DEVELOPMENT OF A TASTE-MASKED ORODISPERSIBLE FILM CONTAINING DIMENHYDRINATE

Maren Preis, Miriam Pein, Jörg Breitkreutz

Institute of Pharmaceutics and Biopharmaceutics, University of Düsseldorf, Germany
Phone: +49 211 8115693, Fax: +49 211 8114251, email: maren.preis@uni-duesseldorf.de

Abstract

Orodispersible dosage forms are promising new approaches for drug delivery. They enable an easy application, as there is no need to drink high amounts of liquids or swallow large solid dosage forms. The aim of the study was to develop an orodispersible film (ODF) as an alternative to tablets, syrups or suppositories for the treatment of vomiting and nausea, especially for the paediatric population. Formulations were investigated by x-ray diffraction, scanning electron and polarized light microscopy. Disintegration time of the films was determined by two different methods. Additionally, two commercially available electronic taste sensing systems (electronic tongues) were used to investigate the applied taste-masking strategies. Different excipients enhancing the solubility of dimenhydrinate were investigated to avoid recrystallization in the film. Furthermore, they were shown to improve the taste attributes of the formulation by interacting with the drug substance. Results obtained from x-ray-diffraction and polarized light microscopy showed no recrystallization of dimenhydrinate in the formulation when cyclodextrin or maltodextrin were used as solubilizing agent. All ODFs disintegrated in an appropriate time (< 120 s) depending on the characterization method. In order to get taste information, the dimenhydrinate formulations were analytically compared to pure drug and drug-free formulations by the electronic tongues. Results obtained from both systems are comparable, but can also be used complementary. Taste masking effects could be detected by both electronic tongues. Merging data of both systems by multivariate data analysis showed improved discrimination between different drug formulations. It was possible to develop an ODF of dimenhydrinate that is fast disintegrating even in small volumes of liquid. Non-human taste assessment by two electronic tongues was successfully performed.

Keywords

Orodispersible film, orally disintegrating dosage form, taste-masking, electronic taste sensing, electronic tongues, dimenhydrinate, cyclodextrin, maltodextrin, solubility, solvent casting

1. Introduction

Orally disintegrating dosage forms are promising new approaches to improve and simplify drug administration. The development of orodispersible films (ODF) containing dimenhydrinate offers an alternative to syrups and suppositories for the treatment of vomiting and nausea. Orodispersible formulations are beneficial especially for the paediatric but also for the geriatric population as swallowing high volumes of liquids can be omitted [1]. Furthermore, risk of choking on this new dosage form is minimized due to its possible adhesion to the oral mucosa and its fast disintegration. In this study different excipients were investigated which, in first place, are known for taste masking effects and additionally enhance the solubility of the poorly water-soluble dimenhydrinate. Hence, recrystallization in the films may be prevented [2, 3]. Two commercially available electronic taste sensing systems were used and obtained data were treated with multivariate analysis [4].

2. Materials and Methods

The following materials were used: Dimenhydrinate (Pharma Roth, Emmerthal, Germany), Captisol® (sulfobutylether-ß-cyclodextrin, Cydex, Kansas, USA), Lycoat® RS 720 (modified pea starch polymer), Kleptose® HPB oral grade (hydroxypropyl-ß-cyclodextrin, HP-ß-CD) and Kleptose® linecaps 17 (high amylose content maltodextrin) - all provided by Roquette (Lestrem, France), coloring agent E124 and glycerinum anhydricum (Caesar&Loretz, Hilden, Germany).

Sample preparation: Cyclodextrin and maltodextrin formulations were premixed with dimenhydrinate in aqueous solution (1:1 molar ratio) and stirred for 24 hours. Subsequently, polymer, plasticizer and coloring agent were added and films were prepared by solvent casting method (Erichsen film applicator, Erichsen, Hemer, Germany) at the calculated thickness (Eq. 1). Drug-free films were prepared accordingly and casted at the same thickness as the drug-loaded films. They were dried at room temperature for 24 hours and cut into rectangular pieces (1.5 cm x 2 cm; drug content per film: 5 mg). Film thickness was determined by a micrometer screw (Mituyo, Neuss, Germany). Composition of films is shown in table 1.

