CHALLENGES IN DESIGN AND PROCESS DEVELOPMENT OF DOSE SIPPING TECHNOLOGY PRODUCTS

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ABSTRACT

Children and elderly are subject groups for new drug administration systems that allow for easier intake of medicines and, thus, a potential for better compliance. Dose Sipping (DS) Technology administering tasteless granules to patients by forming an in-situ suspensions in the patient's favorite beverage requires a complex development with an interdisciplinary approach of different engineering sciences. Plastic engineering employing extrusion, injection molding and fiber spinning including an arrangement process for the fibers leads to three of the components of the DS systems while formulation engineering supplies the effective granules containing the active ingredient. Machine engineering is needed to construe and build equipment that assembles the DS system at commercial scale. Packaging engineering provides storage stability and easy handling for the patient. A lot of surprises and obstacles have to be overcome during such complex development and early set up of Target Product Profiles and application of Risk Management support a successful interdisciplinary development.

Keywords: Dose Sipping, plastic engineering, formulation engineering, machine engineering, packaging engineering

INTRODUCTION

Administration or intake of drugs is not always easy, particularly in the group of children and elderly. Often difficulties in swallowing of dosage forms are an obstacle to patient's compliance. Liquid formulations are easier in swallowing and, thus, application of dissolved or suspended drug may be more suitable. But liquid formulations are often less stable and less exact to dose than pre-dosed solid dosage forms. Bad taste of drug is another obstacle that might be overcome by taste masking. Consequently, a dosage form combining the advantages of liquids as easy swallowing with that of solid dosage forms as storage stability and exact unit dosing as well as taste selection by the patient might improve compliance in children or elderly.

DOSE SIPPING SYSTEM AND DOSAGE FORM

The proposed dose sipping (DS) administration system consists of neutral tasting granules - taste masking often required – packed in a system of a drinking straw like tube closed on the bottom end by a filter plug – called controller – and on the upper end by a removable cap. For administration of the drug the patient removes the cap, holds the lower end into his favorite beverage and sips at the upper end. While sipping the beverage passes the movable controller and suspends the granules in-situ on the way to the patient's mouth. After swallowing the suspension complete application of the drug can be checked by looking whether the controller has reached the upper end of the tube.

Development of the single elements and parts of the dose sipping system, their complex interactions and the assembling requires an interdisciplinary approach between plastic engineering, pharmaceutical formulation engineering, packaging engineering and mechanical engineering.

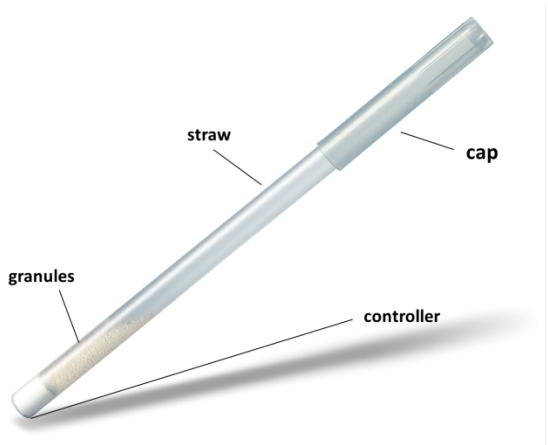

Fig. 1: Dose Sipping System

RESULTS AND DISCUSSION

Plastic Engineering

The three different plastic material elements of the DS system require three different manufacturing techniques:

- Tube is made by extrusion of polypropylene
- Cap is made by injection molding of polypropylene
- Controller is made by fiber spinning of polyolefins and a complex arrangement process of the fibers into a texture followed by cutting into plugs

Critical dimensions are the diameters of each part that need to be in extremely narrow tolerances of ≤±0.1 mm

Formulation Engineering

At least three basic requirements have to be fulfilled by the drug formulation:

- Ability to form an in-situ suspension with a good mouthfeel – particles not too small to block the tube (no fine powder), not too big as to avoid gritty feeling in the mouth (<< 1mm)
- Neutral taste or in case of bad tasting active ingredients a taste masking for at least the holding time in mouth
- Bioequivalence to existing medicinal products as e.g. suspensions, granules or even tablets in case marketing authorization shall be applied for as abbreviated new drug application

Assembling Machine Engineering

The assembling machine needs to be designed to perform following process steps at a speed to fulfill commercial needs (e.g. >10,000 DS system per hour):

- Align tubes in a row
- Fill controller into tube
- Crimp tube at lower end to avoid passing of controller at lower end (special crimping for high mechanical shape stability
- Transport controller to lower end
- Dose and fill granules without defects to coat
- Crimp upper end of tube to avoid passage of controller while patient is sipping
- Close tube by placing cap on top
- Allow for automated sampling for in-process controls
- Handover to further packaging line

Packaging Engineering

- Single package for each DS system protecting from environmental influences like humidity
- Secondary package containing all DS system for one therapy plus patient leaflet

Development process

During development of DS systems a lot of obstacles and surprises occur and have to be overcome from need to find new manufacturers of plastic parts over defining a new understanding of the functions of several parts leading to additional specification items, finding a new manufacturer for an assembly machine since the first equipment delivered not satisfactorily and mechanical deforming of tubes in finished systems by the packaging to several reiterations of taste masked granule development before arriving at bioequivalent products.

Setting up a Target Product Profile (TPP) right at the beginning of the development and applying Risk Analysis and Management during all steps of development helps to overcome challenges and obstacles.

In a clinical trial comparing a new Dose Sipping formulation to a classical liquid suspension of clarithromycin in children the DS system demonstrated a better compliance of the patients.

CONCLUSIONS

Development and manufacture of complex medicinal products like Dose Sipping systems with bioequivalent formulations require an intensive interdisciplinary approach of different engineering disciplines like plastic, formulation, machine and packaging engineering to arrive at a successful manufacturing in commercial scale.