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Research paper

Fast dissolving films made of maltodextrins

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ABSTRACT

This work aimed to study maltodextrins (MDX) with a low dextrose equivalent as film forming material and their application in the design of oral fast-dissolving films. The suitable plasticizer and its concentration were selected on the basis of flexibility, tensile strength and stickiness of MDX films, and the MDX/plasticizer interactions were investigated by ATR-FTIR spectroscopy. Flexible films were obtained by using 16–20% w/w glycerin (GLY). This basic formulation was adapted to the main production technologies, casting and solvent evaporation (Series C) or hot-melt extrusion (Series E), by adding sorbitan monoleate (SO) or cellulose microcrystalline (MCC), respectively. MCC decreased the film ductility and significantly affected the film disintegration time both in vitro and in vivo (Series C < 10 s; Series E ~ 1 min). To assess the film loading capacity, piroxicam (PRX), a water insoluble drug, was selected. The loading of a drug as a powder decreased the film ductility, but the formulation maintained satisfactory flexibility and resistance to elongation for production and packaging procedures. The films present a high loading capacity, up to 25 mg for a surface of 6 cm^2. The PRX dissolution rate significantly improved in Series C films independently of the PRX/MDX ratio.

1. Introduction

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing.

The first developed fast-dissolving dosage form consisted in tablet form, and the rapid disintegrating properties were obtained through a special process or formulation modifications [1]. More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments.

Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot-melt extrusion.

According to the film forming material characteristics, the manufacture of the dosage forms can present different critical issues. Common problems are caused by foaming during the film formation due to the heating of the material or solvent evaporation, the flaking during the slitting and the cracking in the cutting phase. Furthermore, the films should be stable to moisture overtime. Finally, to facilitate the handling they have to be flexible and exhibit a suitable tensile stress and do not stick to the packaging materials and fingers.

The first material employed to produce edible films was pullulan, a glucan consisting of maltotriose units, produced from starch by the fungus *Aureobasidium pullulans* [2]. Even if pullulan-based films are easily manufactured, the use of this material is limited by the low availability and high costs. Therefore, in the last years other edible hydrocolloids have been studied as substitute. The film-forming properties of modified starches, gums, cellulose ethers, alginates, polyvinylalcohols, polyvinylpyrrolidones or blends thereof have been considered [3–6]. Among them, maltodextrins (MDX) with a low dextrose equivalent (DE) were proposed to improve the flexibility and reduce the cracking of modified starch-based films [7]. Nevertheless, the application of MDX as the main film forming material has been scantily investigated [8] and, to our knowledge, no information about the effect of plasticizers on their tensile properties has been reported.

The aim of this work was to design a fast-dissolving film made of a MDX having a DE equal to 12. Since critical issues in the development of a fast-dissolving film are mainly related to its mechanical properties, the influence of the type and the concentration of plasticizers on flexibility, tensile strength and stickiness was preliminarily evaluated. A formulation study was performed to adapt the basic composition to the main preparation technologies, namely solvent casting or hot-melt extrusion.

The loading capacity of the films was assessed by using piroxicam (PRX) as a model drug, since 20 mg fast-dissolving tablets are currently marketed for the treatment of acute pain [9].

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2. Materials and methods

2.1. Materials

Maltodextrin having a DE equal to 12 (Glucidex® IT12, MDX) was obtained by Roquette, (F). Piroxicam (PRX), poly(ethyleneglycol) 400 (PEG 400), sorbitan oleate (SO), glycerol (GLY) and propylene glycol (PG) were purchased from Farmalabor (I). Microcrystalline cellulose (Avicel® PH 101, MCC) was kindly provided by FMC BioPolymer (USA). Tributyl citrate and acetyl tributyl citrate were supplied by Morflex (USA).

All the solvents were of analytic grade, unless specified.

2.2. Film preparation

2.2.1. Casting method

The aqueous dispersion was prepared by dissolving MDX, GLY and the other components of the placebo formulations (Table 1, series C) in distilled water maintained at 80 °C and stirred with a magnetic stirrer. The obtained dispersion was then cooled down to 40 °C and, if necessary, the active ingredient was added in the specific proportion. The suspension was stirred for 1 h and cooled down to room temperature. The suspension was used after at least 24 h of rest to remove all the air bubbles entrapped. The composition of the polymeric dispersions is reported in Table 1. The films were obtained by using a laboratory-coating unit Mathis LTE-S(M) (CH). The aqueous dispersion was cast onto a silicone release liner with a thickness selected to obtain placebo films with a thickness of about 100 μm. The coating rate was fixed at 1 m/min, and the cast dispersion was dried in the oven at 100 °C for 3 min with a horizontal air circulation of 1200 rpm.

