Olanzapine orodispersible films: how preparation methods can impact on the biopharmaceutic performances

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INTRODUCTION

The design of drug products to be administered to pediatric patients should consider the presentation of the treatment to the end-user (i.e., patient, caregiver, healthcare provider) which includes the dosage form, formulation, dose, dosing frequency and packaging. Patient-centric drug products would also avoid the practice of manipulating tablets or capsules which may compromise the dose accuracy, patient safety and treatment efficacy. In this context, orodispersible films (ODF) have been reported to improve administration, compliance and medication adherence in patients having difficulties with swallowing [1]. The main ODF production processes can be referred to solvent-based or heating-based technologies. Alternatively, in the attempt to produce small batches or to compound personalized therapies, printing technologies have been proposed [2]. However, these processes can cause unintended drug phase transformations, which directly affect its dissolution rate and, therefore, biopharmaceutical performances. This work aimed to assess the relevance of the preparation process, namely solvent casting and hot-melt ram printing, on the biopharmaceutical performances of olanzapine orodispersible films (ODF) made of maltodextrins. Beside the clinical rationale, olanzapine (OLZ) was selected since it is subjected to polymorphism which impacts on its bioavailability [2]. OLZ was selected as model drug since it is also used off-label for treating pediatric diseases [3].

METHODS

An amount of 10 mg OLZ was loaded into 2×3 cm ODF prepared by solvent-casting and hot-melt ram-extrusion printing using maltodextrin DE 6 and glycerol as film forming material and plasticizer, respectively. X-ray diffraction and thermal analysis (i.e., DSC and TGA) were carried out to study the drug solid state. ODF were characterized in terms of thickness, stickiness, loss on drying. Moreover, disintegration time and the in vitro dissolution profiles were also evaluated in buffers mimicking pH values of different GI districts.

RESULTS

The adopted experimental conditions permitted to obtain ODF without visual defects, easy to handle with a thickness around 140 μm and 278 μm for cast and printing, respectively. Residual water content in ODF was in the 6-8% w/w range. All ODF disintegrated within 80 s, complying the Pharmacopeia specifications. Dissolution testing in 3 mL of artificial saliva at pH = 6.8 evidenced that cast and printed ODF released after 5 min about 2% and 100%, respectively. At higher volume, a yellow precipitate was formed after disintegration of the cast ODF. At pH = 1.2, the t_{85}% for cast ODF was reached after about 20 min and only the 90% OLZ was dissolved increasing the pH value to 6.8. These differences were explained by DSC, TGA and X-ray diffraction data which demonstrated that the casting method, including the preparation of an aqueous slurry, favors the conversion from Form I to a hydrated one, which could be responsible of this anomalous behavior. Extruded ODF resulted physically stable after 30 months

CONCLUSIONS

The understanding of possible relations between formulation and process variables (e.g., solvents, moisture, and temperature) with solid-state characteristics needs to be addressed also to make the compounding of personalized therapy for pediatric patients a reality. Regarding the loading of OLZ in ODF, the main criticism is the possible conversion from the anhydrous towards hydrated forms with concomitant decrease in solubility. Based on these data hot-melt ram extrusion printing seems to be promising since it limits the exposure of OLZ to stress-factors (i.e., water and temperature) which can trigger solid-state modifications.

REFERENCES

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