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Development of orodispersible polymer films containing poorly water soluble active pharmaceutical ingredients with focus on different drug loadings and storage stability

Christina Woertz, Peter Kleinebudde*

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany

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ABSTRACT

The aim of this work was the development of orodispersible films containing different film forming polymers with focus on different drug loadings of two poorly water soluble APIs. Furthermore, physical stability of films was examined at two different storage conditions.

Loperamide hydrochloride (LPH) and ibuprofen (IBU) were used as model drugs. Hydroxypropyl methylcellulose (HPMC) and three different types of hydroxypropyl cellulose (HPC) were used as film forming polymers. Suspensions were characterized with respect to their viscosity and particle sedimentation and films regarding their content uniformity, thickness, mass and stability. Principal component analysis (PCA) was used to evaluate the correlation between the wet film thickness, dry film thickness, mass of the films, API fraction in the suspension and the viscosity of the suspensions.

The viscosity of the suspensions was dependent on the drug load and the polymer fraction but less so on the type of the utilized polymer. A correlation between the wet film thickness, the solid fraction and the mass of the films was established with an increase in mass by increasing the wet film thickness or the solid fraction. Films containing 50 mg IBU/6 cm^2 film led to acceptable films. Storage experiments did not lead to an AV below 15 in all cases after storage for three and six months, attributed to the storage conditions and the quality of the films. Nevertheless, the development and production of flexible and homogeneous films of LPH and IBU was successfully achieved.

1. Introduction

Orodispersible polymer films represent an advantageous dosage form especially for specific patient groups, e.g., geriatric or pediatric patients. Films can easily be administered without water and do not need to be swallowed because they dissolve quickly in the mouth.

Usually, the active pharmaceutical ingredient (API) is dissolved within the film. As the amount of poorly water soluble drugs is quite high and still raising it would be advantageous to include poorly water soluble drugs in film formulations. Some attempts have been made to include crystalline APIs in film formulations (Beck et al., 2013; Sievens-Figueroa et al., 2012). Beck et al. prepared griseofulvin suspensions with the liquid antisolvent precipitation technique to include drug particles in film formulations, whereas Sievens-Figueroa et al. used suspensions containing various Biopharmaceutical Classification System (BCS) class II drugs for the production of polymer films.

The loading of API which has been included in orodispersible films is limited to date. Low dose, high potent APIs in particular are suitable for film formulations, such as tadalafil or loperamide (Siebenand, 2010). The loading of the films is dependent on the size of the film. Products which are already marketed show drug loadings up to 25 mg/film (exact size/thickness unknown) (Hariharan and Bogue, 2009). It can therefore be deduced that these drug loads result in acceptable films. Nevertheless, a formulation with 62.5 mg of simethicone per film (size: 8.2 cm^2, 118.7 ± 0.5 μm, $n = 6$) was developed (Gas-X Thin Strips®, Novartis). The increase in drug load leads to increased brittleness and longer disintegration times. This is an important consideration, when selecting the drug and the dose per film.

Hydroxypropyl methylcellulose (HMPC) and hydroxypropyl cellulose (HPC) are polymers which are commonly used in film formulations (Dinge and Nagarsenker, 2008; Garsuch and Breitkreutz, 2010; Janßen et al., 2013; Kulkarni et al., 2010; Shimoda et al., 2009). For the film preparation, solvent casting method is a

* Corresponding author.

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common technique and was previously described by Garsuch and Breitkreutz (2009).

Formulations can be characterized regarding the thickness and mass of the film (Cao et al., 2009; Cilurzo et al., 2008), the content uniformity (Shimoda et al., 2009), the viscosity of the solution/suspension (Janßen et al., 2013) as well as the stability of the films (Kianfar et al., 2012; Shimoda et al., 2009).

The formulation of films containing the suspended API in its crystalline form implies some challenges as particle growth during storage due to partly dissolving and recrystallization might occur. Therefore, stability tests need to be carried out. Recommendations for stability tests for drug substances as well as new dosage forms are published in ICH Guideline Q1A (EMA, 2003).

In this study two different BCS class II drugs were incorporated into orodispersible films in crystalline form. Loperamide hydrochloride (LPH) is a drug substance for the treatment of diarrhea (van Rompay and Carter, 1990) whereas ibuprofen (IBU) is used as anti-inflammatory drug (Busson, 1986).

This work focuses on the preparation and characterization of orodispersible polymer films containing one of the above mentioned model drugs.