The same procedure was followed for the preparation of the MDX/plasticizer binary blends (Table 2) used to assess the optimal concentration of the plasticizer. In this case, a corona-treated polyester material characterized by a high critical surface tension was used as a release liner to avoid the shrinkage of the solution during the casting process.

Table 1
Composition (%, w/w) of the placebo and PRX-loaded films prepared by solvent casting (series C) and hot-melt extrusion (series E) technologies

Series	Form.	PRX	MDX	GLY	S80	MCC
C	1	–	79.0	18.0	3.0	–
	2	–	76.0	18.0	6.0	–
	3	9	71.2	17.8	2.0	–
	4	12	68.8	17.2	2.0	–
	5	15	66.4	16.6	2.0	–
E	6	–	66.0	22.0	–	12.0
	7	9	60.0	20.0	–	11.0
	8	12	58.1	19.4	–	10.5
	9	15	56.1	18.7	–	10.2

2.2.2. Hot-melt extrusion

The placebo and loaded films were produced by using a single-screw extruder (Tecnova Extruder, I) with a heating system split into four zones. MDX and PRX were blended into a sigma blade mixer (Erweka, G) for 10 min, and then GLY was slowly added. The mixture was granulated in the presence of an anti-sticking agent, namely MCC. The composition of the granules is reported in Table 1 (Series E). Granules were stored overnight at room temperature and then sieved through a 250 μm sieve in order to remove the excess of powder and standardize the particle size. The dried granular material was fed into the extruder. The screw speed was set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min. The processing temperatures were set at 80 °C (zone 1), 115 °C (zone 2), 100 °C (zone 3) and 65 °C (zone 4). The extrudate (T = 65 °C) was then pressed into a cylindrical calendar in order to obtain a film with a thickness of about 200 μm.

At the end of the preparation processes, the films were cut according to the size required for testing, individually sealed in air-tight packets and stored at 25 °C until use. The films obtained by the casting method were maintained over the release liner used to facilitate the cutting, packaging and handling procedures.

2.3. Film thickness

Film thickness was measured by using a MI 1000 μm (ChemInstruments, USA). The accuracy of the instrument was 2.5 μm ± 0.5%. A 10 × 2.5 cm sample of the film was placed between the anvil and the presser foot of the micrometer, and its thickness was measured in ten different positions. The determination was performed in triplicate.

2.4. Film flexibility

The film flexibility was determined by adapting the ASTM bend mandrel test (D 4338-97). Briefly, a 2 × 3 cm sample was bended over an 8 mm mandrel and examined for cracks over the area of the bend in a strong light. The film was assumed as flexible if no cracks were visible at a 5× magnification.

2.5. Tensile properties

Tensile testing was conducted using a texture analyzer AG/MC1 (Acquati, I), equipped with a 5 N load cell. The film was cut into 100 × 12.5 mm strips and equilibrated at 25 °C for 1 week. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02).

Each test strip was longitudinal by placed in the tensile grips on the texture analyzer. Initial grip separation was 60 mm and crosshead speed was 500 mm min^{-1}. The test was considered concluded at the film break. Tensile strength, elongation at break, elastic modulus and tensile energy to break were computed to evaluate the tensile properties of the films. *Tensile strength (TS)* was calculated by dividing the maximum load by the original

Table 2
Thickness and tensile properties of MDX films plasticized with GLY or PG

MDX (%, w/w)	GLY (%, w/w)	PG (%, w/w)	Thickness (μm)	*E*%	TS (MPa)	EM (MPa)	TBE (J)
84	16		133 ± 4	92.7 ± 7.4	7.72 ± 0.07	1.93 ± 0.18	0.440 ± 0.037
82	18		127 ± 5	196.6 ± 20.4	4.65 ± 0.56	1.06 ± 0.20	0.400 ± 0.023
80	20		130 ± 3	322.4 ± 63.3	1.80 ± 0.20	0.30 ± 0.07	0.287 ± 0.018
78	22		132 ± 2	559.7 ± 31.4	1.12 ± 0.21	0.26 ± 0.06	0.228 ± 0.048
82		18	120 ± 3	349.7 ± 20.1	2.20 ± 0.13	0.55 ± 0.08	0.287 ± 0.023
80		20	140 ± 4	449.6 ± 21.7	2.01 ± 0.05	0.47 ± 0.05	0.328 ± 0.021

cross-sectional area of the specimen and it was expressed in force per unit area (MPa). *Percent elongation at break* (*E*%) was calculated by dividing the extension at the moment of rupture of the specimen by the initial gage length of the specimen and multiplying by 100 according to the following equation:

$$E\% = \frac{L - L_0}{L_0} x100$$

where L_0 is the initial gage length of the specimen and L is the length at the moment of rupture. *Elastic modulus or Young's modulus (M)* was calculated as the slope of the linear portion of the stress–strain curve. The result was expressed in force per unit area (MPa). *Tensile energy to break (TBE)* was defined by the area under the stress–strain curve. The value is in units of energy per unit volume of the specimen's initial gage region. The result was expressed in energy per unit volume.

