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Poly(methyl methacrylate) salt as film forming material to design orodispersible films

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ABSTRACT

This work aims to evaluate the possible use of a poly(sodium methacrylate, methyl methacrylate) ($NaPMM_2$) plasticized by PEG400 in design orodispersible films (ODF). Placebo ODF prepared by solvent casting were intended to study the impact of the polymer/plasticizer ratio and residual moisture on disintegration time, stickiness and mechanical properties. The drug loading capacity was assessed using ketoprofen and paracetamol. Placebo ODF containing PEG400 in the 10–30% *w*/w range and 10–15% of residual moisture content were easy-to-handle, packed without failures and completely dissolved within 30 s.

$NaPMM_2$/PEG400 in 80/20 ratio allowed up to 70% of paracetamol loading, which appeared as the largest value described in literature. This ODF showed good mechanical properties and disintegration time. The same formulation loaded with 25% or 50% ketoprofen ($pK_a = 4.45$) swelled without disintegrating, because of a partial protonation of $NaPPM_2$, as verified by ATR-FTIR spectroscopy. However, the addition of 5% surfactants allowed the formulation of ODF containing 25% ketoprofen that disintegrated within one minute and guaranteed the complete drug dissolution within 5 min. All the presented data, discussed in the framework of information available on such copolymer, highlighted its versatility in the design of orodispersible dosage forms.

1. Introduction

Nowadays, serious attempts are being made to develop medicines, formulations, and dosage forms that are adapted to the specific needs of patients who stand at the edge of the entire population, namely pediatric, elderly and dysphagic patients (Borges et al., 2015; Dixit and Puthli, 2009). The European Medicines Agency stepped into the topic by emitting a guideline on the pharmaceutical development of medicines for pediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) and a recommendation on the need of a reflection paper concerning the quality aspects of medicines for elderly patients (EMA/165974/2013). Indeed, the most critical points are dosage accuracy and swallowing difficulties in pediatric and elderly patients, respectively.

Orodispersible films (ODF) have been proposed to overcome physiologic or psychologic impairments in swallowing tablets and capsules or the fear of chocking and to extend the patentability of these dosage forms (Cilurzo et al., 2017). Moreover, very recent pharmacokinetic studies reported the bioequivalence of ondansetron ODF with orally disintegrating tablets under both fasted and fed conditions (Dadey, 2015), indicating the suitability of ODF as an alternative to orodispersible tablets.

ODF are usually constituted of plasticized water-soluble macromolecules that are predominantly laminated by solvent casting and sealed in moisture-protecting packages. The drug dose is determined by the thickness and size of the dried film. Thus, different dose strengths may be obtained from the same formulation cut in different shapes.

Over the last decade, several film-forming polymers have been proposed to design ODF (Borges et al., 2015). However, each proposed material exhibits peculiar difficulties related to foaming during solvent evaporation, flaking during slitting, cracking during cutting or sticking to the packaging material or patients' fingers during handling. Therefore, the addition of auxiliary excipients is often required, thus decreasing the already limited formulation space of such dosage form. As an example, the mechanical properties of maltodextrin films can be compromised by the loaded drug and/or the taste masking agents (Cilurzo et al., 2011) so that other excipients could be required to reinforce the polymeric film (Selmin et al., 2015; Franceschini et al., 2016). Hence, there is no doubt that the most critical point is the choice of the film-forming polymer and efforts should be invested to assure the appropriate mechanical resistance.

Poly(sodium methacrylate, methyl methacrylate)s, NaPMMs, and poly(potassium methacrylate, methyl methacrylate)s, KPMMs, have been proposed to design drug delivery systems intended for buccal administration of ac-

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tive ingredients (;). These materials are obtained by neutralizing with alkali two grades of pharmaceutical approved polymers having 1:1 (Eudragit® L, $HPMM_1$) or 1:2 (Eudragit® S, $HPMM_2$) monomer ratio. Independently of the monomer ratio, NaPMMs and KPMMs showed promising properties to design ODF exhibiting the substantial characteristics required, namely very fast dissolution rate and a low swelling profile with respect to low molecular weight HPMC (Cilurzo et al., 2003). Among these four polymeric materials, $NaPMM_2$ appeared the most suitable for the design of buccal dosage forms thanks to its taste.