2. Materials and methods

2.1. Materials

IBU (Losan Pharma, Neuenburg, Germany) and LPH (Janssen, Beerse, Belgium) were used as poorly water-soluble model drugs. Different types of HPC (Klucel® JXF, Klucel® EXF, Klucel® LF, Ashland Aqualon, Wilmington, USA) and one type of HPMC (Pharmacoat® 606, Shin Etsu, Tokyo, Japan) were used as polymers. Arabic gum (Merck, Darmstadt, Germany) was used as thickener in some formulations. Glycerol 85% was used as plasticizer in different concentrations and distilled water as solvent.

Acetonitrile (VWR, Darmstadt, Germany) and ortho-phosphoric acid (Applichem, St. Louis, USA) were used for HPLC analysis for IBU. Additionally triethylamine (Sigma–Aldrich, St. Louis, USA) was used for HPLC analysis for LPH.

2.2. Methods

2.2.1. Preparation of suspensions

Suspensions were prepared using an Ultra Turrax® T 18 digital (IKA, Staufen, Germany) equipped with a dispersing tool (S18N19G) for 5 min at a speed of 25,000 rpm. First, the API was dispersed in a water/glycerol mixture and homogenized. Second, the polymer was added and the suspension was homogenized. The suspensions were then stirred on a magnetic stirrer until all air bubbles were removed.

2.2.2. Preparation of film formulations

Films were casted on a release liner (Mixture of polyamide/polyester, MEDIFLEX XM Type AMWL, Ghent, Belgium) on a film applicator (Model 509/1, Erichsen, Hemer, Germany) using a velocity of 6 mm/s. The resulting film had a size of 880 cm^2

Table 1
Composition of formulations (1–22: loperamide formulations; 23–40: ibuprofen formulations), coating height equal to wet film thickness of the films, size of the films: 6 cm^2.

	Polymer	Concentration (%)	Arabicgum concentration (%)	Plasticizer concentration (%)	Coating height (μm)	Shear rate (s^{-1})	API concentration (%)	mg/film
Loperamide								
1	HPMC (P606)	12.5	–	3.5	300	20	1.51	2
2	HPMC (P606)	15	–	3.5	300	20	1.51	2
3	HPMC (P606)	17.5	–	3.5	300	20	1.51	2
4	HPMC (P606)	15	2	3.5	300	20	1.51	2
5	HPMC (P606)	17.5	2	3.5	300	20	1.51	2
6	HPMC (P606)	12.5	2	3.5	300	20	0.38	0.5
7	HPMC (P606)	12.5	2	3.5	300	20	0.76	1
8	HPMC (P606)	12.5	2	3.5	300	20	1.51	2
9	HPMC (P606)	12.5	2	3.5	300	20	3.78	5
10	HPMC (P606)	12.5	2	3.5	300	20	7.56	10
11	HPC (JXF)	12	2	0.1	300	20	0.76	1
12	HPC (JXF)	12	2	0.1	300	20	1.51	2
13	HPC (JXF)	12	2	0.1	300	20	3.78	5
14	HPC (JXF)	12	2	0.1	300	20	7.56	10
Ibuprofen								
15	HPMC (P606)	12.5	–	3.5	300	20	18.91	25
16	HPMC (P606)	15	–	3.5	300	20	18.91	25
17	HPMC (P606)	10	2	3.5	300	20	18.91	25
18	HPMC (P606)	10	3	3.5	300	20	18.91	25
19	HPMC (P606)	12.5	3	3.5	300	20	18.91	25
20	HPC (LF)	14	–	1	500	12	11.35	25
21	HPMC (P606)	10	–	3.5	600	10	18.89	50
22	HPMC (P606)	10	–	3.5	600	10	15.56	50
23	HPMC (P606)	12.5	–	3.5	600	10	18.89	50
24	HPC (JXF)	10	–	0.1	600	10	18.89	50
25	HPC (JXF)	7.5	–	0.1	600	10	18.89	50
26	HPC (JXF)	7.5	2	0.1	600	10	18.89	50
27	HPC (LF)	7.5	–	0.1	600	10	18.89	50
28	HPC (LF)	7.5	2	0.1	600	10	18.89	50
29	HPC (EXF)	7.5	–	0.1	600	10	18.89	50
30	HPC (EXF)	7.5	–	0.1	600	10	14.69	50
31	HPC (EXF)	7.5	2	0.1	600	10	18.89	50
32	HPC (EXF)	7.5	2	0.1	600	10	15.56	50
33	HPMC (P606)	10	–	3.5	500	12	32.47	75
34	HPMC (P606)	10	–	3.5	600	10	37.8	100