An average of five measurements was taken for each type of specimen.

2.6. Stickiness determination

The film stickiness was evaluated according to the texture method usually used for the measurement of the tack of pressure sensitive adhesives [10]. A 2.54 cm^2 sample film was placed on a flat dish plate. A 2.04 kg cylinder with an 8 mm diameter hole was placed on the top of the sample, ensuring to centre the film with the cylinder hole. The cylinder plus sample was then clamped in the testing position of a software controlled dynamometer (AG/MC, Acquati, I) equipped with a 5 DaN cell. The stainless steel probe was then lowered into the cylinder and a constant force of 0.05 N was applied onto the sample for 5 s and, finally, the probe was removed at the constant rate of 100 mm/min. The debonding velocity was set at 5 mm/s.

2.7. ATR-FTIR spectroscopy

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were recorded with an ATR-FTIR spectrometer (SpectrumOne™, Perkin-Elmer, USA) equipped with a diamond crystal. For each sample, 64 scans were collected at a resolution of 2 cm^{-1} over the wavenumber region 4000–650 cm^{-1}.

The experiments were conducted on the pure MDX and the MDX/plasticizer binary blends as such (Table 2).

2.8. Differential scanning calorimetry (DSC)

DSC scans were recorded by using a DSC 2010 TA (TA Instruments, USA). Samples (approximately 5 mg, accurately weighed, ±0.001 mg) were sealed in aluminium pans and heated under nitrogen purging (70 mL/min). The reference was an empty pan. The equipment was calibrated with an indium sample.

PRX and films containing PRX samples were scanned at 10 K/min from 30 to 240 °C in order to evaluate the drug melting events. Furthermore, the pure MDX and film samples were also first scanned at 10 K/min from 30 to 140 °C, cooled down to 0 °C at 20 K/min in order to erase the MDX thermal history and avoid PRX melting which could affect the glass transition temperature (T_g) of the films. The samples were re-heated up to 130 °C at 10 K/min to determine the T_g.

All determinations were performed in duplicate.

2.9. Drug content

A sample of 6 cm^2 was dissolved in an appropriate amount of the mobile phase and the solution was filtered (Durapore® membrane, pore size 0.45 μm; Millex GV, Millipore Corporation, USA) and PRX assayed by HPLC equipped with a Diode array UV–vis detector (HP 1100, Chemstation, Hewlett Packard, USA) by adapting the Ph. Eur. 5.4 method reported below. A 20 μL sample was injected at 40 °C on a reverse phase column (Lichrospher 100 RP-18 E, 5 μm 125 × 4.0 mm), and the flow rate was set at 1.5 mL/min. The mobile phase was prepared as follow: 40 volumes of acetonitrile and 60 volumes of a 6.81 g/l solution of potassium dihydrogen phosphate were mixed and adjusted to pH 3.0 with phosphoric acid. The main PRX impurity, 2-aminopiridine, had a retention time 0.85 times lower than PRX. The drug content was determined by using a standard calibration curve represented by five known concentrations of PRX ranging from 5 to 100 mg/mL (r^2 = 0.999).

The results were expressed as mean of three determinations.

2.10. PRX solid state evaluation

The analyses were conducted on PRX polymorphs, placebo and drug-loaded film.

2.10.1. Preparation of polymorphic forms of PRX

The polymorphic forms of PRX were obtained according to the methods described by Vrecer et al. [11]. Briefly, form II (needle) was crystallized from saturated absolute ethanol solution. Form III was obtained by spray-drying the solution of PRX in absolute ethanol. The monohydrate form was obtained by dissolving PRX in acetone and adding the same amount of water. The precipitate was filtrated and dried until constant weight.

2.10.2. X-ray diffraction

Powder X-ray diffraction spectra of the four PRX polymorphs, placebo and drug-loaded films were collected using a Rigaku DMAX powder diffractometer (J) with Cu–Kα radiation and a monochromator on the diffracted beam.