In the light of above considerations, the aim of the present study was to evaluate the possible use of $NaPMM_2$ as film-forming polymer to design ODF. Taking into consideration that mechanical properties and drug loading are critical attributes of an ODF, the work was organized in two steps. Preliminarily, placebo ODF made of $NaPMM_2$ plasticized by PEG400 were prepared by a solvent casting technique focusing the attention on the ratio and process variables which determine both film flexibility and tenacity. Then, the formulation having the most suitable tensile properties for manufacturing and handling was loaded with two model drugs. Paracetamol was used to determine the maximum loading capacity of the ODF in the attempt to obtain a final dosage form suitable for pediatrics; ketoprofen was selected as an acidic drug model, which can alter the ratio between the sodium carboxylate and carboxylic acid residues of $NaPMM_2$ and, therefore, affect the disintegration time of the ODF. Both disintegration and dissolution tests were carried out in water and artificial saliva to determine the impact of pH and cations on the in vitro performances of the ODF. Indeed, since $NaPMM_2$ is a pH-dependent copolymer sensitive to the presence of bivalent cations (Cilurzo et al., 2005; Cilurzo et al., 2010a, 2010b), the variation of microenvironmental composition can cause the formation of physical cross-linking affecting the polymer dissolution rate.

2. Material and Methods

2.1. Materials

Poly(sodium methacrylate, methyl methacrylate) ($NaPMM_2$, molar proportions of the monomer units 1:2, molecular weight 135,000 Da) was prepared as previously described (Cilurzo et al., 2003). Briefly, 15% *w*/w Eudragit®S100 (Evonik Industries, G) aqueous suspension was salified by adding sodium hydroxide pellets. The required amount of NaOH (0.12 g/g of Eudragit® S100) was calculated after titration on the basis of the Ph. Eur. method. Ketoprofen was kindly provided by MIAT S.p.A. (I).

Paracetamol (Farmalabor, I); PEG400 and Tween®80 (Carlo Erba Reagenti, I); Span®80 (Croda, E).

2.2. Preparation of Films

To prepare the casting solution, PEG400 was added to a 10% *w*/w $NaPMM_2$ solution under magnetic stirring in order to obtain the $NaPMM_2$/plasticizer ratios from 90/10 to 40/60% w/w (Table 1). The active ingredients were added to the slurry to obtain the concentration reported in Table 2. After a rest period to remove bubbles, the dispersion was cast at the rate 1 m/min over a silicone release liner and a coating thickness was set to obtain ~100 μm films (Mathis LTE-S(M), CH). Films were, then, cut into the shape and size required for testing, packed in individual airtight seal packs using a triple layer film, and stored at 25 ± 1 °C until use.

2.3. Film Flexibility

The film flexibility was determined as follow: a 2×3 cm sample was bent for ten times over an 8-mm mandrel and examined for cracks over the bending area. The film was considered flexible if no cracks were visible at a 5× magnification using an optical microscopy (Nikon, I).

2.4. Loss on Drying

The loss on drying (LOD) in films was determined gravimetrically by using a thermobalance (Gilbertini, I). Film samples were kept at 105 °C until constant weight was reached.

2.5. Thickness

Film thickness was measured by using a MI 1000 (ChemInstruments, USA). The accuracy of the instrument was 2.5 μm ± 0.5%. Before samples cutting, the film was placed between the anvil and the presser foot of the micrometer. Film thickness was measured in ten different positions and the result was expressed as the mean value.

2.6. Thumb Tack Test

The ODF stickiness at different plasticizer contents was evaluated by the thumb tack test (Minghetti et al., 2004). Briefly, the thumb was pressed lightly on a film sample for a short time and, then, quickly withdrawn. By varying the pressure and time of contact and noting the difficulty of pulling the thumb from the adhesive, it is possible to perceive how easily, quickly and strongly the adhesive can form a bond with the thumb. All the tests were simultaneously performed and blind. The stickiness of the ODF was expressed by the following score system: very stick, stick and no stick.

