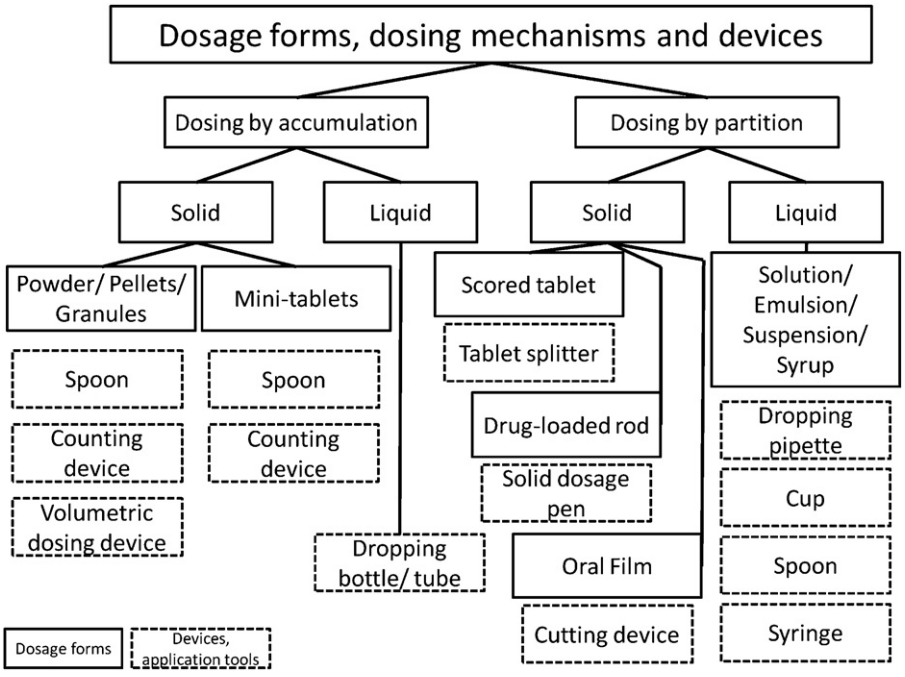

Fig. 1. General classification of oral dosage forms and dosing approaches for individualized therapy.

and are therefore of minor importance. Most probably, these systems require additional dosage forms or devices to cover the needs of all patients which may increase the overall costs of drug therapy. Certainly there are some other parameters to be taken into account when judging on the approaches for individualized dosing. The ideal dosing principle should be simple and accurate in practice, cheap, robust for a long-term application and best suitable for a maximal number of patients.

3. Liquid dosage forms

Liquid drug formulations for oral drug administration are available as solutions, syrups, emulsions or suspensions. Homogeneous liquids like solutions or syrups with completely dissolved APIs show advantages over emulsions and suspensions as they ensure uniform doses when withdrawing single doses out off a multi-dose container. Single-dose containers for oral liquid medications could be sachets or stick-packs, but they are currently not available on the market. Therefore, for accumulating dosing approaches (Fig. 1) only dropping bottles and tubes are considered in this review.

Partition dosing approaches require measuring or counting tools. It can be distinguished between tools which are part of the primary packaging such as dropper inlets or dropping tubes and separate dosing devices like dosing spoons, cups, dropping pipettes and oral syringes.

3.1. Accumulate dosing from primary packages

A dropper inlet in a multi-dose container enables the counting of individual drops from the liquid formulation. Oral droppers may especially useful to administer very small volumes of oral liquids to very young children. Counting errors are a major problem in dosing from dropping bottles. Moreover, adhering to the provided instructions how to hold the package is very important for dose accuracy and consistency (Brown et al., 2004). Some bottles must be used vertically, others in a defined angle, e.g. 45°, to ensure the correct volumes of drops and the dosing of the API. Further critical factors affecting dosing accuracy are temperature and residual volumes. In a recent paper a severe outcome was demonstrated for the inappropriate dosing of codeine from dropping bottles together with morphine treatment (Hermanns-Clausen et al., 2009). Recently introduced dropping tubes ensure higher dose homogeneity as they are designed to deliver precise doses independently from the position or angle of the package during dropping. This is particularly recommended for high potent drugs with elevated toxicity risks such as codeine or morphine.