2.10.3. ATR-FTIR spectroscopy

ATR-FTIR spectra were recorded with an ATR-FTIR spectrometer (SpectrumOne™, Perkin-Elmer, USA) equipped with a diamond crystal. For each sample 64 scans were collected at a resolution of 2 cm^{-1} over the wavenumber region 4000–650 cm^{-1}.

2.11. Disintegration test

Disintegration test was performed according to the specifications of orodispersible tablet reported in Ph. Eur. 5.4 ed. (2.9.1) by using samples of 6 cm^2.

2.12. In vitro dissolution test

The in vitro dissolution test was carried out in a Ph. Eur. 5.4 ed. paddle dissolution apparatus. Samples of PRX-loaded films were exactly weighed in order to assure the sink condition (solubility of PRX cubic form: 35 mg/L). *Experimental conditions.* The dissolution medium was 900 ml freshly deionized water, maintained at 37 ± 1 °C and stirred at 100 rpm. PRX concentrations were assayed spectrophotometrically at 285 nm (DU-640 Beckman Coulter, USA). The results were the average of three determinations. The dissolution profile of PRX cubic form was also determined using the same experimental set-up.

2.13. Measurement of the disintegration in the oral cavity

The study was designed to determine the disintegration time of the MDX/plasticizer binary blends in the buccal cavity. The same protocol was followed to evaluate the compliance of placebo and drug-loaded films prepared by hot-melt extrusion and casting.

The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and followed the ICH-GCP guidelines of the 17-01-1997, and was in compliance with local regulatory requirements. All the subjects were completely informed concerning the pertinent details and the purpose of the study. A written consent form was supplied, understood and signed by each subject prior to dispensing the test materials.

Films were randomly administered to six healthy male volunteers at 1 h time intervals. A specimen of 6 cm^2 was placed in the buccal cavity by the volunteer, directly on the tongue. The time required for the complete disintegration of the films in the oral cavity was recorded. Moreover, all the subjects are asked to give an evaluation of the samples by answering questions related to taste, comfort and sensation after administration, using a score: 0 (very satisfied), 1 (quite satisfied), 2 (not satisfied) and 3 (not at all satisfied). The parameters for comfort included convenience of administration, quickly of disintegration and suitability of pharmaceutical form for taking without water. Sensation was evaluated considering residues left in the mouth after administration.

3. Results and discussion

3.1. Plasticizer selection

In the preliminary phase, particular attention was given to the selection of a proper plasticizer able to provide a suitable ductility and flexibility to MDX films under different types of mechanical stress.

PEG 400 as well as the esters of citric acid was excluded because of the lack of miscibility with MDX. Satisfactory results were obtained adding both GLY and PG to MDX. The plasticizing effect of these low molecular-weight molecules was demonstrated by the ATR-FTIR spectra where weak modifications of the main bands of MDX were detected. As exemplified in Fig. 1 which shows the specific stretching regions of the pure MDX and MDX/GLY or MDX/PG blends in the ratio 82/18, the peaks of MDX at 1012 and 992 cm^{-1} attributed to the C–O stretching vibration shifted to higher wavenumbers indicating the H-bond formation between the C–O group of MDX and O-H moieties of both the plasticizers. No differences in the intensities and shape were ascribed to the addition of PG or GLY to MDX. Using a conventional DSC, it was not possible to record a clear signal associated to the transition from the glassy to the rubbery state of the binary blends and, hence, evaluate the effect of both the plasticizers on the MDX T_g (T_g = 121 ± 3 °C) probably because of the too low Cp.

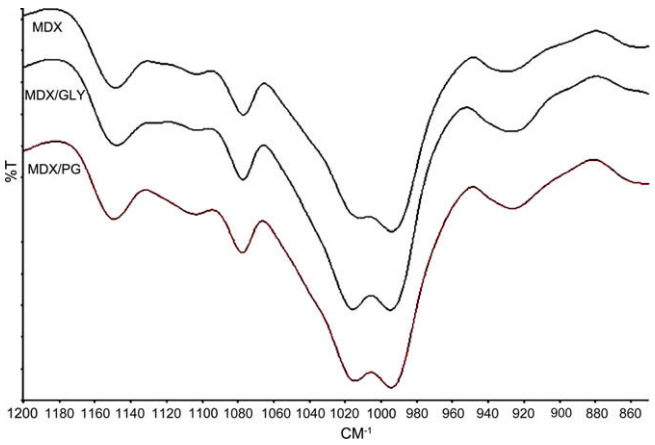

Fig. 1. ATR-FTIR spectra of MDX (a) and MDX films plasticized with 18% w/w (b) GLY or (c) GP.