Table 1
Effect of concentration of PEG400 and water (LOD, %) on film mechanical properties. Results are expressed as the mean of five measurements ± standard deviation. Tensile pattern is classified according to an alphabetic code referring to the high elongation at break (D) or sharp (N) or slow (T) variation of the film cross section. For a more detailed description, refer to the text.

Form. no	$NaPMM_2$ (% w/w)	PEG400 (% w/w)	LOD (%)	Flexibility	Thumb tack test	Y (MPa)	σ_{max} (MPa)	ε (%)	TEB (MPa)	Tensile pattern
1a	90	10	35 ± 2	Y	No stick	0.33 ± 0.17	1.49 ± 0.44	44.2 ± 13.6	0.42 ± 0.07	N
1b			29 ± 1	N	No stick	-[b]				
2a	80	20	31 ± 1	Y	No stick	2.61 ± 0.39	9.04 ± 1.12	31.2 ± 5.2	1.86 ± 0.65	N
2b			25 ± 1	Y	No stick	3.70 ± 0.29	13.46 ± 1.67	32.4 ± 10.7	3.24 ± 1.43	N
2c			19 ± 2	N	No stick	-[b]				
3a	70	30	24 ± 2	Y	No stick	1.32 ± 0.29	4.71 ± 0.35	81.3 ± 6.1	1.97 ± 0.50	T
3b			20 ± 1	Y	No stick	1.94 ± 0.18	8.18 ± 0.43	112.8 ± 29.6	6.84 ± 1.73	T
3c			16 ± 2	N	No stick	-[b]				
4a	60	40	19 ± 1	-[a]	Stick	0.46 ± 0.16	0.46 ± 0.04	510.1 ± 80.1	1.63 ± 0.31	D
4b			16 ± 1	Y	No stick	0.89 ± 0.20	1.09 ± 0.10	235.9 ± 62.8	2.33 ± 0.56	D

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Table 2
Technological performance of films obtained $NaPMM_2$ plasticized by 20% PEG400 and loaded with ketoprofen (KP) and paracetamol (PAR). Results are expressed as the mean of five determinations ± standard deviation. Tensile pattern is classified according an alphabetic code referring to the high elongation at break (D) or sharp (N) or slow (T) variation of the film cross section. For a more detailed description, refer to the text.

Form	Thickness (μm)	Drug content (mg/cm^2)	Disintegration time		t_{80} (min)		Y (MPa)	σ_{max} (MPa)	ε (%)	TEB (MPa)	LOD (%)	Tensile pattern
			Water	Saliva	Water	Saliva						
6 (PAR 50%)	192 ± 10	12.5	< 30 s	< 30 s	< 5	< 5	0.34 ± 0.21	1.31 ± 0.43	47 ± 8	0.50 ± 0.14	12 ± 2	T
7 (PAR 70%)	189 ± 8	20.5	< 30 s	< 30 s	< 5	< 5	1.33 ± 0.19	1.80 ± 0.16	6 ± 1	0.10 ± 0.00	12 ± 2	N
8 (KP 25%)	168 ± 48	4.2	> 15 min	> 15 min	< 5	10 ± 1	4.17 ± 1.14	1.58 ± 0.23	181 ± 22	1.65 ± 0.26	11 ± 1	N
9 (KP 25% + TA)[a]	109 ± 3	4.2	< 30 s	1 min	< 5	< 5	1.24 ± 0.41	2.86 ± 0.62	52 ± 4	1.21 ± 0.25	19 ± 0	T
10 (KP 50%)	173 ± 9	8.3	> 15 min	> 15 min	< 5	< 5	0.14 ± 0.07	0.61 ± 0.24	197 ± 53	0.88 ± 0.33	18 ± 5	D

[a] In case of KP loaded films, 5% surfactants (TA), namely 2.5% Tween®80 and 2.5% Span® 80, were added to counterbalance the effect of weak acidic drug on $NaPMM_2$.