3.2. Dosing devices

Dosing devices may be provided with the package or separately purchased. Typical target dose volumes are ≤5 ml for children under 5 years and ≤10 ml for those of 5 years and older. In former times dosing with a teaspoon or a tablespoon was assumed to provide acceptable doses. However, as modern spoons may have different shape and volumes, dosing with household spoons is considered as inappropriate today (Catzel, 1977; Breitkreutz et al., 1999). For liquid dosage forms that require administration with a measuring device, it is important that graduations on the dosing device are clearly visible (e.g. embossed or printed) to enable accurate and precise dosing. In the pharmaceutical development, the physical characteristics of the liquid in relation to the proposed dosing device must be considered. The shape of the measuring devices can affect dosing accuracy. Indeed, dosing devices with a small base area appear to have better accuracy than those with a broad base area. Graduations on dosing spoons used to measure doses less than 5 ml can lead to inaccurate and variable dosing (Fig. 3). In a recently published survey on antibiotic suspensions in marketed German products (Griessmann et al., 2007) it became evident that the accomplished dosing devices like dosing spoons and cups are inappropriate to measure correct doses, at least if lower doses than the standard doses are required. Parents make numerous administration errors especially when dosing the oral medication by dosing cups. Only 30% of the parents can accurately (±20% of the labelled dose) administer the correct dose by a cup with printed graduations and 50% by a cup with etched marks. Significant dosing errors (more than 40% deviation) were made by a quarter of all parents enrolled in the study (Yin et al., 2010). Oral syringes are much more precise (Hattori et al., 1999; Griessmann et al., 2007), but also more expensive. Oral syringes with caps should be avoided due to the risk of choking from the cap (Breitkreutz et al., 1999). Graduated dosing cups may be an alternative to dosing spoons or oral syringes, especially if volumes larger than 5 ml are required to be administrated, as they avoid multiple dosing operations. However, dosing cups have disadvantages, for example there is potential for residual liquid to remain in the device after administration of the dose, in particular with viscous liquids and suspensions. Furthermore, investigations comparing the accuracy of dosing of oral liquid suspensions using dosing cups, oral syringes and droppers have found that carers are more likely to measure unacceptable doses with dosing cups compared to the other devices, with the majority of errors resulting in overdose (Sobhani et al., 2008). Plastic cups must be handled with care in paediatric as they may be choked by the child (Weiss et al., 1996).

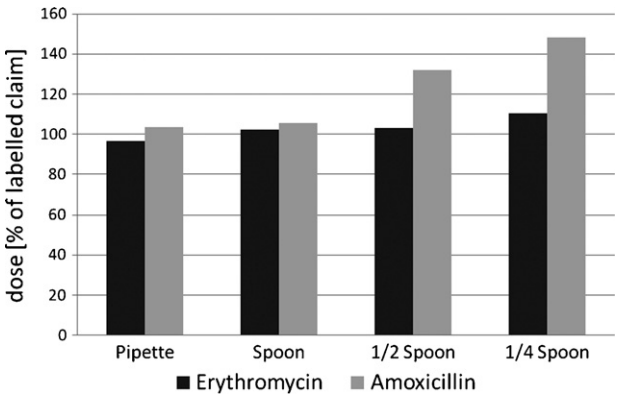

Fig. 3. Dosing accuracy in marketed medicinal products with different dosing devices (modified from Griessmann et al., 2007).

Dosing cups and spoons can be classified into Class III (Fig. 2). They are cheap in production, but offers minor dosing flexibility. Dropping pipettes, dropping bottles or tubes and oral syringes are also cheap in production but offer high dose flexibility and are therefore classified into Class I. However, dosing liquid medications is associated with numerous risks and challenges. Even modern dosing devices do not always deliver accurate and precise doses. Oral syringes are considered as the best dosing devices.

4. Solid dosage forms

4.1. Tablets

Tablets are still the most accepted and cheapest oral dosage forms. Scored tablets can be used for individual therapy when breaking them into subunits. Unscored tablets can usually not be employed for individual therapy. The main reason for tablet splitting should be dose adjustment. Another important reason for tablet splitting is saving costs, which could be reduced by 30–45% in some cases (Quinzler et al., 2006). Breaking of unscored tablets due to financial or reimbursing reasons and the associated problems are

not considered in this review. Commonly available scored tablets can be split either into halves or quarters. The risks and problems of dividing tablets into segments have been well investigated. The frequency of inappropriate tablet splitting in Germany was reported in a recent study (Quinzler et al., 2006). 24.1% of all prescribed tablets were split, whereof 8.7% were unscored and 3.8% were not allowed to be split at all, e.g. due to an applied functional coating. The U.S. Food and Drug Administration has recently released a warning letter on the risky practice of tablet splitting (FDA, 2009). The International Association of Pharmaceutical Technology (APV) and the German Pharmaceutical Society (DPhG) provided some general rules for good practice of tablet splitting to ensure efficacy and safety (Breitkreutz et al., 2007).

There are several scientific reports on tablet splitting. Van Santen et al. (2002) focused in their review on breaking of scored tablets. They could show that breaking of scored tablets often leads to deviations in segment mass and also drug content. The authors claimed that tablets should be at least 8 mm in diameter to break them accurately. The review also discusses the technical difficulties in tablet splitting. Snap-Tab® tablets and similar innovative geometries could be split more accurately than conventional tablets. In a study, in which pharmacists should split tablets into halves, 10 of 22 dispensed prescriptions displayed mass deviations of more than 15% (Rosenberg et al., 2002). In another study, the halves of 11 scored and unscored tablets were analyzed. Almost 8 of 11 tablets failed the uniformity test according to the USP (Teng et al., 2002). Another risky practice in tablet splitting has been shown for 6-mercaptopurine tablets (Wessel et al., 2001). In addition to poor mass and content uniformity hazardous dust may be formed when the parents split these tablets in the domestic environment for their children with acute lymphoblastic leukemia. It is also a matter of concern how to deal with the residual segments of the split tablets. Usually there are no instructions how to store or to eliminate the segments.