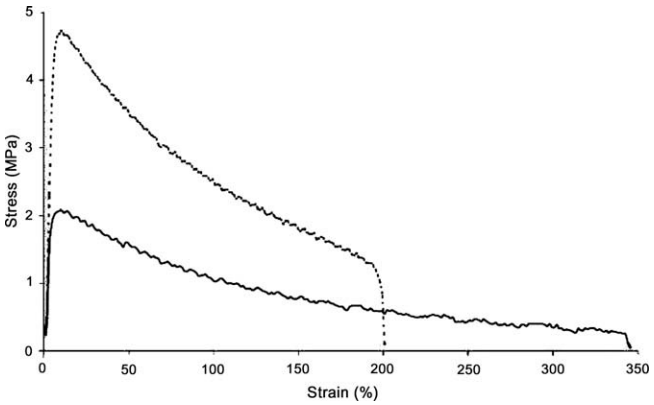

Fig. 2. Strain–stress curves of the MDX films plasticized with 18% w/w GLY (dotted line) or GP (solid line).

Flexible films were obtained at GLY or PG content of at least 16% w/w or 18% w/w, respectively. Films prepared by using GLY or PG amount higher than 22% or 20% w/w, respectively, resulted too ductile for handling.

Fig. 2 shows force-deformation curves for the MDX films plasticized with 18% w/w GLY or GP. At low strain, the deformation of the samples was elastic in both the cases. Rising the load, the patterns progressively shifted from linearity and the deformation became irreversible, increasing until the maximum load was reached. Afterwards, the stress–strain curves showed that the deformation increased with an apparent lower stress. This pattern was due to a local reduction of sample cross section (neck), which propagated along the length of the sample until rupture. The values of the film tensile properties are reported in Table 2. As expected, the increase of the plasticizer content caused a decrease of the elastic modulus (EM), which is an index of stiffness, and the tensile stress (TS). The ductility, that is expressed as elongation at break (*E*%), increased increasing the plasticizer amount. The toughness, expressed as the tensile energy to break (TBE), resulted reduced only at the highest concentration of GLY.

The comparison of the tensile properties of the films prepared with both plasticizers highlights that the ductility, which can be considered as an indication of the plasticization of the film, increased until the critical values of *E*% at 400–500. This observation can indicate that MDX and the plasticizers were not freely mixable, and the number of the MDX/plasticizer interpolymeric entanglements is saturable. Such hypothesis is in agreement with the PG and GLY blooming phenomena evidenced on the release liner at a plasticizer concentration higher than 18% w/w. The oozing of the excess of the plasticizer towards both the film surfaces is also responsible for the stickiness of the films [12]. Indeed, only when the MDX/plasticizer ratio was higher than 18% w/w, the maximum detachment force was registered and it was in the 200–250 cN/cm^2 range.

As far as the effect of the two plasticizers on the tensile properties of the films is concerned, a different behaviour was evident only at MDX/plasticizer ratio of 82/18% w/w. When PG was used, the elongation at break values resulted about 2-fold higher than that measured in the presence of the same concentration of GLY, while the stiffness and tensile strength resulted lower in the same order of magnitude.

All the films dissolved in the disintegration apparatus within few seconds, and the same feature was reported by the volunteers after the administration of a 6 cm^2 sample. All the subjects were pleased with a quick disintegration time and comfort of films (score 0). The films containing GLY satisfied the requirements for the taste (score lower than 1); meanwhile PG was discarded

because the unpleasant taste (score higher than 2) compromises patients' compliance. The subjects expressed a high degree of satisfaction with sensation (score 0) since after disintegration no film residues remained in the mouth.

3.2. Fast-dissolving film preparation

3.2.1. Placebo film

On the basis of the previous results, GLY was chosen as the suitable plasticizer for MDX and the concentration at 18% w/w was selected to formulate and produce MDX fast-dissolving films both by casting and hot-melt extrusion technologies.

The film thickness prepared by casting was not homogeneous because of the shrinkage of the mixture spread on the silicone release liner selected to facilitate the handling by the patient. Therefore, the addition of a surfactant agent was necessary. Benefits were achieved only by adding surfactants with a low HLB value (formulations C1 and C2, Table 1). The addition of SO caused a slight increase of stiffness dependent on the surfactant concentration (Table 3). The highest concentration of SO determined a significant reduction of ductility and an increase of the film fragility that could cause the rupture of the dosage form during the cutting and packaging procedures.