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2.7. Probe Tack Test

The probe tack test measures the force required to separate the test probe tip from a placebo ODF. Experimental conditions were set according to an internal standard procedure, using a tensile testing machine equipped with a 50 N load cell (Instron 5965, UK) (Cilurzo et al., 2015). Measurements were carried out after a 5-min period of exposure to ambient conditions. Film samples were cut to obtain 2×2 cm specimens. A strip of double-coated tape (TESA, G), having the same size of the film specimen, was applied on the flat bottom plate of the tensile testing machine. The specimen was superimposed against the double-coated tape. The flat stainless steel probe (diameter: 6 mm) was placed about 0.05 mm above the film. The probe was then lowered onto the film surface and a constant force of 0.05 N was applied onto the sample for 5 s and, finally, the probe was removed at the debonding rate of 0.1 mm/s. The absence of film residues on the probe surface (adhesive failure) was visually determined. The whole force–distance curve (compression and traction) was recorded. Maximum detachment stress was calculated by dividing the maximum detachment force by the probe surface and it was expressed in force per unit area (kPa).

2.8. Tensile Properties

Tensile testing was conducted according to ASTM International Test Method for Thin Plastic Sheeting (D 882–02) using an Instron 5965 texture analyzer (Instron, UK), equipped with a 50 N load cell. The films cut into 80×15 mm strips, were equilibrated at 25±1 °C for 2 weeks.

Each test strip was placed longitudinally in the tensile grips on the texture analyzer. Initial grip separation and crosshead speed were 40 mm and 12.5 mm/min, respectively. The test was considered concluded at the film break. The following parameters were determined:

Tensile strength (σ) was calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa).

Percent elongation at break (ε) 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 Eq. (1):

$$\varepsilon = \frac{L - L_0}{L_0} \times 100 \quad (1)$$

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* (Y) 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 (TEB) was defined by the arean under the stress–strain curve. The value is in units of energy.

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

2.9. Optical Microscopy

The overall morphology and appearance of the ODF were evaluated by optical microscopy with a stereomicroscope (Nikon, I). Micrographs were acquired at 20× magnification with a digital camera of 3.1 Mpx (CCD 3, ToupView, ToupTek, China).

2.10. Thermal Analysis of Drug Loaded ODF

Specimens of the drug as such and of the drug loaded ODF exactly weighted were sealed into 40 μL pin holed aluminum standard pans and subjected to a heating ramp at the rate of 10 K/min in a DSC1 Stare System (Mettler Toledo, CH). The DSC cell was purged with a dry nitrogen flow of 80 mL/min. The system was calibrated using an indium standard. Data were treated with Stare System software (Mettler Toledo, CH).

2.11. Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR)

FTIR measurements were performed using a Spectrum™One spectrophotometer (PerkinElmer, USA), by placing the samples on a diamond crystal mounted in ATR cell (PerkinElmer, USA). The spectra recorded at 4 cm^{-1} resolution and 32 scans were collected over the wavenumber region 4000–650 cm^{-1}. The analyses were performed on raw polymers and ODF.

To assess the homogeneity in composition, FTIR spectra were recorded at least in two different points of the cast materials.

2.12. Disintegration Test

The disintegration test of films was carried out in water and pH 5.7 artificial saliva (Cilurzo et al., 2003) on 3×2 cm sample according to specifications of the monographs on "Disintegration of tablets and capsules" reported in the Ph. Eur. The test was considered satisfied when the disintegration time was lower than 3 min according to the Ph. Eur. requirement for orodispersible tablets.

2.13. In Vitro Dissolution Test

The in vitro dissolution test was carried out in a Ph. Eur. paddle dissolution apparatus. Samples of drug loaded films were exactly weighed in order to assure the sink condition. The dissolution medium was 900 ml freshly deionized water or pH 5.7 artificial saliva (Cilurzo et al., 2003), maintained at 37±1 °C and stirred at 50 rpm. Drug concentrations were assayed spectrophotometrically at 233 nm and 243 nm for ketoprofen and paracetamol, respectively (UV–Vis spectrometer, Lambda 25, Perkin Elmer, I). The calibration curves built in both dissolution media, ranged from 1 μg/mL to 70 μg/mL ($R^2 > 0.99$). The results are expressed as t_{80}, namely the time required to dissolve the 80% of the drug.