Tablet splitting devices are sometimes assumed to enable more accurate splitting, but the use of these tools does not necessarily lead to exact divided doses (Cook et al., 2004). In another study 37.3% of the segments deviated more than 10% from ideal mass when using a marketed tablet splitter (McDevitt et al., 1998). Still, the risk is reduced by using these medical devices if compared to a knife or breaking by hand. Summarizing the studies on tablet splitting it has to be concluded that scored tablets might be a fairly reasonable opportunity for individualized dosing, but is still a risky practice in terms of adequate dosing and potential poisoning. Usually only four different doses can be obtained from a conventional tablet, which does not really match the term “individual therapy”. Therefore, scored tablets with up to 4 segments are classified into Class III: they are cheap to develop and to produce, but they offer only limited dosing flexibility.

In a recent study novel tablets (Fig. 4) with anti-malarial agents were introduced enabling splitting into eight regular segments (Kayitare et al., 2009). Thus, dose flexibility could be at least doubled compared to conventional scored tablets. However, the known problems of incorrect doses and dust release might still occur. Another interesting concept is the development of oblong matrix tablets for sustained release which can be split in up to five different segments (Dicke, 2008). Beside the different drug loads of the divided compartments the resulting surfaces may lead to different release profiles and hence, to varying pharmacokinetic properties. In this particular case the problem of incorrect splitting had also to be taken into account for the pharmacokinetic evaluation of the system. Correct dosing is rather complicated when using a combination of different tablet segments resulting in scattering total doses and also scattering drug release kinetics. It can also be assumed that the loss of material is high. The residuals of the tablet had to be discarded or alternatively used for further therapy which raises concern regarding drug safety.

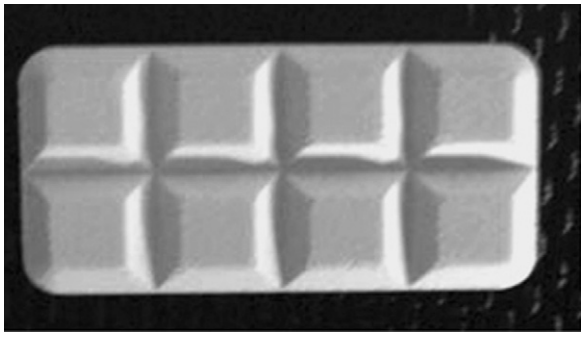

Fig. 4. Tablet divisible in up to eight segments (Kayitare et al., 2009)

Improved accuracy of dosing could be achieved by developing special tablet geometries. The already mentioned Snap-Tab® tablets can be broken accurately into their four subunits, depicted in detail by Van Santen et al. (2002). An alternative tablet design with small fracture areas have also been introduced (Shah and Britten, 1990). The small areas could be designed by a flat shape of the tablets and deep scores. These tablets can be split into halves or into a triple form to obtain one third of the original dose. Another interesting idea to overcome incorrect tablet splitting was recently proposed (Solomon and Kaplan, 2010; Green et al., 2009) using tablets with drug-free compartments (Fig. 5). Splitting is made trough the unloaded layers where the scores are located. In these formulations unequally splitting does not influence the drug content of the halves or quarters. It can be concluded that correct splitting has to be proven when using scored tablets for individual therapy. Today, the regulatory agencies require the proof of accurate splitting if scored tablets are filed for marketing authorization. Improved tablet designs may improve the dose uniformity. However the dosing flexibility is still limited for the scored tablet approach in individual drug therapy.

4.2. Multiparticulate dosage forms

Another opportunity to deliver solid doses individually is to select a defined number or volume of drug-loaded particles. This concept comprehends powders, granules, pellets (spherical granules) or mini-tablets. The measured doses could be swallowed directly, dissolved or dispersed in a potable medium, or given with a meal. In all cases a device is needed to select or extract a predefined volume or to choose a specific number of dosage units

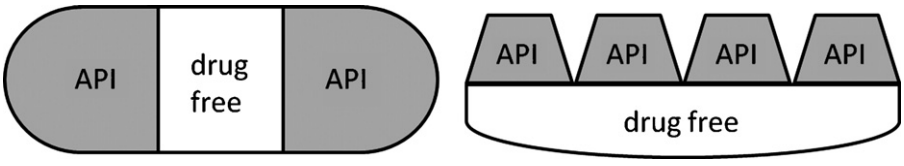

Fig. 5. Innovative tablets with improved dose uniformity of segments by introducing drug-free compartments (white) separated from drug-loaded segments (grey). Left: tablet geometry for two halves, right: tablet geometry for quarters (modified from Solomon and Kaplan, 2010).

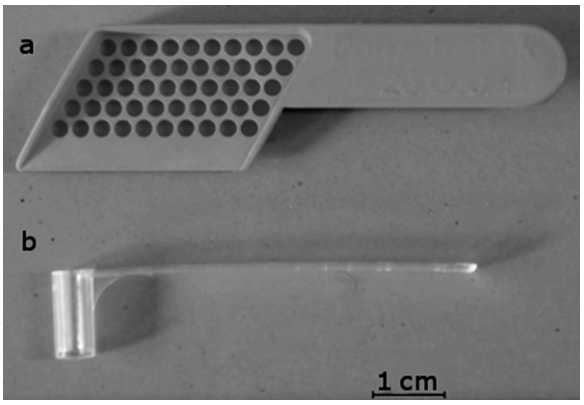

Fig. 6. Dosing spoons for determining and withdrawing small-sized solid drug carriers from multi-dose containers. (a) Dosing spoon for the delivery of 50 mini-tablets (Panzytrat OK, Axcan); (b) dosing spoon to measure a predefined volume of pellets (Kreon, Solvay).

