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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.

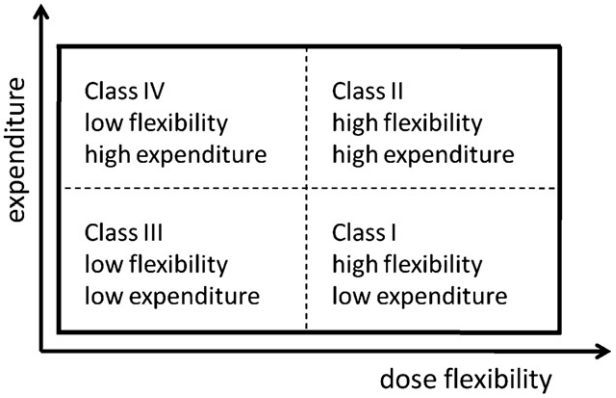

Fig. 2. Classification of different concepts for individual therapy with oral dosage forms considering dose flexibility and production/development costs.

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)

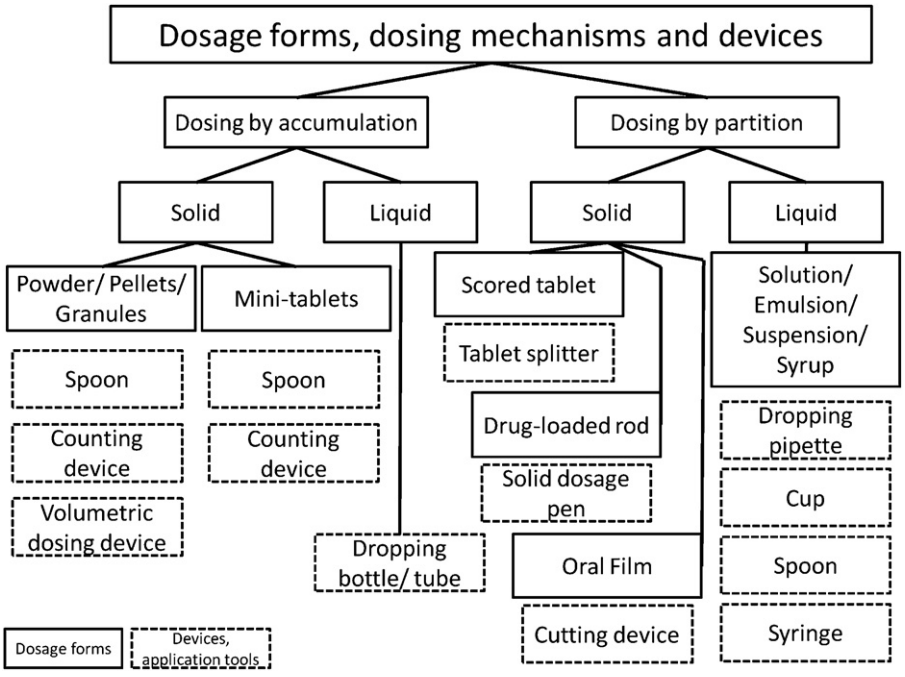

Fig. 1. General classification of oral dosage forms and dosing approaches for individualized therapy.