European Journal of Pharmaceutics and Biopharmaceutics 88 (2014) 455–461

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Lean production of taste improved lipidic sodium benzoate formulations

C. Eckert, M. Pein, J. Breitkreutz *

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine University Duesseldorf, Germany

ARTICLE INFO

Article history:
Received 21 January 2014
Accepted in revised form 7 May 2014
Available online 21 May 2014

Keywords:
Melt granulation
Hard fat
Taste masking
Electronic tongue
Sodium benzoate
Orphan drug
Food interaction

ABSTRACT

Sodium benzoate is a highly soluble orphan drug with unpleasant taste and high daily dose. The aim of this study was to develop a child appropriate, individually dosable, and taste masked dosage form utilizing lipids in melt granulation process and tableting. A saliva resistant coated lipid granule produced by extrusion served as reference product. Low melting hard fat was found to be appropriate as lipid binder in high-shear granulation. The resulting granules were compressed to minitablets without addition of other excipients. Compression to 2 mm minitablets decreased the dissolved API amount within the first 2 min of dissolution from 33% to 23%. The Euclidean distances, calculated from electronic tongue measurements, were reduced, indicating an improved taste. The reference product showed a lag time in dissolution, which is desirable for taste masking. Although a lag time was not achieved for the lipidic minitablets, drug release in various food materials was reduced to 2%, assuming a suitable taste masking for oral sodium benzoate administration.

1. Introduction

Sodium benzoate is commonly known as a preservative, but it is also an orphan drug used for the treatment of non-ketotic hyperglycinemia, NKH [1,2], and urea cycle disorders (UCD) [3]. NKH is caused by a disorder in the glycine cleavage system inducing too high glycine levels in plasma, urine, and cerebrospinal fluid. The disease mainly affects small children [4], who suffer from lethargy, coma, seizures, apnea, and mental retardation. The glycine levels can be reduced by the intake of benzoate: after activation by coenzyme A, it binds glycine, thus forming hippurate. After separation of coenzyme A, it is eliminated by the kidney. In UCD, sodium benzoate is used with co-administered sodium phenylbutyrate, implemented in the most recently introduced taste masked Pheburane [5].

For the development of a child appropriate dosage form containing sodium benzoate, the following requirements should be considered: the drug loading should be high, as the daily dose goes up to 750 mg per kilogram bodyweight per day [1]. Moreover, an individually dosable formulation is required on basis of the bodyweight dependency and different severities of the disease. A taste masking is desirable, owing to the unpleasant taste of the API (active pharmaceutical ingredient).

A licensed formulation containing sodium benzoate as API was developed by the company Ethicare (Haltern, Germany). It is produced with sodium benzoate and hard fat (80/20 w/w) in an extrusion process; afterward the extrudates are rounded in a spheronization step. A saliva resistant coating with a copolymer based on dimethylaminoethylmethacrylate (Eudragit® E 100) is applied for taste masking properties [6]. The coating step in particular is time consuming and has high energy expenditure. Eudragit® E100 is a non-biodegradable polymer, with an acceptable daily intake of 13.3 mg/kg/d for children [7]. Taste masking of unpleasant APIs is desirable for child-appropriate dosage forms [8], as an unpleasant taste may have a negative impact on the compliance [9,10].

Lipids have already successfully been applied for taste masking approaches [11,12]. They are able to cover the API crystals and avoid the contact between unpleasant tasting API and taste receptor so that the bad taste is not recognized by the patient any more. Furthermore, it should be noted that lipids do not have any health risks and, as parts of pharmaceuticals, no daily intake limit.

Lipids can be used as binders in a melt granulation process, which represents a suitable method for the production of small multiparticular dosage forms like pellets or granules. Furthermore, the drug loading can be high as the required binder amount is usually less than 20% [13–15]. In melt granulation processes the agglomeration of single particles is obtained by the addition of a solid binder, which melts or softens during the process [16].

Abbreviations: API, active pharmaceutical ingredient; ED, Euclidean distance; HPLC, high performance liquid chromatography; NKH, non-ketotic hyperglycinemia; UCD, urea cycle disorders.

* Corresponding author. Tel.: +49 2118114220; fax: +49 2118114251.
E-mail address: joerg.breitkreutz@uni-duesseldorf.de (J. Breitkreutz).

http://dx.doi.org/10.1016/j.ejpb.2014.05.013
0939-6411/

The aim of this work was to develop a child-appropriate, taste masked drug formulation without the use of functional coatings. Within this study, lipid granules should be produced by melt granulation with hard fat as a binder in a high shear mixer. In order to further improve the taste and to obtain homogeneous drug-loaded particles, these granules should be subsequently compressed to minitablets. The formulations were compared to the saliva-resistant coated lipid granule regarding dissolution behavior, taste masking properties, and drug release in food and in dissolution testing according to pharmacopoeias.

2. Materials and methods

2.1. Melt granulation process

Powdered crystalline sodium benzoate was provided from Ethicare (Haltern, Germany), powdered Witocan®42/44 from Cremer Oleo (Hamburg, Germany). Witocan®42/44 is a hard fat registered as food ingredient and complies with Ph. Eur. quality [6]. It is a semisynthetic lipid based on coconut and palm kernel oil containing more than 90% triglycerides with long-chain fatty acids (C12–C18). Both excipients were deagglomerated by sieving before further processing (mesh 1000 μm).

