Formulation, Preparation, and Evaluation of Novel Orally Disintegrating Tablets Containing Taste-Masked Naproxen Sodium Granules and Naratriptan Hydrochloride

ULRIKE STANGE,[1] CHRISTIAN FÜHRLING,[2] HENNING GIESELER[1,3]

[1]Freeze Drying Focus Group (FDFG), Division of Pharmaceutics, University of Erlangen, Erlangen 91058, Germany
[2]Niederbronner Pharmacy, Nürnberg 90491, Germany
[3]GILYOS GmbH, Würzburg 97076, Germany

Received 4 November 2013; revised 4 January 2014; accepted 24 January 2014

Published online 15 February 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23896

ABSTRACT: The purpose of this study was to develop and manufacture novel freeze-dried orally disintegrating tablets (ODTs) for migraine therapy containing taste-masked naproxen sodium and naratriptan hydrochloride. The formulation was optimized based on freeze-drying of sucrose solutions with different binders (hydroxyethylstarch, sodium alginate, methylcellulose, and gelatin) and varying amounts of Eudragit® E-coated naproxen sodium granules. Excellent product performance of the ODTs in terms of hardness and disintegration time (<10 s) independent of the mass of particles embedded was found for the solution consisting of sucrose and hydroxyethylstarch. Poloxamer 188, menthol flavor, naratriptan hydrochloride, and taste-masked naproxen sodium granules corresponding to 200 mg of naproxen were then added, and the final batches of ODTs for migraine therapy were produced. The ODTs were fully characterized, and subsequently stored for 1 month at room temperature and at 40°C. The amount of free naproxen sodium after freeze-drying and storage was below the threshold bitterness value, and the coating remained intact. Additionally, the particle size distribution of taste-masked granules was preserved, and more than 90 % naproxen sodium was released after 30 min. Naratriptan hydrochloride was dissolved immediately after disintegration, hence facilitating buccal absorption of the active pharmaceutical ingredient. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1233–1245, 2014

Keywords: orally disintegrating tablet; fast melting tablet; freeze drying/lyophilization; taste masking; excipients; oral drug delivery; formulation; microparticles; migraine

INTRODUCTION

Adapting dosage forms to meet the patients' needs is a very important aspect in pharmacotherapy. One outcome of these efforts was the development of orally disintegrating tablets (ODTs). ODTs have proven their ability to enhance patient compliance because they disintegrate in the mouth and there is no need to swallow a whole tablet.[1,2] Improved bioavailability was reported for formulations containing nimesulide,[3] selegiline,[4] hydrochlorothiazide,[5] valsartan,[6] or griseofulvin.[7] ODTs are therefore outstanding as a drug delivery dosage form, especially for geriatric and paediatric patients with problems swallowing, or for patients with migraine attacks accompanied by nausea.[2,8,9]

Orally disintegrating tablets can be prepared using a variety of technologies including freeze-drying, direct compression, and molding.[2] The key advantages of ODTs manufactured by freeze-drying are very fast disintegration, smooth mouthfeel, and low residue.[2,8] Incorporation of the active pharmaceutical ingredient (API) can be easily achieved by processing API solutions,[4,10] emulsions,[7,11] or suspensions.[3,6,12–14] Excipients are used to ensure sufficient mechanical strength and a low disintegration time in such tablets, and are classified as binders, fillers, or additives.[15,16] Each substance has several influences, for example, using gelatin as a binder increases the hardness of the ODTs with increasing concentration.[16,17] Increased binder concentration also leads to elevated tablet disintegration time.[6,13,17,18] Gelatin,[3,12,15–17,19] xanthan gum,[6,13,14] pectin,[6] cellulose derivatives,[13,20] carrageenan,[20] and povidone[20] have all been used as binders for freeze-dried ODTs. Fillers are used to cement the porous structure of the lyophilized matrix and positively influence tablet characteristics.[15–17] Various saccharides, polyols, and carbohydrates, including mannitol,[3,12,16] sorbitol,[3,6,12,16] maltodextrin,[13,14] lactose,[20] maltotriose,[17] and sucrose,[16] have been applied, and an increase in the mechanical strength of freeze-dried ODTs was evident after adding the fillers to binder solutions.[3,13,16,17] As an example, addition of moderate concentrations of mannitol was found to enhance tablet hardness (TH) while shortening disintegration time compared with a pure-binder solution.[3,16,17] New approaches employed amino acids as fillers in gelatin-based solutions to prepare freeze-dried ODTs.[15,19] Incorporating either alanine or glycine yielded the best results with regard to mechanical strength and disintegration time.[15]

However, it is not sufficient to achieve adequate mechanical properties and a low disintegration time—for many patients the taste of an ODT is of major importance.[21] Therefore, masking the unpleasant, possibly disgusting taste of APIs is vital to ensure patient compliance.[21] The most effective approach is the addition of sweeteners and flavors combined with physical taste masking that prevents the interaction of the drug substance with taste buds.[22,23] However, only incorporation of taste-masked APIs into ODTs prepared by direct

Correspondence to: Henning Gieseler (Telephone: +49-931-90705678; Fax: +49-931-90705679; E-mail: info@gilyos.com)

Journal of Pharmaceutical Sciences, Vol. 103, 1233–1245 (2014)

compression has been reported up to now.[23–30] Different methodologies have been used to achieve proper taste masking of APIs, including spray drying with Eudragit® E,[29,30] coating with hydroxypropylcellulose[28] or Eudragit® RL30-D,[24] and granulation or extrusion with different excipients and polymers.[23,26,27] However, these taste masking methods result in particles or granules that have to be incorporated into the tablet matrix. Thus, problems may arise during direct compression because of the low compactibility of coated drug particles, or because of the destruction of the film coating, leading to faster dissolution.[31–33] To prevent this, a new technology was invented by Kondo et al.[28] to ensure incorporation of the granules preferably in the core of ODTs made by direct compression.

