INNOVATIVE FUID BED TECHNOLOGIES FOR TASTE-MASKED MICROPELLETS DESIGN

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INTRODUCTION

The oral administration of drugs exhibiting poor organoleptic qualities through solid dosage forms requires an acceptable degree of palatability, enhanced performance and acceptability. In the pharmaceutical industry, the desire of improved patient compliance has prompted the development of taste masking techniques to prevent active pharmaceutical ingredients exposing an unpleasant taste, aftertaste or smell. In the recent years, enormous progress in formulation design and development has given rise to more sophisticated novel oral drug delivery systems in which the role of micropellets is increasing. For this purpose, pelletization technologies provide ideal cores for application of functional coatings and to mask inconvenient taste, and therefore, offer a great scope for innovations in taste masking to reduce bitterness. This work presents innovative strategies for the taste masking of micropellets using different fluid bed pelletizing technologies and indicates the most interesting features of each approach.

HS Wurster

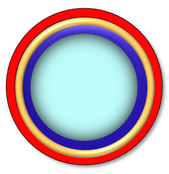
Fluid bed bottom spray layering and coating process

Challenge

The purpose of this study was to mask the intensely bitter taste of a drug in an hydrochloride salt form used for the treatment of veterinary diseases. The medication is administered directly into the mouth of the animal or with small amount of food. The formulation must prevent drug migration into coating layers.

Taste Masking Strategy

- *Starting beads*: Cellets® 100
- *Drug layering*: low drug load
- *Seal coating*
- *Taste masking*



Taste Masked Micropellets Design

Microcrystalline cellulose pellets, Cellets® 100 (150 µm) were used as starting material. Drug layer (DL), seal coating (SC) and taste masking (TM) were each applied in a batch mode using a direct fluid bed bottom spray process. Processes were performed in a Glatt GPCG equipped with Wurster insert. Micropellets size were 180 µm, 200 µm and 220 µm after DL, SC and TM respectively.

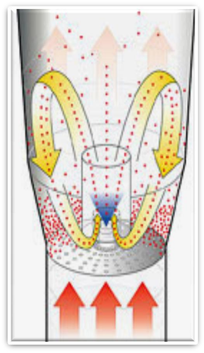
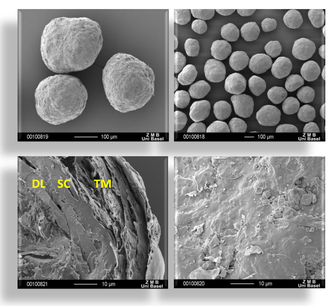


Figure 1: Representation of Glatt fluid bed bottom spray coating process (Wurster mode).

Micropellets Evaluation

The micropellets were evaluated using a Scanning Electron Microscope (SEM) equipped with Energy-Dispersive X-ray microanalysis (EDAX). The location of chlorine in the pellets was selected as a marker for the presence of the hydrochloride drug in the drug layer and in the seal coating, and therefore as a taste masking assessment.



Round shaped micropellets with a smooth surface and a uniform particle size distribution are observed in SEM pictures (Figure 2).

Figure 2: SEM pictures of TM micropellets. The drug layer (DL), seal coat (SC) and taste masking layer (TM) can be observed in the cross section (bottom, left).

A chlorine peak can be clearly detected in the drug layer (Figure 3, (DL)). No chlorine peak is observed in the seal coat (Figure 3, (SC)). The seal coating process is considered suitable to prevent drug migration into the outer coating layers

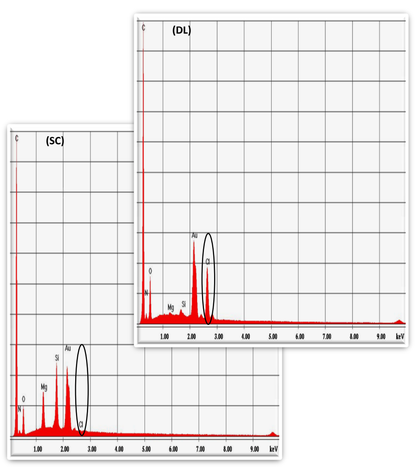


Figure 3: EDAX microanalysis at an acceleration voltage of 15 kV of the drug layer (DL) and of the seal coat (SC). Chlorine peak location is encircled.

MicroPx Technology™

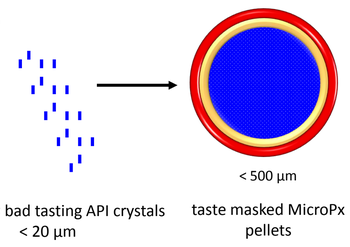
Continuous fluid bed pelletization process

Challenge

An antimicrobial agent exhibiting very unpleasant organoleptic properties was designed as a ready to use oral suspension for pediatric application. High drug load micropellets have to be achieved. After extemporaneous preparation, the taste masking in aqueous suspension must be stable for a 14 days period.

Taste Masking Strategy

- MicroPx core pellets
- Seal coating using HPMC
- Taste masking Eudragit L 30 D



Taste Masked Micropellets Design

The agent was processed as an aqueous solution/suspension and directly pelletized in a Glatt MicroPx continuous fluid bed spray granulation process. No inert starting beads were required to reach high strength micropellets. A *Classifying Device* allowed continuous discharge of well-sized micropellets and separation/rejection of fines back into the process. Seal coating and taste masking coating applications were achieved using a Glatt GPCG fluid bed bottom spray process (Wurster mode).