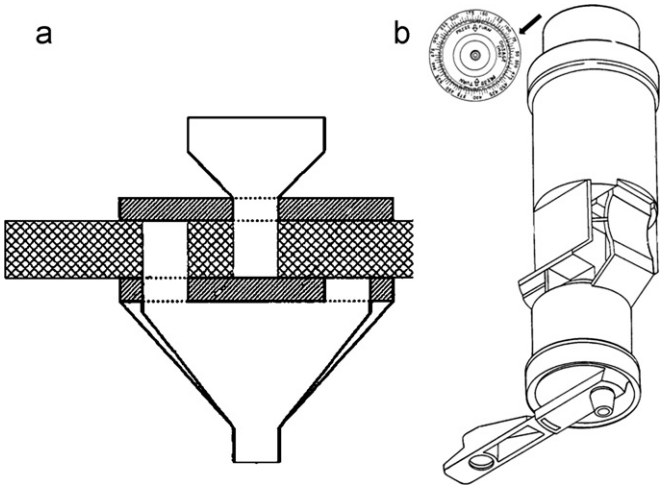

Fig. 7. Modified schematic drawings of powder dispensers. (a) Device with double funnel system (Bauriegel, 2007), (b) device with graduation wheel (Heimlich, 1984).

from the multi-dose container. A simple way is the use of dosing spoons, already established in the therapy of pancreatic diseases, particularly for children (Fig. 6). Using the spoon a defined volume of enteric-coated granules can be measured. To achieve different doses the spoon has to be refilled several times. A drawback is the high number of pellets required for paediatric dosing. Pellets may drop away and children might refuse a meal with plenty of solid multiparticulates. A more sophisticated spoon (Fig. 6) is available on the market to accurately withdraw the correct number of pancreatin mini-tablets out of a bulk container (Knoll, 1999). The spoon contains fifty gaps which should be completely filled with mini-tablets of 2 mm diameter each. However, it might occur that one hole of the spoon remains unfilled causing a dosing error, but the pharmacopoeial limits for dosing accuracy would be still met. If spoons are developed with a smaller number of gaps for minitablets, the loss of few drug carriers might automatically cause a failure in the pharmacopoeial test and hence, an out-of-specification result. The range of dose flexibility is still very limited for both types of measuring spoons introduced so far. In enzyme replacement therapy dosing errors might not be particularly dangerous, but for multiparticulate dosage forms containing potent APIs dosing of multiparticulates by measuring spoons is hardly feasible with common devices. Powders or granules can also be dosed by measuring spoons. For example ascorbic acid (vitamin C) powder is marketed together with a dosing spoon. Hardly recognizable graduation marks, as already described for liquid formulations, may hinder wide use and accurate dosing practice. An improvement was recently proposed (Bauriegel, 2007) by using a simple, but effective dosing instrument (Fig. 7a). Two filling funnels are connected with a slider. By moving the slider a defined powder volume is extracted from the upper funnel and in the next step transferred to the lower funnel. However, a counting of the dosing units is still necessary and dose flexibility is quite limited. Solid dosage forms dosed by measuring spoons or the funnel-system are therefore classified into Class III.

Another device for dispensing flowable formulations volumetrically (Fig. 7b) was proposed by Heimlich (1984). A spherical ring with graduations allows the selection of a predefined volume of solid particles, which could be transferred from a reservoir into a delivery chamber by rotating the housing. The flowable material leaves the device by gravity. The devices of Bauriegel and Heimlich would be only suitable for free-flowing powders, which is a major limitation. If these devices could deliver an appropriate number of different doses, it could be classified into Class II.

A device to volumetrically deliver pellets has been marketed in Germany in the 1990s by Boehringer Ingelheim for the treatment of bronchial asthma. The system is filled with sustained-release pellets and delivers one sub-dose per actuation (Fig. 8). Up to six sub-doses could be gathered in the spoon placed at the bottom of the device. The completeness of the single dose can be verified by the graduation marks at the spoon. It was recommended to give the dose with a meal, particularly yoghurt. The major disadvantage of this delivery system is the handling of a spoon filled with hundreds of pellets. The spoon is connected with the device and the transfer of all pellets into the food is a major challenge. Moreover, the high number of pellets to be swallowed may be unpleasant for the patients. Freely dispensable multiple-unit dosage forms are inappropriate for use with APIs at very high doses. Due to only six different doses and the high expenditure for production, this device is classified into Class IV.

In conclusion, the volumetric dosing of solid dosage forms is applicable for individual therapy with some restrictions. These are limited dose flexibility and an increased risk for dosing errors. Stability problems might occur when the dosage forms are stored in a container with ambient air contact.