As far as the hot-melt extrusion process is concerned, there was no enough flow of the MDX/GLY mixture to permit the homogeneous loading and feeding of the mixture in the extrusion chamber. Therefore, the multi-step process described in the method section was developed. The granulation of MDX was necessary to properly feed the screw, and the addition of MCC (formulation E6, Table 1) was crucial in order to obtain smooth and no-sticking films. It is well known that the water fraction of the wet mass has a dramatic influence on the extrusion process [13] and MCC shows very high water absorption capacity [14]. Thus, it may be assumed that the moisture retained by MCC exerted a lubricating activity resulting in a reduction of frictional forces and heat generated during the extrusion process. When the weight ratio between MDX and GLY was 82/18%, the films did not result flexible probably because MCC adsorbed a fraction of GLY which, therefore, resulted insufficient. Satisfactory results were obtained by decreasing the MDX/GLY ratio to 75/25% w/w (formulation E6).

To compare the technological properties of the two final placebo formulations, the thickness of formulation C1 was set at 200 μm (formulation C1a, Table 3) which corresponds to the thinnest film obtained by means of the hot-melt technology. The main difference of the tensile properties between the two formulations concerned the fragility. Indeed, in the case of the formulation E7 the value of E% resulted about 100-fold lower than that of formulation C1a (Table 3). The different patterns can be ascribed to the highest GLY/MDX ratio. Moreover, it can be assumed that the dispersion of MCC in the MDX matrix caused the formation of a non-continuous film and originate the initial point of break during the tensile stress.

Both the films satisfied the requirement of disintegration time for fast-dissolving dosage forms. Indeed, the film prepared by casting disintegrated in 10 s, while the film obtained by hot-melt extrusion in 45 s. This difference was mainly attributed to the presence of MCC in the films of the series E because upon hydration, the swelling of MCC retarded the MDX dissolution. A similar behaviour has been already described in the extrusion/spheronization process when MCC was used as filler [15].

The differences in the in vitro disintegration time were also confirmed in the in vivo testing. Moreover, the subjects expressed a high degree of satisfaction only with the films of the series C in terms of disintegration time, comfort, sensation and taste (score lower than 1). On the other hand, in the case of the films of the series E, an unpleasant sensation in the buccal cavity was caused by the residues of MCC after disintegration and, consequently, the subjects judged the film as unacceptable (score higher than 2).

3.2.2. PRX films

The addition of PRX to the two basic formulations did not compromise the film preparation. Indeed, all films resulted flexible and appeared homogeneous and pale yellow; the HPLC analyses did not evidence any degradation peak. The main bands of PRX in cubic form were detected in the X-ray diffraction patterns and ATR-FTIR spectra of all films, indicating that the preparation processes did not modify the drug solid state (data not shown). Nevertheless, in the case of the extruded formulations, the onset melting temperature of PRX in the films was depressed to lower values in comparison to that of the cubic form of PRX and the fusion enthalpy decreased, indicating that a fraction of the active ingredient was dissolved in the MDX matrix (Table 4). In the case of the formulations prepared by the casting method, the presence of SO determined several endothermic events up to 130 °C which were ascribed to the thermal degradation of the film and did not permit to quantify the onset melting temperature of PRX and, therefore, the melting enthalpy.

Considering the drug-loaded amount per square centimeter and the PRX required dose (20 mg), the film size of all formulations (<8 cm^2) resulted suitable for the preparation of an orodispersible dosage form (Table 4).

The presence of the drug significantly modified the tensile properties of the film prepared by the casting method, determining a relevant increase of the film stiffness (EM, Table 3). This result confirmed that the dispersion of a powder to a film determines an increase of the film fragility, even if the flexibility assay is still satisfactory. Indeed, the values of tensile properties of the PRX-loaded films prepared by the casting method are in the same order of magnitude than those of the extruded placebo films (Tables 2 and 3).

The films prepared by hot-melt extrusion disintegrated in about 1 min, while the films prepared by casting required only few seconds in agreement with the placebo formulations.

These results were in agreement with the in vivo disintegration time. As far as the taste is concerned, the volunteers expressed sat-

Table 3
Thickness and tensile properties of the films

Form.	Thickness (μm)	*E*%	TS (MPa)	EM (MPa)	TBE (J)
C1	128 ± 3	106.9 ± 10.8	5.24 ± 0.33	1.29 ± 0.12	0.356 ± 0.017
C1a	203 ± 3	870.0 ± 120.0	0.16 ± 0.08	0.04 ± 0.01	0.161 ± 0.023
C2	120 ± 2	20.2 ± 5.3	9.85 ± 1.76	2.36 ± 0.34	0.112 ± 0.020
C3	204 ± 1	9.6 ± 0.4	0.65 ± 0.04	0.14 ± 0.00	0.008 ± 0.001
C4	205 ± 3	10.8 ± 1.8	0.94 ± 0.13	0.21 ± 0.03	0.008 ± 0.003
C5	204 ± 2	11.4 ± 0.1	1.02 ± 0.04	0.23 ± 0.04	0.013 ± 0.001
E6	200 ± 1	19.7 ± 3.9	0.91 ± 0.16	0.44 ± 0.13	0.031 ± 0.002
E7	238 ± 2	7.8 ± 0.1	1.92 ± 0.06	0.21 ± 0.04	0.015 ± 0.004
E8	230 ± 17	13.3 ± 0.4	1.07 ± 0.17	0.26 ± 0.06	0.009 ± 0.001
E9	229 ± 4	10.6 ± 0.1	1.35 ± 0.05	0.39 ± 0.05	0.016 ± 0.001