Table 1: Dimenhydrinate and drug-free formulations

	D	P	DCA	PCA	DCD	PCD	DCDS	PCDS	DMD	PMD	DS	PS
Dimenhydrinate	x	-	x	-	x	-	x	-	x	-	x	-
HP-ß-CD	-	-	-	-	x	x	x	x	-	-	-	-
Captisol ®	-	-	x	x		-	-	-	-	-	-	-
Maltodextrin	-	-	-	-	-	-	-	-	x	x	-	-
Saccharin sodium	-	-	-	-	-	-	x	x	-	-	x	x
Film base:	Lycoat RS 720, ethanol & glycerol											

Equation 1: Calculation of casting thickness

$$Eq.1: h[\mu m] = \frac{m(Batch)[g] * m(desired\ API\ p.Patch)[g] * 10000}{\rho(Batch)\left[\frac{g}{cm^3}\right] * m(API)[g] * A(Film)[cm^2]} + \mathrm{f}$$

Drug Content: Films were dissolved in 100.0 ml of 0.1 M hydrochloric acid and dimenhydrinate content was measured by UV spectroscopy (Spekol 1200, Analytik Jena, Jena, Germany) at 277 nm.

Disintegration: Methods were modified for small size films from literature [5].

Method 1: one film was placed onto a small glas beaker. One drop (0.2 ml) of distilled water was placed on the film. Time till film broke was measured.

Method 2: one film was placed in a petri dish. After adding two milliliters of distilled water, the petri dish has been shaked constantly. Time till patch disintegrated was measured.

Structure analysis: Crystal structure was investigated by x-ray diffraction (X'pert-MPD, Panalytical, Almedo, Netherlands) and polarized light microscopy (Leica, Leica Microsystems Q500/550, Wetzlar, Germany).

Scanning electron microscopy: Gold sputtering was performed by Agar manual Sputter Coater B7340 (Agar scientific Ltd., Stasnded, Essex, UK) and scanning electron microscopy (Leo 1430 VP, Leo Elektron Microscopy, Cambridge, UK) was used for imaging.

Electronic Taste Sensing: Two commercially available systems were used: TS-5000Z (Insent, Atsugi-Chi, Japan) equipped with seven lipid membrane sensors corresponding to human taste attributes (bitter, salty, sour, umami and astringent) and αAstree (Alphamos, Toulouse, France) equipped with seven ChemFET-sensors for pharmaceutical use (ZZ, AB, BA, BB, CA, DA, JE), which are cross-selective [2]. 20 ODFs were dissolved in 100.0 ml distilled water (corresponding to one dose in 5 ml). All samples were measured in triplicates. Measurements by Insent system were performed as recommended by the company. αAstree measurement setup has been changed after validating different modes to improve repeatability [6]. Principal component analysis was performed by multivariate statistic program Simca-P+V12 (Umetrics, Sweden).

3. Results and Discussion

Properties of the developed ODFs are shown in table 2. Mean disintegration times for all formulations varied between 10.87 s and 41.73 s. Disintegration behavior varied depending on film thickness and weight. Disintegration method 1 using only a drop of water resulted in longer disintegration times than those obtained by method 2, where two milliliters of water were used. Furthermore, method 2 is more dynamic due to the slight shaking of the petri dish. Nevertheless, disintegration time of all films are in an acceptable range (< 180 s) according to orodispersible tablets [7]. It has been observed that films became very sticky immediately after first water contact. Variation of drug content was acceptable for all formulations, even if the labelled amount of dimenhydrinate was not achieved in all formulations. The low standard deviations lead to the conclusion that drug was homogeneously distributed in the formulations.