To avoid volumetric dosing each drug-loaded subunit has to be counted which is impossible for small pellets, but minitablets or larger pellets could be employed. A simple option is a medical device dispensing one single unit per actuation. Such systems for pharmaceutical products have been patented since the

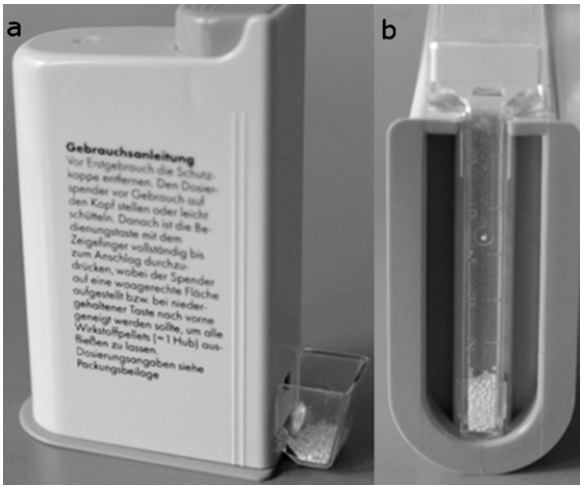

Fig. 8. Pellet dispenser containing sustained release theophylline pellets. (a) Delivery system from lateral side, (b) spoon with graduation marks.

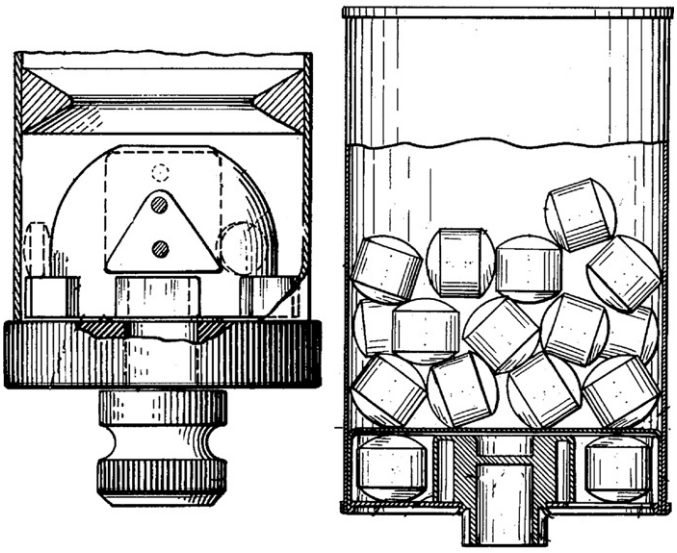

Fig. 9. Modified schematic drawings of containers dispensing single tablets. Left: patent from Warren (1940), right: patent from Dobkin (1950).

1940s, mainly in the USA. However their potential for personalized medicine and individualized therapy was not seen in those times or at least not described in the patents. Today, tablets are usually distributed in press-through packages (blisters), bottles or other multi-dose containers. To deliver a single drug-loaded subunit from multi-dose containers various concepts have been developed. Two patents (Warren, 1940; Dobkin, 1950) propose cylindrical dispensers for tablets (Fig. 9) which deliver one single tablet per actuation. By a semi-rotation of the container one tablet is withdrawn from the multi-dose container leaving the device after a full rotation. Both systems work similarly and have even been claimed for the same substances such as artificial sweeteners or carbohydrates. To achieve an accurate withdrawal of tablets from multi-dose containers various technical solutions have been proposed in patent literature. These concepts are often based on devices which could be connected to containers serving as a reservoir of tablets or pellets. In most cases just one single tablet or pellet can be delivered. However, for individualized therapy different numbers of sub-units have to be delivered. Thus, dose variation opportunities depend on the API content in a single unit. By counting the delivered sub-units a great risk of dosing errors is evident. The easy devices from Warren and Dobkin have served as templates for more advanced tablet or pellet dispensers. They mainly differentiate in the mechanism how the tablet is withdrawn from the multi-dose container and delivered by the device (McConnel and Williamson, 1971; Neavin, 1973; Thomas and Ryder, 1976). An easy, but efficient setup of device (Fig. 10) was developed for dispensing pellets and homeopathic globuli (Laboratoires, Suppo-Steril, 1977). The device, 6.5 cm in height and 1.5 cm in diameter enables the delivery of one 4 mm pellet on full rotation of the housing. An advantage of this delivery system is the minor production expenditure if compared to later discussed more sophisticated, mechanically or electronically controlled systems. The main disadvantage of the device is the requirement that the patient still has to count the dosage units on his own. This practice is very susceptible for dosing errors in practice. Numerous devices similar to those in Fig. 10 have been proposed in patent literature (Chadwick, 1952; Le Blanc, 1960; Neavin, 1973; Schoenefeld, 1980; Debont, 1989; Bramlage, 2007). All the devices are cylindrical in shape and can be used to deliver single units from a reservoir. The device of Schoenefeld is exemplarily shown in Fig. 11a. The devices differentiate only in the mechanism to transport the single dosage form to the outlet die. The device proposed by Le Blanc is assumed to be used for dispensing capsules. Further patents with dispensing items particularly focus on child safety (Uroshevich et al., 1975), (Fig. 11b) or protection against counterfeiting (Graff, 1985). In another concept a mechanism is actuated when pressing a button to deliver one tablet (Fig. 11c), with a particular focus on the protection of the tablet (Hansen, 1993). All these devices selecting single drug-loaded units need a personal counting of the patient or caregiver. Due to the limited dosing flexibility or the high risk of dosing errors