Table 4
Drug content and DSC data of the films containing PRX

Form.	Drug content (mg/cm^2)	T_m (°C)	ΔH (J/g)
C3	2.5 ± 0.2	–*	–*
C4	3.7 ± 0.1	–*	–*
C5	4.7 ± 0.2	–*	–*
E7	2.5 ± 0.0	187 ± 1	73 ± 2
E8	3.7 ± 0.1	186 ± 1	84 ± 3
E9	4.5 ± 0.1	186 ± 1	92 ± 2
PRX		200 ± 1	116 ± 3

* Not-determinable.

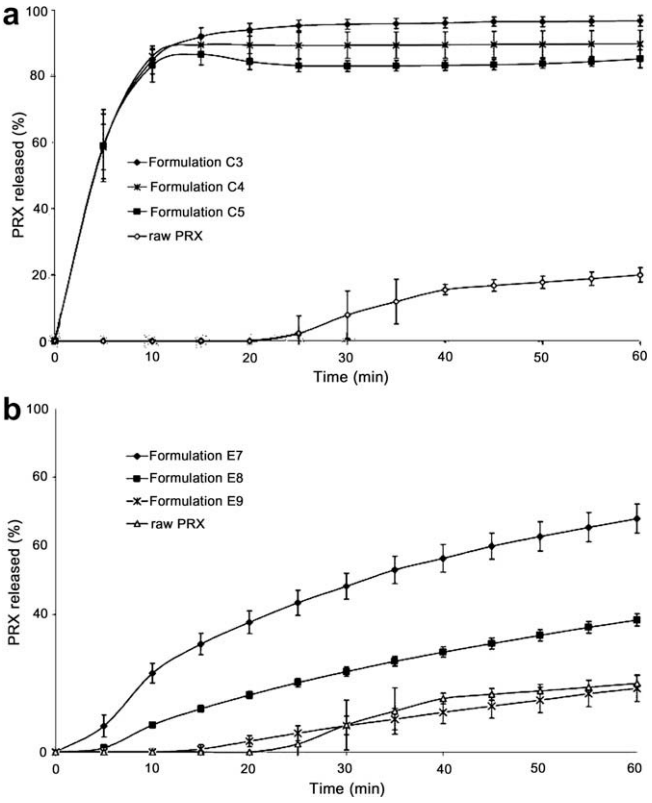

Fig. 3. *In vitro* release profiles of PRX from the films prepared by (a) casting and (b) hot-melt extrusion methods.

isfaction (score lower than 1) only when the amount of loaded PRX was lower than 9% w/w. In the other case, the films did not satisfy the requirements for the taste because of bitter aftertaste (score higher than 2).

The in vitro release profiles of PRX films are reported in Fig. 3. The dissolution rate of PRX resulted greatly influenced by the preparation method. The films of the series C promptly released PRX, which was completely dissolved within 10 min (Fig. 3a). These data indicated that the components of the film promote the dissolution rate of the active ingredient independently of the amount loaded in the film.

The dissolution rates of the PRX from the film of series E resulted slower than those registered in the case of series C (Fig. 3b). The different patterns registered in the two series were mainly ascribed to the presence in the formulation of MCC which, in the hydrodynamic conditions of the dissolution apparatus, stopped the film disintegration. As a consequence, the film produced by hot-melt extrusion after coming into contact with water formed a swelled matrix, and the dissolution process was mainly governed by the diffusion of PRX through the film gel layer. Indeed, good linear correlations (correlation coefficients: 0.9896–0.9999) were obtained from the plots of the release ratios of PRX from the formulations of the series E against the square root of time in agreement with the Higuchi's model.

The solid state of PRX also played a fundamental role in the dissolution process. Indeed, the ΔH values in Table 4 suggest that the higher the PRX loaded in the films, the greater the crystalline fraction, thereby the lower the amount of PRX dissolved which in the case of formulation E9 overlapped with that of the micronized drug.