Table 2. Properties of film formulations: thickness, weight, drug content and disintegration time (all values ± standard deviation)

	D	P	DCA	PCA	DCD	PCD	DCDS	PCDS	DMD	PMD	DS	PS
Thickness [µm]	143.40	136.60	114.70	116.00	158.00	142.40	171.20	152.70	125.00	119.40	156.60	127.50
	7.23	7.03	3.23	6.65	3.40	25.35	7.48	6.65	2.31	9.36	11.35	7.62
Weight [mg]	59.38	55.56	50.46	51.19	64.75	66.82	71.90	67.13	55.33	52.19	64.86	53.35
	2.26	1.65	1.76	3.26	1.14	2.72	2.98	5.17	2.57	3.30	3.90	2.74
Drug Content [mg]	4.74	-	5.22	-	4.70	-	5.62	-	5.01	-	5.46	-
	0.13	-	0.05	-	0.08	-	0.13	-	0.05	-	0.35	-
Disintegration [s]	35.47	49.02	27.42	35.97	117.85	62.03	104.41	78.03	41.06	31.72	74.67	84.97
Method 1	7.81	5.89	8.58	9.35	9.27	17.01	8.18	8.15	10.58	5.95	20.07	15.68
Disintegration [s]	29.07	20.97	11.27	10.87	41.73	30.57	36.57	35.93	15.47	12.87	26.37	20.47
Method 2	4.83	1.70	1.10	1.70	5.46	3.44	4.05	3.42	0.51	0.45	2.97	3.59

Thickness, Weight, Drug Content (n=10); Disintegration (n=3)

Crystal reflexes were only found for cyclodextrin and maltodextrin free films, respectively, indicating that drug solubility enhancement was given by these excipients not only during preparation in solution but also in solid state when films were dried and water was almost completely evaporated. Signal intensity was low, which can be explained by the low dose of the formulation and detection limits of the x-ray system (Fig. 3).

After drying, films containing neither cyclodextrin nor maltodextrin appeared opaque, whereas all other formulations were transparent. Polarized light microscopy showed crystal growth in formulation D and DS (Fig. 1). Surface images of a drug-loaded and a drug-free formulation obtained from scanning electron microscopy showed crystal growth on upper side (Fig. 2).

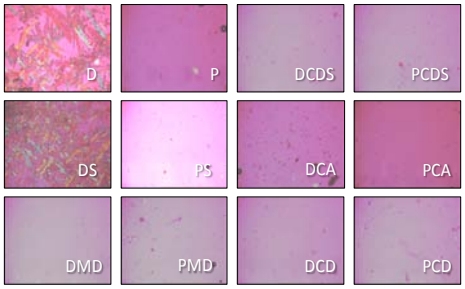


Fig. 1: Polarized light microscopy: pictures of drug-free and drug-loaded films, abbreviations: see table 1.

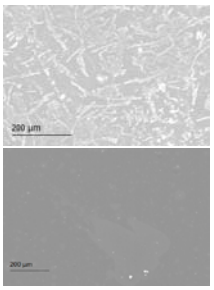


Fig. 2: SEM surface images of drug-loaded (top) and drug-free (bottom) formulation