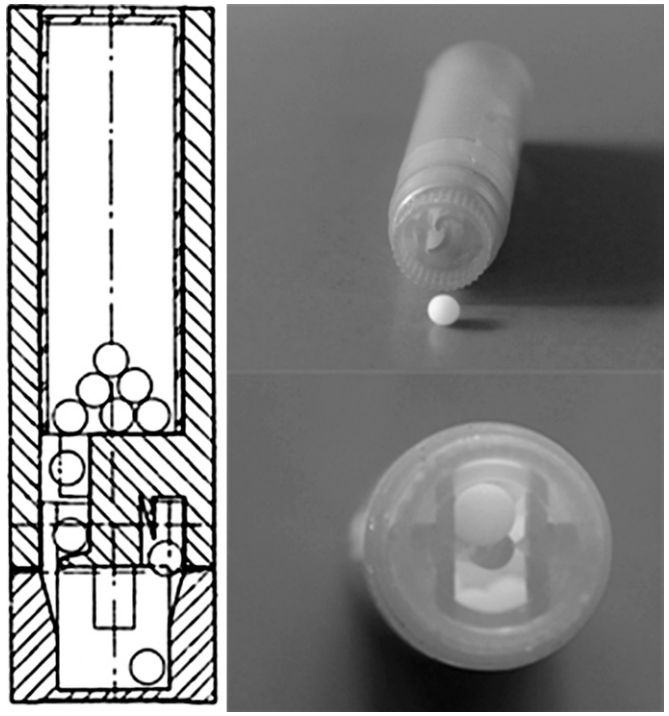

Fig. 10. Suppo-Steril pellet dispenser (Laboratoires, 1977). Left: schematic drawing modified from the patent, right: prototype for single delivery of 4 mm pellets.

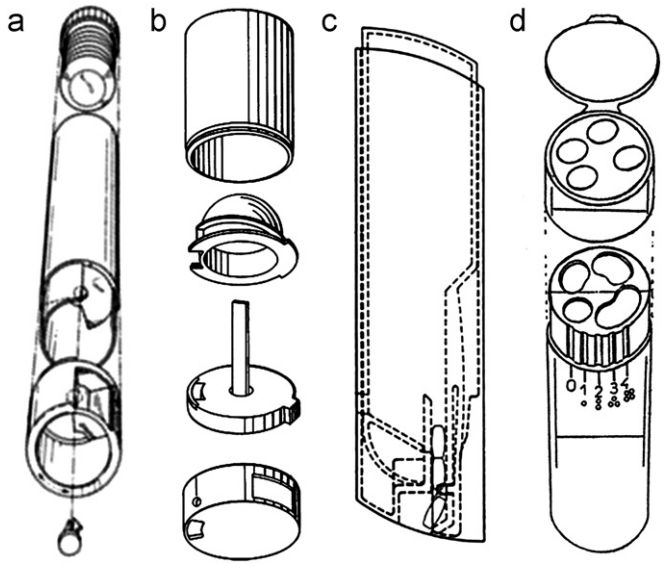

Fig. 11. Schematic drawings according to patent applications for pellet dispensers. (a) Device from Schoenefeld (1980) dispensing one drug carrier by a single rotation, (b) child-resistant device from Uroshevich et al. (1975) dispensing one drug carrier by a single rotation, (c) device from Hansen (1993) dispensing one drug carrier by actuation on the top, (d) device from Salamé (1991) dispensing one to four drug carriers.

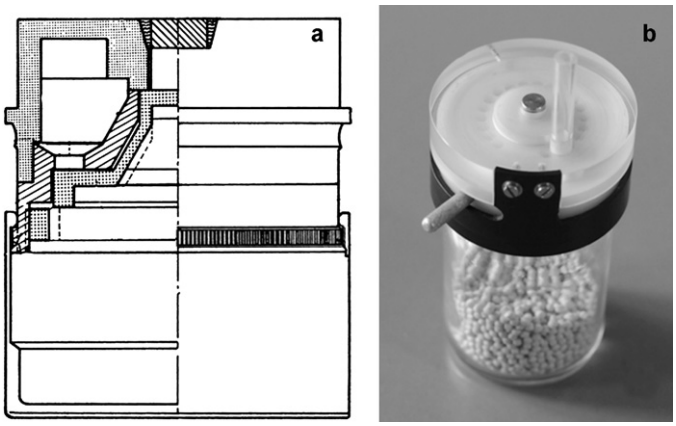

Fig. 12. Dosing devices automatically counting a variable number of subunits by rotation disks. (a) Schematic drawing modified from Schuster (1988), (b) prototype of device proposed by Breitkreutz and Wazlawik (2005) in the upright position. For counting the device must be turned and actuated by rotation.

when counting multiple dose carriers, they are classified into Class III.