In contrast to direct compression, freeze-drying is a gentle method free of compaction stresses for preparing ODTs containing coated particles. So far, no studies have described freeze-dried ODTs containing taste-masked particles or granules. Only one study is available dealing with incorporation of enteric coated, commercially available omeprazole pellets into a freeze-dried matrix consisting of gelatin, carrageenan, and alanine.[34] The lack of data is probably because of the observed loss in ODT hardness when insoluble APIs were dispersed in the excipient solution.[13,35] Furthermore, sedimentation has to be prevented by either keeping the particle size smaller than 50 μm, or by adding viscosity enhancing agents.[10,34] Finally, process conditions and formulation design need to ensure integrity of the coating during and after the freeze-drying process.

The purpose of this study was to develop a novel formulation for ODTs for migraine therapy, prepared by freeze-drying and containing a combination of naratriptan hydrochloride and naproxen sodium, the latter taste-masked by fluid-bed coating with Eudragit® E.[36] The taste-masked particles were successfully incorporated in a freeze-dried matrix along with naratriptan hydrochloride. Note that only two previous studies examined the formulation of an ODT for migraine therapy, prepared by direct compression and containing taste-masked sumatriptan succinate.[29,37] Nevertheless, the combination of a triptan and a nonsteroidal anti-inflammatory drug (NSAID) is more effective than the API alone, and a synergistic effect of both substances has been described,[38–41] with the result that the recurrence of migraine attacks could be reduced.[38,41] The authors conclude that the remarkable pharmacokinetic profile of the combination tablet is beneficial for migraine therapy.[40] Note that the medications applied in these published studies were conventional tablets.[38–40] However, most patients prefer ODTs to conventional tablets in migraine therapy.[9] Hence, a combination of the advantageous characteristics of a triptan/NSAID coadministration and the unique properties of an ODT seems highly appealing. Therefore, different formulations for freeze-dried ODTs were investigated in the scope of this study, and their ability to embed taste-masked naproxen sodium granules while maintaining optimum product characteristics was assessed. Sucrose was always used as a filler excipient, but the binder and the amount of coated particles were varied. TH, disintegration time, porosity, and appearance were evaluated. After optimizing the formulation, two individual batches of ODTs for migraine therapy containing taste-masked naproxen sodium granules and naratriptan hydrochloride were prepared. The tablets were fully characterized, and the integrity of the coating and the *in vitro* dissolution of the APIs were validated. Additionally, the particle size distribution of the taste-masked granules was determined before and after freeze-drying. The ODTs were stored for 1 month at both ambient conditions and at 40°C and subsequently reevaluated. This provided initial data about the stability of the ODTs, which is of major importance because it is likely that the freeze-dried matrix interacts with the Eudragit® E layer, possibly contributing to a loss in coating efficiency, especially at elevated temperatures.

MATERIAL AND METHODS

Material

Sucrose ≥99.5%, methylcellulose, sodium phosphate dibasic dodecahydrate, sodium phosphate tribasic dodecahydrate, and Hydranal®-Coulomat Ag-Oven (Karl Fischer Reagent) were purchased from Sigma–Aldrich Chemie GmbH (Steinheim, Germany). Sodium alginate was a gift from Fagron (Barsbüttel, Germany), and hydroxyethylstarch was kindly donated by Fresenius Kabi (Bad Homburg, Germany). Additionally, hydrochloric acid 37% (v/v) was purchased from Carl Roth (Karlsruhe, Germany), citric acid monohydrate from UD Chemie GmbH (Wörrstadt, Germany), poloxamer 188 from BASF SE (Ludwigshafen, Germany), menthol flavor from Firmenich (Kerpen, Germany), and polysorbate 80 from Caesar & Loretz GmbH (Hilden, Germany). Gelatin 80 and gelatin 250 blooms were donated by ITALGELATINE (Santa Vittoria d'Alba, Italy). Naratriptan hydrochloride was acquired from USP U.S. Pharmacopoeial Convention (Rockville, Maryland). Double-distilled water from an all-glass apparatus was used for preparation of the solutions. The sodium alginate and polysorbate 80 were Pharm. Eur. quality; all other reagents were of analytical grade. The filters used were 0.2 μm filter purchased from VWR International (Darmstadt, Germany). Blisters were produced on a RC800 blister machine (Rohrer & Collin AG, Möhlin, Switzerland) from PVC blister foil that was supplied by ac-Folien GmbH (Müllheim, Germany). The diameter of an individual blister mold was 22 mm.

Preparation of ODTs

Formulations

First, incorporation efficiency of the previously taste-masked naproxen sodium granules into the freeze-dried matrix was evaluated as a function of the type of binder. Note that the term incorporation efficiency is used to describe the ability of the different ODT formulations to sufficiently embed taste-masked naproxen sodium granules in the freeze-dried matrix. The taste masking of naproxen sodium granules by fluid-bed coating is described elsewhere.[36] The mass of granules required to obtain the target dose of 200 mg naproxen per ODT was in the range of 690–797 mg because of variations in the drug entrapment efficiency. The targeted load of naproxen sodium in the taste-masked granules was about 28% of the total mass of coated granules. This is because of the required masses of Eudragit® E and talcum to ensure sufficient taste masking.[36] However, the drug entrapment efficiency of all produced batches was between 96.34% and 120.12% of the desired amount of naproxen sodium. Only batches with a drug entrapment efficiency lower than 110% were applied in this study (97.57%–109.47%). It is important that the excipients added result in satisfactory properties of the freeze-dried ODTs, which are robust for different