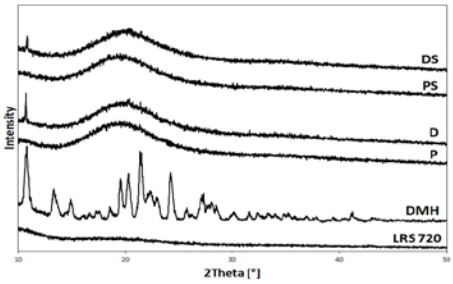
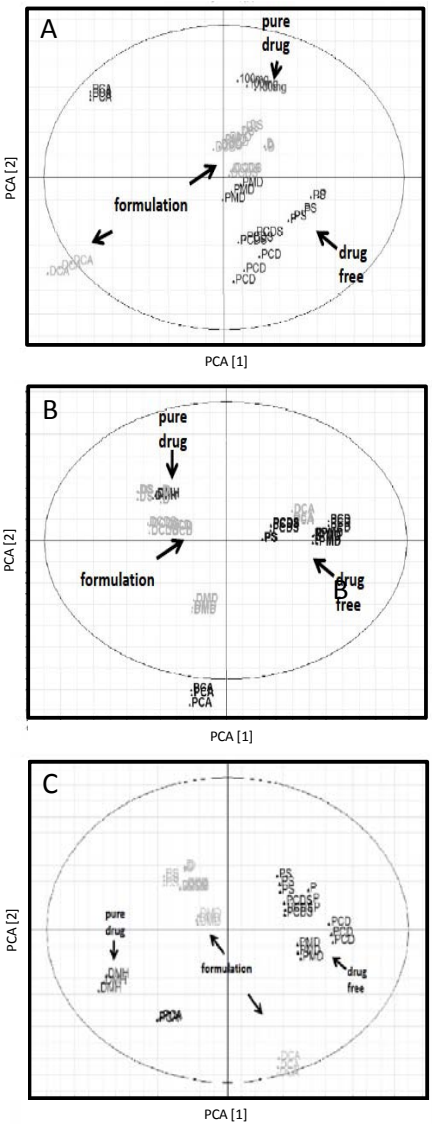


Fig. 3: X-ray pattern of polymer (LRS 720), pure drug (DMH), drug-free (P and PS) and drug-loaded formulation (D and DS).

Taste prediction by electronic taste sensing systems:



Comparative investigations of two different electronic taste sensing systems exhibited similar results in formulation testing. Both systems were able to distinguish between drug-free and drug-loaded formulations in principal component analysis (Fig. 4A+B). Captisol® formulation (DCA) has been detected particularly by both systems. Insent system could not detect a difference between Captisol® formulations and drug-free formulations containing other added excipients, whereas αAstree also detected differences between Captisol® and HP-ß-CD and maltodextrin formulations, respectively. Regarding the longest distance in principal component analysis between pure drug and formulation, taste masking has been most successful for Captisol® formulations. This result has been confirmed by both systems. A taste masking effect of the maltodextrin was also detectable by Insent, whereas αAstree was able to distinguish between pure drug and non-taste masked formulations. Therefore, influences of the film forming polymer could be shown by αAstree electronic tongue only. Combining the sensor responses of Insent and αAstree in multivariate data analysis showed improved discrimination between formulation, drug-free formulation and pure drug substance (Fig. 4C).

Fig. 4:

A: Principal component analysis of αAstree system. All seven sensors included (n=3) - R^2[PC 1] = 0.51 / R^2[PC 2] = 0.24

B: Principal component analysis of Insent system. All seven sensors included (n=3) - R^2[PC 1] = 0.64 / R^2[PC 2] = 0.23

C: Principal component analysis of Insent and αAstree systems. All 14 sensors included (n=3) - R^2[PC 1] = 0.45 / R^2[PC 2] = 0.24

4. Conclusions

Captisol®, HP-ß-CD (Kleptose®HPB oral grade) and the maltodextrin (Kleptose®linecaps 17) were able to improve the solubility of dimenhydrinate and could prevent the recrystallization of the drug substance in solid state of the film. Furthermore, solubility enhancers can be used as excipients for orodispersible films not least because they ensured a uniform distribution of the drug in the film by avoiding irregular crystal growth and improved the taste of these orodispersible formulations.
A non-human taste assessment by electronic taste sensing systems was successfully perfomed. As the drug is released in the oral cavity, a bad taste could worsen the patient's compliance especially when considering children. Hence, electronic tongues are able to distinguish between formulations, pure bad tasting drug and its non-taste-masked formulations. Therefore, a successful taste masking can be assumed, when formulations are displayed close to drug-free, good tasting, comparative formulations.
It was possible to compare data from two electronic taste sensing systems. Furthermore, data merge of sensor responses gave even more information on formulation. Therefore, combining information of these two systems could be a new tool in formulation development. Nevertheless, the use of electronic taste sensing systems in orodispersible dosage form development is a new approach to confirm a successful taste masking in the formulation without the need of a human tast panel in early stage of development.

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