Delivery devices, which are able to collect the total number of subunits and dispend the complete individual dose, fit the basic idea of individual therapy superiorly. Salamé proposed a dispenser allowing the counting of up to 4 pellets by using two punched disks (Fig. 11d) with different diameters (Salamé, 1991). Dependent on the position of the second disk 1 to 4 holes are opened and thereby dropping out one pellet each. Higher flexibility could be applied with systems releasing a higher number of units (Fig. 12). A disk with cylindrical holes (Schuster, 1988) is filled with the desired number of mini-tablets from a reservoir on top of the disc. The selected mini-tablets are transferred into a chamber for final removal of an individual dose. This basic idea was further developed, generalized and processed for the dispensing of mini-tablets, pellets and molded bodies (Breitkreutz and Wazlawik, 2005). Rotatable disks enable easy counting of the units by drawing the spherical plate in the freely selected position (Fig. 12). When returning the disc to the starting position the counted units leave the device by a tube for exact placement of the dose, e.g. into a meal. Dosing errors might only occur for both concepts, if holes in the disk are incompletely filled. A similar concept is used for an electronic dispenser (Bredenberg et al., 2003). The dose can be predefined and mini-tablets are counted automatically by one actuation (Fig. 13). The correctness of the dosing is determined and indicated by an electronic display. This concept may be the safest device for dispensing multiple-unit dosage forms. However, such a system is rather expensive and produces a lot of environmental burden, especially when considering the required energy cell. In comparison to all other proposed dispensing devices for multiparticulate dosage forms, the electronic dispenser has already been used in clinical practice treating 20 patients with Parkinson disease (Bredenberg et al., 2003). The other proposed devices still have to prove their practical feasibility. All counting devices can be categorized in Class II. However, actually none of these devices is available on the market.

Fig. 13. Electronic dispenser for mini-tablets (Bredenberg et al., 2003).

4.3. Thin film strips and other buccal dosage forms

The idea for individual dosed buccal dosage forms is more than forty years old. Different concepts have been proposed in patent literature. Buccal dosage forms can be produced in the form of long drug-loaded strips with graduation marks of different nature. Drug-free strips can also be impregnated or coated with the API. One proposal was to sectionalize a strip and place it directly into the mouth (Fig. 14a). The length of the cut strip defines the individual dose for the patient (Russell, 1966). Perforation of the wafers at predefined positions to tear of segments is also suggested in the patent literature in order to enable the individualized therapy of adults and children (Deadman, 1967; Culpitt, 1978; Schmidt, 1986). Dosing flexibility depends on the number of graduation marks on the strips or films. Deadman had also suggested that longer graduated strips can be wound on a spool for further application. Such dosage forms could be classified into Class II or III dependent on their nature and dosing flexibility of the contained API. Stability

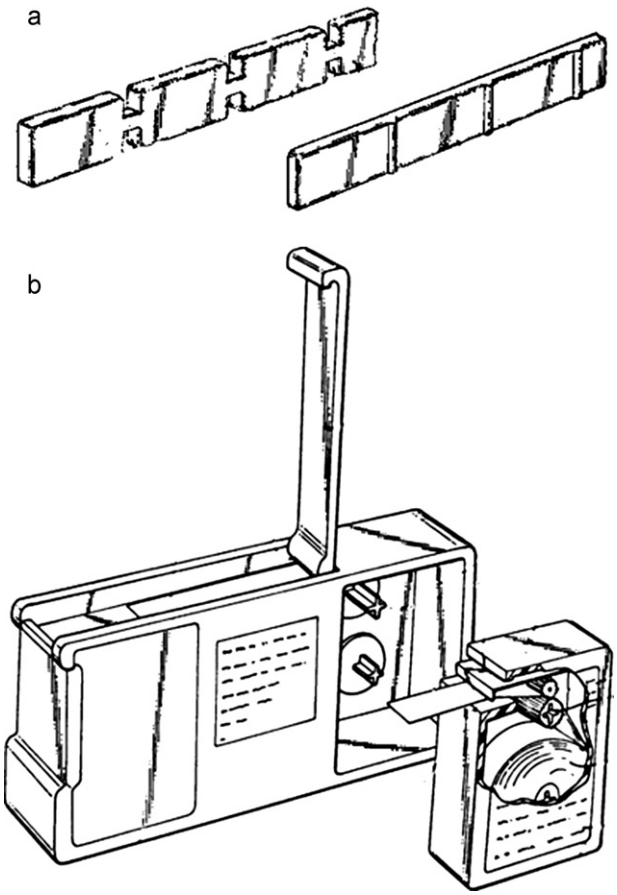

Fig. 14. Modified schematic drawings for application of individual buccal dosage forms. (a) Strips, which could be manually sectionalized for direct placement into the mouth (Russell, 1966), (b) electronic dispenser for dosing of individualized film strips (Allen et al., 1992).

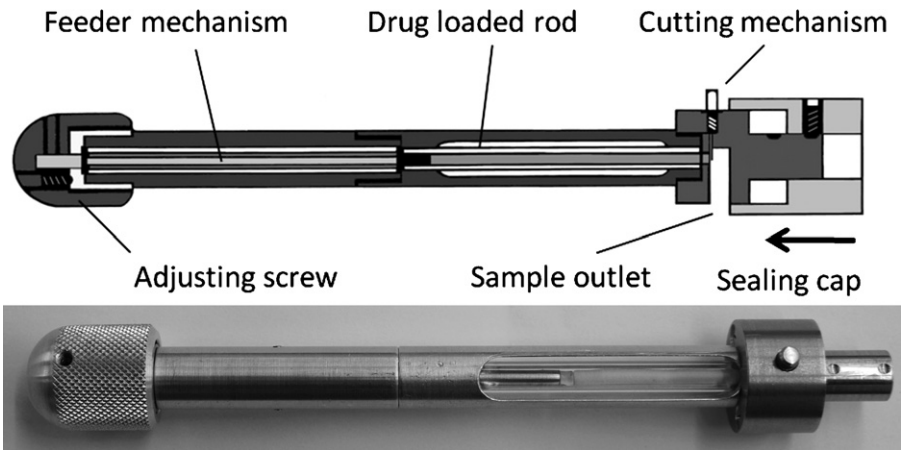

Fig. 15. Solid dosage pen enabling freely selectable dosing by individual tablet-like API-loaded slices (Wening and Breitkreutz, 2010).