These findings led us to conclude that the dissolution behaviour of PRX from the MDX-based films is influenced by several factors, namely the wettability by the hydrophilic carrier, the solid state of the drug and MCC in the case of film of series E. While in the films of the series C the effect of the hydrophilic excipients resulted clearly predominant on the other parameters, the release pattern of the films of the series E was probably influenced by three variables: MCC reduced the PRX diffusion process and the solubilizing effect of the hydrophilic carrier; meanwhile the PRX fraction solubilized in the matrix improved the amount of PRX dissolved. The predominance of one feature on the others governs the dissolution behaviour.

4. Conclusions

Maltodextrins having DE equal to 12 plasticized with 16–20% w/w glycerin are suitable to produce fast-dissolving films by different manufacturing processes, such as casting and solvent evaporation or hot-melt extrusion. Homogeneous films are achievable by loading a large amount of water insoluble powders, namely more than 15% w/w. When PRX was selected as a model drug, the film can contain more than 25 mg of active ingredient for a surface of 6 cm^2. The loading of a drug as a powder in the film determined a decrease of the ductility, but the formulations maintained satisfactory flexibility and resistance to elongation for the production and packaging procedures.

Compared to the hot-melt extrusion method, the casting method appeared more reliable for the production of fast-dissolving films since the dosage forms exhibited the highest patients' compliance and best performances in terms of in vitro and in vivo disintegration time. Furthermore, the films of series C can also remarkably improve the dissolution of poorly soluble drugs, such as PRX which completely dissolved within 10 min independently of the drug loading.

References

[1] G. Sandri, M.C. Bonferoni, F. Ferrari, S. Rossi, C. Caramella, Differentiating factors between oral fast-dissolving technologies, Am. J. Drug Deliv. 4 (4) (2006) 249–262.
[2] T.D. Leathers, Biotechnological production and applications of pullulan, Appl. Microbiol. Biotechnol. 62 (2003) 468–473.
[3] H.G. Zerbe, J.H. Guo, Dosage form adherent to oral mucosa, Ger. Offen. DE 19646392 (1998).
[4] S. Ali, Q. Anisul, High molecular weight povidone polymer-based films for fast-dissolving drug delivery applications, Drug Deliv. Tech. 7 (6) (2007) 36–43.
[5] R.C. Mashru, V.B. Sutariya, M.G. Sankalia, P.P. Parikh, Development and evaluation of fast-dissolving film of salbutamol sulphate, Drug Dev. Ind. Pharmacy 31 (2005) 25–34.
[6] M. Pinna, F. Pinna, Quick water dissolving film containing cosmetic, aromatic, pharmaceutical or food substances, US 20044086539 (2004).
[7] A.H. Chapdelaine, D. Zyck, M.J. Dzija, Improved edible film formulations containing maltodextrin, WO 03/011259 (2003).
[8] S. Shamekh, P. Myllarinen, K. Poutanen, P. Forssel, Film formation properties of potato starch hydrolysates, Starch 54 (2002) 20–24.
[9] G. Nappi, G. Miceli, C. Tassorelli, E. Viotti, T. Altavilla, Effectiveness of a piroxicam fast dissolving formulation sublingually administered in the symptomatic treatment of migraine without aura, Headache 33 (6) (1993) 296–300.
[10] C. Craton, P. Fabre, Tack of PSA's, in: A. Pocius, D. Dillard (Eds.), Comprehensive Adhesion Science: The Mechanics of Adhesion, Rheology of Adhesives, and Strength of Adhesive Bonds, vol. 2, Elsevier, 2002. (Chapter 14).
[11] F. Vrecer, M. Vrbinc, A. Meden, Characterization of piroxicam crystal modifications, Int. J. Pharm. 256 (2003) 3–15.
[12] D. Lourdin, L. Coignard, H. Bizot, P. Colonna, Influence of equilibrium relative humidity and plasticizer concentration on the water content and glass transition of starch materials, Polymer 38 (21) (1997) 5401–5406.
[13] E.I. Keleb, A. Vermeire, C. Vervaet, J.P. Remon, Cold extrusion as a continuous single-step granulation and tabletting process, Eur. J. Pharm. Biopharm. 52 (2001) 359–368.
[14] G. Tomer, H. Patel, F. Podczeck, J.M. Newton, Measuring the water retention capacities (MRC) of different microcrystalline cellulose grades, Eur. J. Pharm. Sci. 12 (3) (2001) 321–325.
[15] P. Kleinebudde, The crystallite-gel-model for microcrystalline cellulose in wet-granulation, extrusion, and spheronization, Pharm. Res. 14 (6) (1997) 804–809.