3. Results and Discussion

3.1. Placebo Formulations

The placebo formulations were designed by adding different PEG400 amount to $NaPPM_2$ (Table 1) since the films made of 100% *w*/w $NaPPM_2$ cracked after being bent 5 times on the mandrel. The polymeric dispersions were dried in different operative conditions (i.e., temperature, time and air speed) in order to identify the possible effect of the drying parameters on the aspect and mechanical properties of the film. A preliminary screening revealed that drying above 80 °C, independently of the residue of water, led to a brittle film containing bubbles, while low temperatures (lower than 60 °C), or the lowest air inlet, gave a film characterized by a ripple surface. In the 60–80 °C range, the LOD content can be easily controlled by drying time and air inlet and, therefore, its impact on film features was investigated.

The placebo ODF listed in Table 1 had a uniform thickness of about 100 μm and were homogeneously transparent in appearance, easy-to-cut without cracks or other visible failures.

A critical attribute for an ODF is the stickiness that can affect patient's handling. In the case of $NaPMM_2$ this property should be carefully evaluated since this material was proposed for the design of pressure sensitive adhesives suitable for the development of transdermal patches (Cilurzo et al., 2014). Thus, the stickiness of the formulations was evaluated qualitatively by thumb tack test and quantitatively by probe tack-test. Both assays evidenced that non-sticking films were obtained only at PEG400 contents lower than 40% *w*/w. At highest concentration, the ODF stickiness was also related to the water content. In particular the probe tack test evidenced that, at the highest LOD value, the maximum detachment stress ranged from 12±2 kPa (Form. 4a, Table 1) to

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44 ± 14 kPa (Form. 5, Table 1) suggesting the former value as the limit which would assure that an ODF can be easily handled and removed from the primary packaging (Borges et al., 2015).

Focusing on film tensile properties, Fig. 1 exemplifies the possible patterns exhibited by the designed formulations. All films exhibited a linear region at low strain, which is associated to the reversible deformation. Increasing the strain, the behaviour shifted from elastic to plastic, the curve lost linearity and the deformation became irreversible, until the maximum force (tensile strength, σ) was reached. Afterwards, the general profiles were outlined on the basis of PEG400 concentrations and LOD, and three different patterns were identified. Based on the profiles and for the sake of completeness, an alphabetic code corresponding to tensile profile was assigned to each film formulation. First, the maximum value was followed by a plateau at a lower value due to a local reduction of the cross section, namely "*tear*" or "*necking*", which propagated along the length of the sample until rupture. The necking profile of films can be referred to a pronounced and sharp reduction at a lower value (code N, Fig. 1) or a slow and smooth decrease of cross section upon increasing the tensile stress (code T, Fig. 1). Finally, the elongation at break, which is an index of film ductility, increased up to 200% (code D, Fig. 1).

From a quantitative point of view, increasing the PEG concentration, both σ_{max} and Y values dropped down and the ductility prevailed. This trend, along with the progressive increase of the ε values, is in line with a plasticization-dominated mechanism, even if it is significantly influenced by the LOD value. Indeed, for formulations with PEG400 content lower than 40% *w*/w, the pattern shifted from brittle toward flexible, according to the LOD values. At the 40% w/w PEG400 concentration, the increased in the LOD value improved the film ductility and at the highest value films became sticky (Table 1).

On the basis of the tensile properties, the optimal plasticizer concentration ranged from 10 to 30% w/w. Indeed, a certain degree of elasticity is desired to avoid film brittleness, which would make it impossible to roll the film on itself for intermediate storage and transport (i.e., jumbo roll), to cut it into smaller reels of variable width and finally to punch or cut it to the desired size (Dixit and Puthli, 2009). Indeed, in this plasticizer range, ε values ranged from 30 to about 100%, that are in the same order of magnitude of ODF prepared with other polymers, such as PVA, HPMC (Tayel et al., 2016), Carbopol® and hypromellose (Visser et al., 2015; Visser et al., 2017), already used to manufacture some of marketed dosage forms (Preis et al., 2014). Moreover, the suitable ε values were associated to σ_{max} values at least doubled with respect to those reported in literature for the above-mentioned materials, which ranged from 0.6 to 4 MPa. Therefore, it can be assumed that $NaPMM_2$-based films can bear the tangential stresses applied during manufacturing and packaging procedures. Conversely, at the 40% *w*/w PEG400 content, the too high ductility imply that the film easily undergoes elongation when a tangential stress is applied (Table 1). Therefore, during unrolling and cutting these films could present problems, which might lead to a variation of the drug amount per film.