problems might occur when strips of sheets are once removed from the package. To avoid the stability problem and to achieve higher dose flexibility another device is proposed in a patent application by Allen et al. (1992). The electronic tape dispenser should contain a rechargeable box with a drug loaded tape on a spool (Fig. 14b). Individual strips can be dispensed controlled by an electronic system with a display. Due to high cost of the electronic system it has to be categorized into Class II. However, in comparison to all other proposed concepts so far this is the most flexible dosing system. Therefore, it could be an extremely flexible solution, which could be proposed for Class I, if only a cheaper device could be invented.

Buccal dosage forms could also be used for individual therapy, when API-containing liquid is used to impregnate a solid dosage form. Horstmann and Laux (2004) proposed a fast soluble drug-free film, which could be impregnated by individual doses of a fat-soluble API-containing liquid. Another idea is to impregnate defined drug-free cores by API containing liquids (Ronca, 2007). To ensure, that the solution is spread completely on the solid carriers the preparation should be made by pharmaceutical industry or community pharmacists only. A generalized oral therapy with individualized doses is difficult to realize by these concepts. Therefore these systems are categorized into Class II and not suitable for domestic care.

Another approach for buccal delivery has been proposed with an individually filled chamber containing a liquid formulation (Stanley, 1989). Afterwards the filled system should be placed at the buccal mucosa. The bottom of the chamber needs a special tissue for adhesion to the buccal mucosa. The API should subsequently diffuse through this barrier. This concept is quite a complicate system with a lot of restrictions. Only a small volume can be filled into the system and the validity of fixation is crucial. Similar principles have been proposed by using implantable pumps (Velten et al., 2006; Scholz et al., 2008). Such pumps could be placed instead of two molar teeth. The system should deliver a defined amount from a liquid drug reservoir at predefined time-points. It is driven by a small battery for a use of maximal 14 days. The system is electronically controlled. After an impulse the liquid drug formulation is released by osmotic pressure. Such a system can only be used for a small patient population, due the loss of molar teeth and it needs a refill at least every two weeks. For APIs used at higher doses the fluid volume might be too large for placement into the device. The costs for these systems are very high. Therefore, both systems are classified in Class IV. In our opinion they are not suitable for a common daily individual drug therapy. None of the buccal dosage forms described in this chapter is already available on the market. Most of them are only patent applications and no studies for realistic practice of these approaches could be found.

4.4. Solid Dosage Pen

A novel device delivering a swallowable solid monolithical oral dosage form containing individual doses has recently been introduced and used for various in-vitro studies (Wening and Breitkreutz, 2010). The device disclosed in this paper is based on a previous patent application (Schomakers and Grummel, 2002). The device houses a drug loaded rod (Fig. 15), manufactured by an extrusion method, which can be fed forward. A cutting mechanism is used to easily cut off tablet-like slices from the rod. The thickness of the slice, which is freely selectable by rotating the feeding mechanism, defines the dose precisely. The cut tablet-like slices can be swallowed directly or can be mixed with food. The system could be used for children as well, due to different rod diameters down to 2.7 mm. The uniformity of the divided doses to European pharmacopoeial standards 2.9.27 “uniformity of mass of delivered doses from multidose containers” and 2.9.40 “uniformity of dosage units” was demonstrated for metoprolol and carvedilol (Wening and Breitkreutz, 2010). The costs might be high due to the highly sophisticated device. Therefore, the system was constructed to enable refilling of API-loaded rods. The rods are produced by a continuous extrusion process and can be contemporaneously filled into the primary packaging material. Therefore, this system could be categorized into Class I if the costs for the delivery device are reduced to an acceptable value. If the costs are higher or the device is not refillable, Class II would be more appropriate.

5. Conclusions

Up to now, there is a huge need for the development of novel dosage forms and delivery devices for oral individual drug therapy. Various approaches have been proposed, predominantly in patent literature. However, practical implementation and clinical studies are still missing, but needed to prove the quality and success of these concepts. The only practices commonly used are dosing liquids by droppers, spoons and syringes or splitting tablets into segments, but this bears various risks as continuously claimed by different organizations. Dispensers for multiparticulate dosage forms have been developed but up to now there is only one dispenser for pellets available on the market with minor dosing flexibility. More advanced delivery devices have been proposed, but did not reach the market most probably due to financial reasons. The recently introduced concept using a Solid Dosage Pen may serve as a future platform technology for completely individual choice of doses. Systems which will be investigated in clinical studies should allow a therapy of all subpopulations, including children. Devices like the solid dosage pen or the electronic dispenser for film strips

would lead to novel standards for oral drug dosage forms in the regulatory procedures. Up to now, only different insulin formulations and some other biotechnological parenteral formulations for application with pens have been authorized for individualized drug therapy. An advantage of these advanced concepts could be an authorization for children and adults with only one dosage form and delivery device.

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