Innovative Formulation Strategies for orodispersible Loratadine Dosage Forms

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Introduction

Loratadine, an antihistamine medication, is widely prescribed for the treatment of various allergic conditions in pediatric patients because of its efficacy in the treatment of allergic disorders. Considering the unique physiological and psychological needs of children, kids-friendly orodispersible mini-tablets and films were developed. The API Loratadine is classified as a class II drug based on the Biopharmaceutical Classification System due to its low water solubility [1]. To increase the low solubility, it was aimed to produce orodispersible films by hot melt extrusion - a solvent-free process which, through mixing and heating, disperses the API with a matrix polymer, helping to increase the dissolution rate and improving the solubility. Loratadine's high thermal stability makes it suitable for this technology. Due to its intensively bitter taste, the high-intensity sweetener neotame was added to the formulation for taste optimization and enhanced acceptability by the patients.

Methods

Orodispersible mini-tablet (ODMT, 3 mm): produced by wet granulation with low shear mixer (planetary mixer N50/ Hobart with peristaltic pump Pump Drive 5201/ Heidolph™; speed 10 rpm, flow rate 10 g/min; drying process in vacuum oven (Thermicon/Heraeus; vacuum: 200 mbar, temp.: 50°C, drying time: 20 h). A free-fall mixer is used for the tableting mixture (Turbula® T2A/Willy A. Bachofen AG; mixing time: 5 min, rotation speed: 47 rpm). For tableting, a single punch press is used (STYL'One Evo/MEDELPHARM; pressure: 1.7 kN, speed: 10%). The tablets are characterized by diameters, tensile strength, tablet hardness (MultiCheck ERWEKA, n=20), disintegration time (DISI4 BIOMATION; n=6) and dissolution profile of API in simulated gastric fluid, pH 1.2 (SOTAX Xtend™ dissolution tester; n=6).

Formulation: Loradatine (50% w/w), mannitol-based ODT excipient system (46% w/w), magnesium stearate (1% w/w), polyvinyl alcohol (PVA) 4-88 (0.9% w/w), SiO_2 (0.5% w/w) and neotame (0.06 % w/w).

Orodispersible film (ODF): produced by hot melt extrusion technology (twin-screw extruder connected with sheet take-off unit/Thermo Scientific is used, extruding temp.: 190 °C, screw speed: 500 rpm). The pre-mixed powder of Loratadine and particle-engineered PVA 4-88 (Parteck® MXP 4-88 Polymer) is continuously fed into the Thermo Process HYG extruder feeder by using the twin-screw feeder, and triacetin is continuously fed into the extruder by peristaltic pump after the feeding port of powder feeding. Set up the feeding speed of solid material (mixture of PVA 4-88 and Loratadine) and liquid material (triacetin) at about 9:1. Tools are used to cut the cooled film into different shapes and sizes to achieve the desired film weight. The films are characterized by diameters, weight, disintegration time in 900 ml water (ERWEKA ZT 322; n=3) and dissolution profile of API in 500 ml simulated saliva (pH 6.7) with 0.6% polysorbate 80 (ERWEKA DT 828); n=3) at 37°C (USP Type II).

Formulation: Loratadine (7.5% w/w), PVA 4-88 (82.47% w/w), triacetin (10% w/w), neotame (0.03% w/w)

Results

Robust and hard ODMTs are obtained (figure 1). The measured average disintegration time of 78 ± 7 s in DI water is meeting the requirements of Ph Eur that specifies a disintegration time of below 180 s for ODTs (table 1). However, it has to be noted that US FDA guidelines recommend that ODTs should disintegrate within 30 s or less. A fast drug release is achieved in simulated gastric fluid which is comparable with the release time of a commercial drug product (figures 2a and 2b).

Figure 1: Loratadine mini-tablets (3 mm)

Parameters	Ø 3 mm tablet ODT + 1 % MST
Tablet weight [mg]	10.3
Diameter [mm]	3.0
Height [mm]	1.2
Tablet hardness [N]	19
Tensile Strength [MPa]	3.20
Loratadine [mg]	**5**
Disintegration time* [s]	**78**