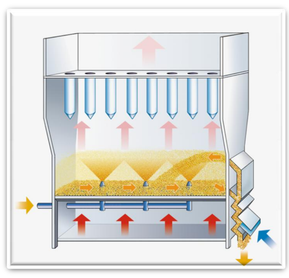


Figure 4: Representation of Glatt MicroPellet Delivery System, MicroPx™.

Micropellets Evaluation

The micropellets were evaluated using a Scanning Electron Microscope (SEM). The drug content in aqueous suspension was assayed and used as a taste masking characterization of the coated micropellets.

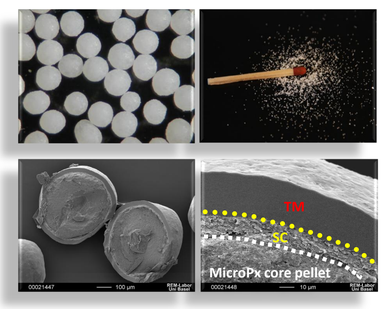


Figure 5: Light Microscopy picture (top left) and visual observation (top right) of MicroPx core pellets The MicroPx core pellet, seal coat (SC) and taste masking layer (TM) can be observed in the SEM cross section (bottom).

Highly dense and spherical micropellets are observed in SEM pictures (Figure 5), offering a smooth surface and narrow particle size distribution for coating applications.

When placed into suspension, the coated micropellets exhibit almost no drug release even after 7 days (Figure 6). The taste masking is supposed to be complete and stable in the desired period.

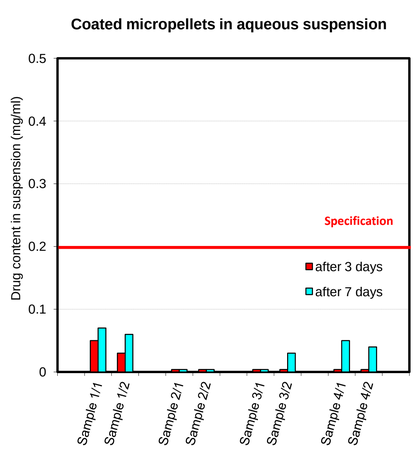


Figure 6: Drug release in aqueous suspensions from coated MicroPx core pellets over time.

CPS Technology™

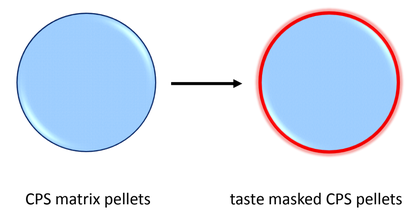
Direct modified rotor fluid bed pelletization

Challenge

This work addresses the strong astringency taste masking of a potent pain relieving weak acid agent, having a pH dependant solubility. Optimal administration compliance is reached by rapid oral dosage form disintegration, releasing taste masked micropellets into the mouth. The formulation must prevent drug release during approximately 3 to 5 minutes to avoid any bitter aftertaste.

Taste Masking Strategy

- CPS matrix pellets 50% drug load
- Taste masking Eudragit E



Taste Masked Micropellets Design

The drug was mixed/pre-wetted with suitable excipient in a Glatt High Shear Mixer, followed by pelletization (at high moisture level) in CPS unit and a final drying step. No inert starting beads were required. The process was performed in a Glatt CPS modified fluid bed rotor system, equipped with a conical shaped rotating disc and additional devices for directed particle movement. Defined particles densification is achieved by means of controlled particle movement.

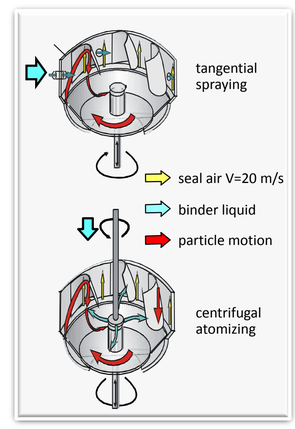


Figure 7: Representation of Glatt Direct Pelletizing System, CPS Technology™.

Micropellets Evaluation

Micropellets shape was evaluated by Light Microscopy. The taste masking of the designed micropellets was assessed by *in vitro* biorelevant dissolution performance in simulated saliva at pH 7.4. The investigated time frame of 3-5 min was correlated to a lag time between the dosage form disintegration and the micropellets swallowing. Decreased drug release in simulated saliva leads to a significantly reduced amount of drug available for taste perception.

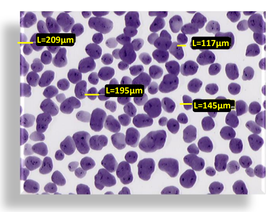


Figure 8: Light Microscopy picture of taste masked CPS micropellets.

Homogeneous and round taste masked micropellets are observed in Light Microscopy picture (Figure 8). Micropellets exhibiting suitable size for oral administration (< 350 µm) were successfully manufactured.

The drug release in simulated saliva was significantly decreased with Eudragit E coated CPS micropellets (Figure 9). *In vitro* data suggested that no astringency could be detected by the taste buds, as the drug solubilised is kept below taste threshold.

Figure 9: Dissolution performances of pure drug, 50% drug load CPS micropellets and taste masked micropellets in 5 ml simulated saliva pH 7.4.

CONCLUSION

The methods most commonly involved for achieving taste masking often fail in novel oral drug delivery systems. More sophisticated strategies using Glatt MicroPx and CPS micro pelletization technologies, associated with HS Wurster coating process, offer a solution for effective taste masking of highly bad tasting drug substances.