All films disintegrated in < 30 s satisfying both the FDA and European Pharmacopeia requirements for orodispersible dosage forms.

3.2. Drug Loaded Formulations

One of the main drawback of ODF as dosage forms is the limited amount of drug that can be loaded in an 8 cm^2 surface which is the largest dimension of an ODF perceived as acceptable by patients. The simple increase in drug loading can affect not only the viscosity of the casting solution (Visser et al., 2015), but also the mechanical properties of the film (Cilurzo et al., 2011) and the drug stability (Visser et al., 2017). Therefore, these dosage forms are generally intended to administer potent drugs (Borges et al., 2015; Dixit and Puthli, 2009).

In the current work, the feasibility of drug loading was evaluated on ODF plasticized by 20% *w*/w PEG400. ODF containing 50% and 70% w/w of paracetamol appeared white and opaque with a very irregular surface (Fig. 2a–b). Such irregularities were more evident at the highest drug loading, suggesting that the amount of $NaPMM_2$ might not be enough to uniformly coat the dispersed drug particles. Moreover, the casting process did not cause variation on the drug solid state since the onset of the melting event of paracetamol loaded in ODF (T_m = 164.4 ± 0.4 °C) overlapped with that of paracetamol as such (T_m = 168.0 ± 0.0). However, the drug resulted partially dissolved in the ODF matrix as evidenced by the decrease of melting enthalpy (raw paracetamol ΔH_m = 174.6 ± 0.1 J/g; Form. 6 = 8.15 J/g; Form. 7 ΔH_m = 92.0 ± 1.2 J/g). Table 2 enlists the main characteristics of the loaded ODF. As expected, maintaining the coating thickness of the casting solution constant, the final ODF thickness increased. Nevertheless, the disintegration time did not prove to be influenced and the ODF promptly released paracetamol, which was completely up to 80% in < 5 min both in water or in artificial saliva (Table 2).

The presence of paracetamol did not influence either the film stickiness or flexibility, independently of the drug content. On the contrary, the higher the drug content, the lower the film tenacity (Table 2) which remained in the range of acceptability.

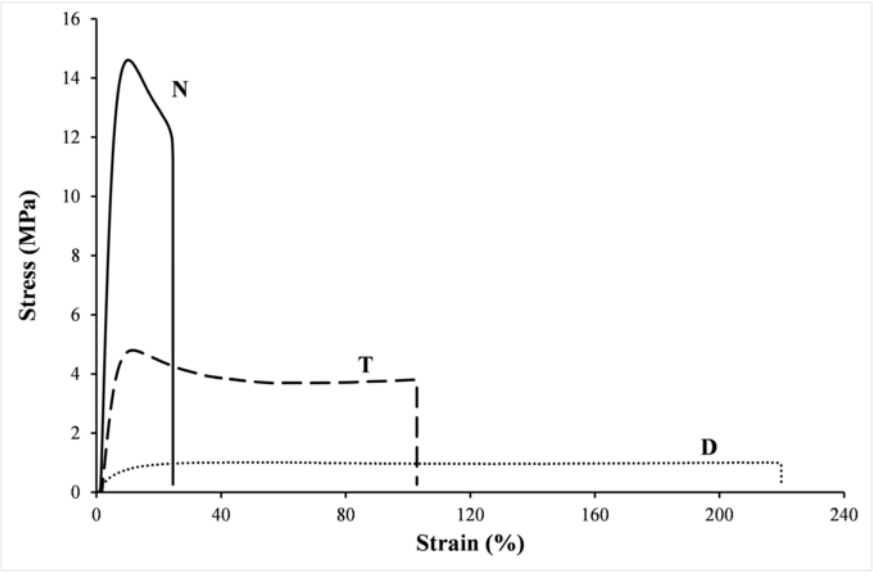

Fig. 1. The representative stress–strain curves. Tensile behaviour is classified according to an alphabetic code referring to the sharp (N, dashed line, Form. 2b) or slow (T, solid line, Form. 3a) variation of the film cross section and pronounced elongation at break (D, dotted line, Form. 4b). For a more detailed description, refer to the text.

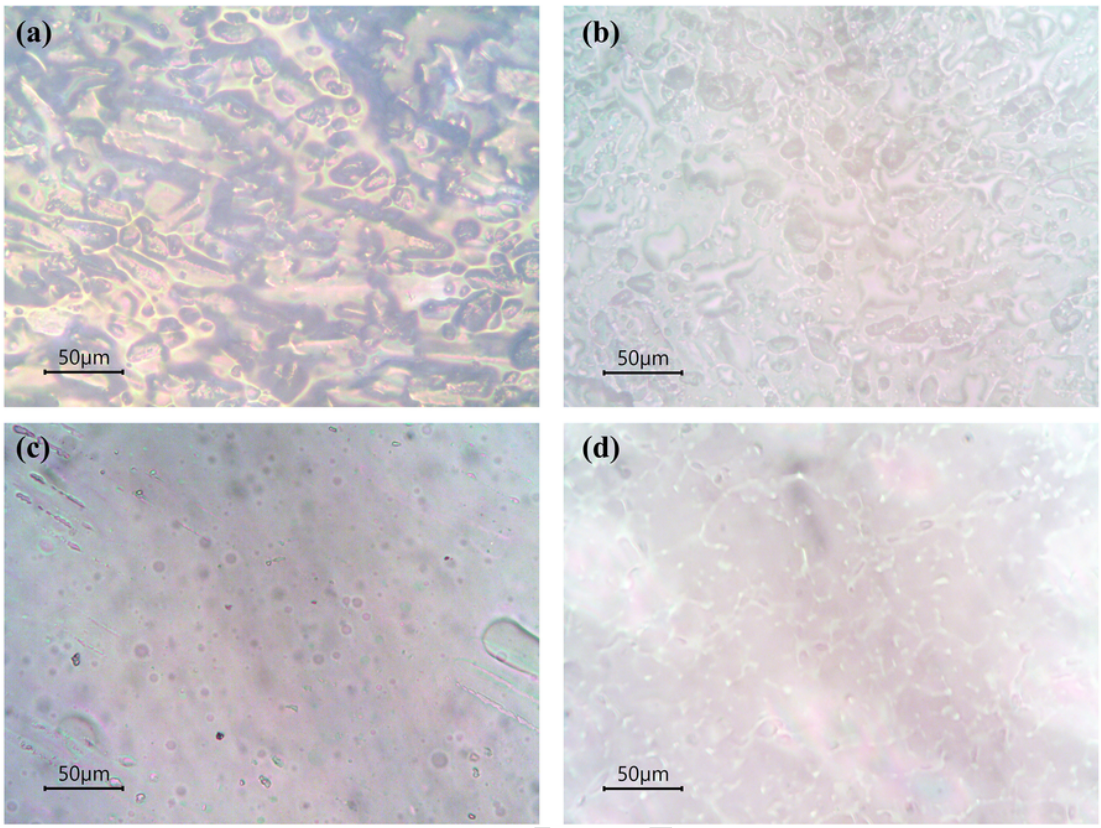

Fig. 2. Microscopic images of the surface of ODF loaded by paracetamol at the concentration of (a) 50% *w*/w and (b) 70% w/w and ketoprofen at the concentration of (c) 25% w/w and (d) 50% w/w.

Hence, it can be assumed that $NaPMM_2$ allows designing ODF containing 125 mg paracetamol on a surface of about 6 cm^2, maintaining acceptable tensile and biopharmaceutical properties.

ODF loaded with 25% *w*/w ketoprofen were transparent with a smooth surface similarly to the placebo formulation suggesting the ability of $NaPMM_2$ to solubilize ketoprofen (Fig. 2c). Increasing the drug content to 50% w/w, brittle films with a cracked surface were obtained (Fig. 2d). The differences in morphology were consistent with thermal data, since in DSC traces of ketoprofen loaded films, no events at about 96 °C attributed to drug melting were evident.

The addition of a weak acidic drug, i.e. ketoprofen ($pK_a = 4.45$), prevented the disintegration of the ODF which swelled both in water and artificial saliva (Form. 8 and 10 in Table 2) suggesting a partial protonation of $NAPMM_2$. Indeed, in the case of water the disaggregation medium pH significantly dropped from 7.6 to 4.4. The lack of disintegration influenced the drug dissolution only in the case of the film loaded with the lowest drug amount (Form. 8), using artificial saliva as dissolution medium. In this case the t_{80} increased to about 10 min (Table 2).

To verify the protonation of $NaPMM_2$, ATR-FTIR spectra of ketoprofen loaded formulations were compared to that of the placebo film and $HPMM_2$. The attention was focused in the region from 1800 to 1300 cm^{-1} where the anti-symmetrical and symmetrical vibrations of the carboxylate groups on $NaPMM_2$ are detected at 1560 cm^{-1} and between 1400 and 1300 cm^{-1}, respectively. In case of the loaded ODF, the intensity of both bands underwent a significant depression with respect to the placebo film (Fig. 3). The ratio between the intensity of the C=O of the ester group at about 1730 cm^{-1} and anti-symmetrical vibration of the COO^- at about 1555 cm^{-1} increased as a function of the drug content confirming the re-protonation of methacrylate groups.

The lack of disintegration in presence of the acidic ketoprofen was overcome by adding Span®80 and Tween®80 at 5% *w*/w. As an example, in the case of 25% w/w ketoprofen-loaded ODF (Form. 9, Table 2), the presence of the surfactants allowed to satisfy the disintegration test without compromising the film mechanical properties (Table 2).

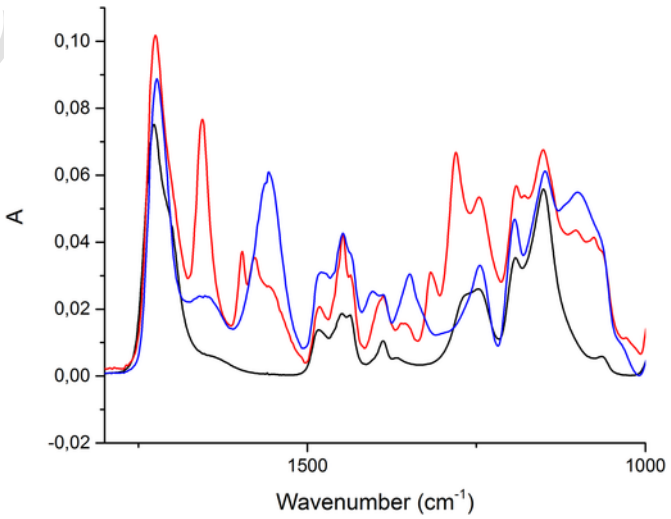

Fig. 3. ATR-FTIR spectra of $HPMM_2$ (black line), placebo ODF (blue line) and film loaded by 50% w/w ketoprofen (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Conclusions

All the presented data, discussed in the framework of the information available on $NaPMM_2$, underlined the versatility of such material that can be easily obtained by a simple salification of poly(methyl methacrylate)s that are safe excipients already included in the main pharmacopeia monographs. Indeed, the surface, mechanical and dissolution properties of $NaPMM_2$ can be modulated by adding a bivalent inorganic salt (Cilurzo et al., 2005) or a plasticizer. In the former case, it is possible to tailor the residence time of mucoadhesive dosage

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forms. In the latter case, their film-forming properties can be exploited to design pressure-sensitive adhesive suitable for medicated plasters (plasticizer amount higher than 40% *w*/w) or, as demonstrated in this work, ODF (PEG400 content lower than 30% w/w) with improved mechanical properties with respect to several polysaccharides already proposed to formulate these dosage forms. Indeed, all ODF showed satisfactory ductility, flexibility and resistance to elongation for the production, packaging and handling procedures. Last but not least, the drug loading up to 70% w/w of film weight appears to be the largest value described in literature.

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