***Limit Ph Eur: < 180 s, USP: < 30 s**

Table 1: Galenical properties of orodispersible mini-tablets

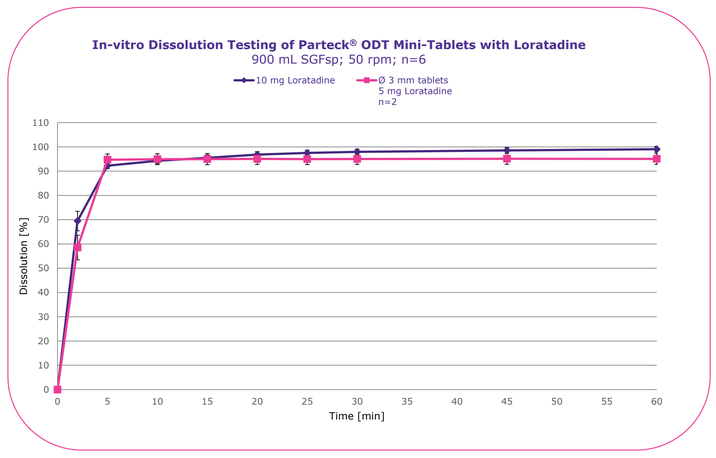

Figure 2a: Dissolution profile of 5 mg Loratadine mini-tablet vs. pure API

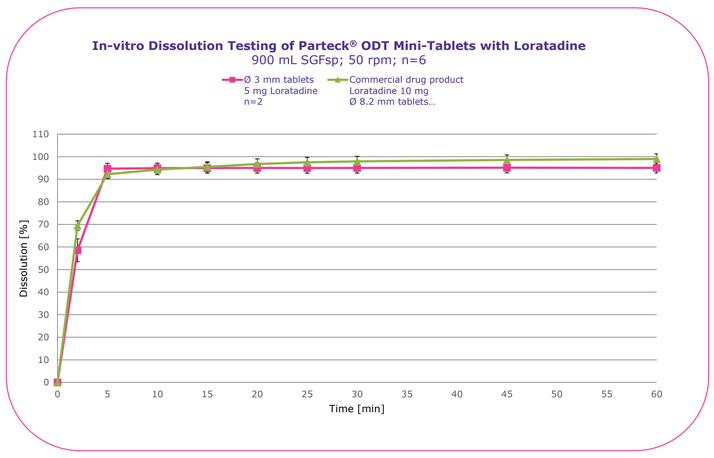

Figure 2b: Dissolution profile of 5 mg Loratadine mini-tablet vs. commercial drug product

For the ODFs, a smooth processibility is recognized, and homogeneous and fast integrating films are obtained with a disintegration time of 35±2 s, 33±1 s and 45± 6 s (table 2). As the disintegration time is not specified for ODFs, the disintegration time requirements for ODTs (see above) might be adopted for ODFs. The developed ODFs show a fast drug release profile with enhanced solubility of the API Loratadine in simulated saliva (pH 6.7) - faster than pure API (figures 3a and 3b).

Parameters	2.5 mg API		5.0 mg API
Thickness [µm]	60-70		70-80
Width [mm]	24		24
LOD [%]	1.31		1.31
Shape	**Heart**	**Balloon**	**Rectangle**
Size [cm]	**W: 2.4 H: 1.8**	**W: 1.9 H: 2.3**	**W: 1.9 L: 2.9**
Film weight [mg]	**34**	**34**	**66**
Strength [mg API]	**2.5**	**2.5**	**5.0**
Disintegration time* [s]	**35**	**33**	**45**

*Note: in 900 ml water, clamping top center of the film with slow swing, **limit Ph Eur:** < 180 s (ODTs)
Small scale test run

Single layers:
W: width
H: height
L: length

Table 2: Galenical properties of orodispersible Loratadine films

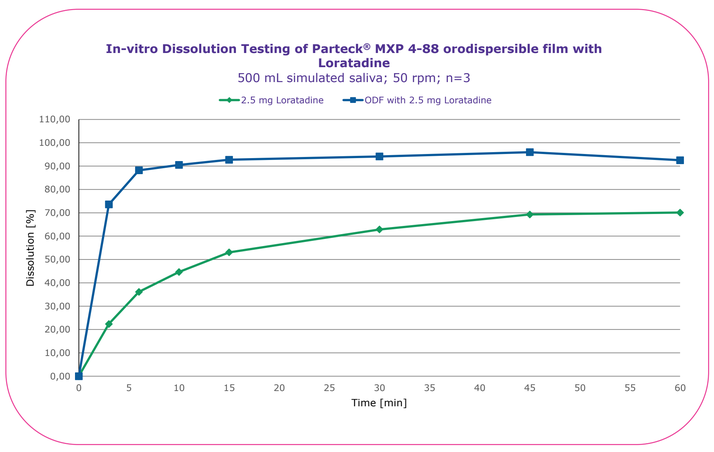

Figure 3a: Dissolution profile of 2.5 mg Loratadine ODF vs. pure API

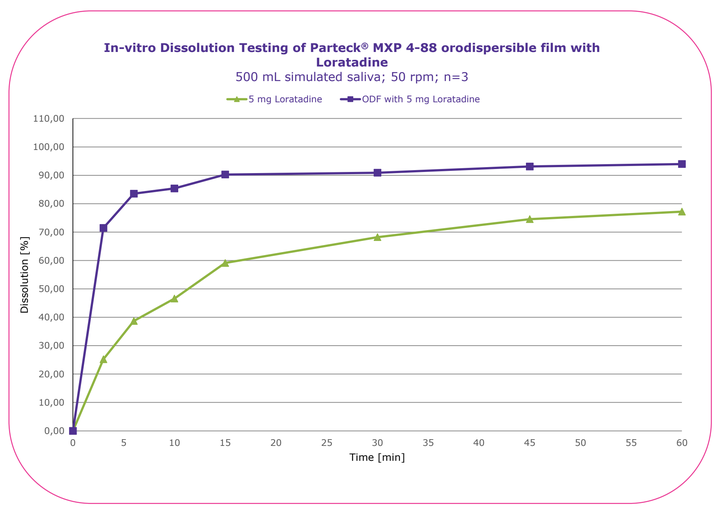

Figure 3b: Dissolution profile of 5 mg Loratadine ODF vs. pure API

Summary

The obtained ODMTs and ODFs meet the requirements of Ph Eur for the disintegration time of ODTs and fast drug release is achieved for both dosage forms. A method to quantify the effectiveness of the taste masking by neotame (e.g. with an electronic tongue) is under further evaluation.

ODFs of the drug Loratadine may offer enhanced therapeutic benefits for children. Due to their potential for age-tailored API doses by varying thickness and shapes, they offer an interesting potential for personalized and age-appropriate dosages.

References

1. Classification of loratadine based on biopharmaceutics drug classification concept and possible in vitro-in vivo correlation, Khan et al., Biol. Pharm. Bull 27(10) 1630-1635 (2004)