Melt granules were produced in a 2 L high shear mixer (P-VAC 10) from Diosna (Osnabrueck, Germany). Compositions and the labeling of the granule batches are given in Table 1. Sodium benzoate and Witocan®42/44 were blended for 10 min at an impeller speed of 200 rpm. The temperature of the heating jacket was adjusted to 38 °C. After blending, the impeller speed was increased to 800 rpm. When a power value of 440 W was achieved, the granulation was stopped. The granules were removed from the high shear granulator and cooled down to room temperature. For the production of the granule batches W25/10, W25/12.5, and W25/15 (Table 1), granules consisting of 75% API and 25% lipid binder were produced as described before. When 440 W were reached, the lid of the mixer was opened and 10–15 g Witocan®42/44 was manually sprinkled on the warm granule surfaces. The lid was closed again and the stirrer was turned on for 10 s with an impeller speed of 100 rpm.

2.2. Powder and granule analysis

The particle sizes of the unprocessed powders were investigated using laser light diffraction (Helos, Sympatec, Clausthal-Zellerfeld, Germany) equipped with a lens with a detection range between 1.8 and 350 μm and a pressure of 3 bar.

Differential scanning calorimetry was carried out using a DSC 1 Star (Mettler Toledo, Giessen, Germany) at a heating rate of 10 K/min with samples of approximately 3 mg.

X-ray powder diffraction was performed with an X'Pert MDP PW3040/00 DY 653 diffractometer system (PANalytical, Almelo, Netherlands) equipped with a 16 mm sample holder in the reflection mode. Samples were scanned from 10° to 50°.

Table 1
Composition of investigated batches.

Batch	Previous formulation (100%)		Subsequent treatment
	API amount (%)	Witocan® W42/44 (%)	Lipid addition (g)
W25	75	25	/
W30	70	30	/
W25/10	75	25	10
W25/12.5	75	25	12.5
W25/15	75	25	15

After granulation, lumps bigger than 3150 μm were separated by sieving and the size distribution of granules was analyzed using the Camsizer XT free fall tool (Retsch Technology, Haan, Germany).

Flowability was tested with granules of 315–630 μm according to Ph. Eur. using a funnel and measuring the time a sample of 50 g required to flow through. Furthermore the bulk and tapped density were measured to calculate the Hausner ratio.

Scanning electron micrographs were taken using a Phenom G2 Pro (Phenom World, Eindhoven, Netherlands) without previous sputtering procedure.

2.3. Compression to minitablets

Granules with a particle size from 315 to 630 μm were used for the production of minitablets. Before tableting 5% magnesium stearate (Merck, Darmstadt, Germany) was added to avoid breaking of the tablet when passing the wiper. The components were blended for 2 min in a turbula mixer. Tablets were compressed using a rotary press (Pressima, IMA Kilian, Cologne, Germany) with a 19-fold 2 mm minitablet punch (Ritter-Pharma Technik, Stapelfeld, Germany) and applying a compression force of 10 kN.

2.4. Minitablet analysis

For testing the friability, 1 g minitablets were weighed into a glass container (2.5 cm diameter, 5 cm high), which was clamped into an overhead shaker (Heidolph, Schwabach, Germany). It fulfilled a two-dimensional rotation with 25 rpm. The rotation was stopped after 100 turns. Minitablets were freed from dust by air sieving (mesh size 125 μm, Hosokawa Alpine, Augsburg, Germany) and the weight was measured again.

2.5. Dissolution

Dissolution was performed at 37 °C using the Ph. Eur. basket method (DT 700, Erweka, Heusenstamm, Germany) in demineralized water with 150 rpm ($n = 6$). The released amount (300 mg sample) was detected using Lambda 25 (Perkin Elmer, Waltham, USA) spectrometer at 273 nm.

2.6. Electronic tongue measurements

Granules and minitablets were investigated utilizing two electronic tongues: the taste sensing system TS5000Z (Insent, Atsugi-Shi, Japan) and the αAstree electronic tongue (Alpha MOS, Toulouse, France). The Insent taste sensing system was equipped with eight lipid membrane sensors (SB2AAE, SB2CT0, SB2CA0, SB2C00, SB2AE1, SB2AN0, SB2AC0, SB2BT0), the αAstree electronic tongue with seven cross selective sensors (ZZ, GA, DA, AB, CA, BB, JE). Measurement procedure and preparations of the measurement solutions were carried out according to Woertz et al. [17] for the Insent taste sensing systems and according to Pein et al. [18] for the αAstree electronic tongue.

Tests of linearity were performed using all Insent sensors with concentrations of 0.0005–250 mM of sodium benzoate in demineralized water, for the αAstree electronic tongue concentrations up to 100 mM were used. For testing the taste masking effect of the granules and minitablets, 900 mg sample was released over a predefined time (10–120 s) using a basket apparatus according to Ph. Eur. with 150 rpm in 900 ml demineralized water at a temperature of 37 °C. Data analysis was performed uni- and multi-variate using Simca-P+12.0.1 (Umetrics, Umea, Sweden).

Euclidean distances in a two dimensional PCA map were calculated between two data points P1(x_1/y_1) and P2(x_2/y_2) by the following equation: