



Extemporaneous Printing of Diclofenac Orodispersible Films for Pediatrics

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Extemporaneous Printing of Diclofenac Orodispersible Films for Pediatrics

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Abstract:

Objective: The possible application of a hot-melt ram extrusion printing to the preparation of diclofenac orodispersible films (ODF) made of maltodextrin was studied focusing the attention on the effects of taste-masking agents (i.e., namely mint, licorice-mint, and sucralose) and an opacifier (TiO₂).

Significance: This is a proof-of-concept of the feasibility to print ODF loaded with a thermosensitive drug substance by hot-melt technologies.

Methods: DNA ODF made of maltodextrin (DE=6) plasticized with glycerol were prepared by hot-melt extrusion printing. ODF were characterized for disintegration time, drug content and solid state, *in vitro* dissolution in deionized water and simulated salivary fluid pH 5.7, tensile, and adhesive properties. Moreover, the stability of ODF was assessed in accelerated conditions over six months.

Results: After the preparation, no variation in drug solid state was evident and the formation of impurity A of DNA was detected even if it remains below the Ph. Eur. limits (< 0.2%). Only the addition of DNA significantly improved the ODF tensile properties: the tensile strength increased from 0.17±0.03 MPa (placebo ODF) to 2.21±0.54 MPa (p≤0.03). All ODF disintegrated in about 1 min, and the t_{80%} was lower than 3 min. TiO₂ reduced the static and dynamic peel forces (p≤0.006) favoring the detachment the ODF from the primary packaging material. During the accelerated stability study, ODF were easy to handle without fracture; the drug content, impurity A, and dissolution profiles remained superimposable.

Conclusion: Hot-melt printing can be suitable to prepare palatable ODF loaded with bitter thermosensitive drugs.

Keywords: chemical stability; maltodextrins; hot-melt; printing; taste masking; tensile properties; pediatrics; diclofenac; ODF

Introduction

Orodispersible films (ODF) are unique unit dosage forms intended to be placed onto the tongue where they rapidly dissolve or disintegrate in contact with saliva to form a suspension or solution of the loaded drug easily to be swallowed. ODF exhibit several merits over the conventional oral dosage forms. For instance, their administration does not require water or chewing. These features make them relevant for groups of patients, such as uncooperative, those with swallowing deficits, patients with restricted water/fluid intake, or travelers with limited or no access to water [1]. ODF have been recently also proposed as an alternative technological platform for customizing small batches [2] to address the unmet needs of a patient, and therefore, to improve therapeutic adherence [3, 4], or to overcome a limitation in dose or dosage forms of medicinal products available on the market [5].

Among the critical quality attributes of ODF, satisfactory tensile properties to guarantee packaging and handling during administration without breakage, the disintegration and dissolution in the oral cavity, acceptable taste [6, 7, 8], aesthetic appearance, and stability of the dosage form itself and the loaded drug(s) are of paramount importance.

In particular, appropriate selection of taste-masking agents (TMA; i.e., sweeteners and/or flavoring agents) is fundamental to improve the palatability of oral dosage forms and patient compliance [8, 9], but it is required to consider also the drug properties, the compatibility with other formulation components, the possible impact on the drug dissolution rate [10] and mechanical properties [6].

The preparation of ODF can occur by traditional solvent casting technique or printing technologies which have received extensive attention to develop ODF especially for personalized dosing [11, 12]. Recently, we proposed a novel hot-melt extrusion printing technique for the extemporaneous preparation of small batches of ODF made of

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2
3 maltodextrins plasticized with glycerol [12]. This technology is solvent-free and,
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5 therefore, can be advantageously used to load drugs which are chemically or physically
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7 unstable in aqueous or solvent systems and to eliminate the use of organic solvents. On
8
9 the other hand, the relatively high working temperature (~95 °C) could cause
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11 degradation of thermosensitive components.
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14 The present study investigated the feasibility to print ODF loaded with diclofenac
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16 sodium (DNa) which is a well-known thermosensitive and bitter drug. The possibility to
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18 tune the ODF surface in the attempt to prepare age-appropriate dosage form for
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20 pediatric patients was also studied. Indeed, diclofenac is frequently prescribed for
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22 pediatrics in special medical needs [13], but no liquid formulations (i.e. syrup or
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24 suspension) are commercially available due to its instability. Based on previous work,
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26 taste-masking agents (i.e., mint, licorice-mint and sucralose or a combination thereof)
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28 [7], and an opacifier (titanium dioxide, TiO₂), were also added to the formulation and
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30 their effects on ODF properties were assessed in terms of disintegration time, *in vitro*
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32 dissolution profile, tensile properties, and peel test. The solid state of the model drug
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34 was determined by differential scanning calorimetry (DSC) and thermogravimetric
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36 analysis (TGA). Moreover, to evaluate the robustness of this approach, a stability
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38 study in accelerated conditions was carried out over six months.
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47 **Materials and methods**

48 **Materials**

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50 Maltodextrin, with a dextrose equivalent equal to 6 (MDX, Glucidex® IT6), was
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52 obtained from Roquette (France). Diclofenac sodium (DNa), glycerol, and titanium
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54 dioxide (TiO₂) were purchased from Farmalabor (Italy). Sucralose was obtained from
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56 Sigma Aldrich (Italy). Mint and licorice mint flavors were kindly donated by Kerry
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Ingredients and Flavors Italia (Italy). All solvents were of analytical grade unless otherwise specified. For the dissolution studies, the following Simulated Salivary Fluid (SSF) was prepared: 1 L contained 0.844 g NaCl, 1.2 g KCl, 0.193 g $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, 0.111 g $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ and 0.342 g K_2HPO_4 , the pH was adjusted at 5.7 ± 0.1 using 1M hydrochloric acid (HCl).

ODF preparation

ODF were prepared by hot-melt printing as already described by Musazzi et al., [12].

As exemplified in **Figure 1**, a paste of the various excipients (**Table 1**) was prepared in a mortar and transferred into the extruding chamber heated at 95 ± 1 °C for 10 min. The melt was extruded to print the ODF of the desired dimensions (1×1 cm, 1×2 cm 2×3 cm or 2×10 cm) on a 20×20 cm aluminum primary packaging foil kindly provided by IBSA Spa (Italy). The printed ODF were sealed with another packaging aluminum foil without further manipulations. The ram speed (12 mm/s) and the chamber temperature were controlled by Repetier-Host 2.0.1 software (Hotword GmbH, Germany); the film dimension and number per each print were designed by 3D Builder® (Microsoft, USA) and converted in G-code.

Film thickness

The film thickness was measured by using a micrometer MI 1000 μm (ChemInstruments, USA). The accuracy of the instrument was $2.5 \mu\text{m} \pm 0.5\%$.

ODF water content

Loss on drying (LOD): the LOD of the ODF was determined gravimetrically by using a thermobalance (Gilbertini, Italy). Film samples were kept at 100 °C until constant weight, and the percentage of moisture loss was calculated.

Karl-Fisher titration water content determination: The apparatus (Mettler Toledo, Switzerland) was initially calibrated with anhydrous methanol. ODF sample was accurately weighed and transferred into an empty glass vial; then, 1.5 mL anhydrous methanol was added and sealed with a rubber closure. The vial was sonicated for 30 min; afterward, 0.5 mL of the prepared sample suspension was injected into the titration chamber. The water content was calculated according to Equation (1):

$$\text{water content (\%)} = \frac{M_s - M_m}{M_o} \times 100 \quad (1)$$

where:

M_s is the mass of water in the sample introduced into the titration chamber,

M_m is the mass of water in the anhydrous methanol

M_o is the initial mass of the ODF.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) analysis was performed using a DSC 1 Star^e system (Mettler Toledo, CH) operating with a Star^e software using (4–6 mg) samples in 40 µL aluminum pans with pierced lids at heating rate of 10 °C min⁻¹ and nitrogen purge at 80 mL min⁻¹. The system was calibrated using an indium standard.

Thermogravimetric analysis

Thermogravimetric analysis (TGA) analysis was performed using a Perkin Elmer system (Perkin Elmer 4000, Perkin Elmer, I) heating the samples from 30 to 200 °C at the heating rate of 5 K min⁻¹. The system was purged by nitrogen at 20 mL min⁻¹.

Drug content

A specimen of 2×3 cm was dissolved in 10 mL purified water, sonicated for 15 min and filtered by a 0.45 µm polypropylene membrane filter (VWR®, Italy). The filtered solution was then diluted 1:1. The drug concentrations were quantified by HPLC analysis (Agilent HP 1100, Chemstation, Hewlett Packard, Santa Monica, USA). The following chromatographic conditions were used: column: InterClone™ (5 µm ODS, 100 Å, 150×4.6 mm, Phenomenex®, USA); mobile phase: methanol/phosphate buffer pH 2.5 (66/34, % v/v); flow rate: 1.2 mL/min; wavelengths: 254 nm and 275 nm; temperature: 45 °C; injection volume: 10 µL. The drug concentrations were determined from a known standard curve in the 4–300 µg/mL range ($R^2 = 0.999$). The retention times of DNA and impurity A were 7.7 min and 4.7 min, respectively.

Tensile properties

Tensile tests were done using an Instron 5965 texture analyzer (Instron, UK) as previously described [11]. Briefly, 2×3 cm strips were equilibrated at 25±1 °C for one week, and the test was performed with a 2 cm initial grip separation and at 50 mm/min crosshead speed until sample breaks. The following parameters were calculated:

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

- Young's modulus or elastic 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 area under the stress-strain curve. The value is in units of energy per unit volume of the specimen's initial gage region;
- percent elongation at break (ϵ) was calculated by dividing the extension at the moment of rupture of the specimen by the initial gauge length of the specimen and multiplying by 100 according to Equation (2):

$$\epsilon(\%) = \frac{L - L_0}{L_0} \times 100 \quad (2)$$

where:

L_0 is the initial gauge length of the specimen,

L is the length at the rupture.

An average of five measurements was taken for each formulation.

Peeling from the packaging materials

The test was conducted on 2×10 cm printed ODF using an Instron 5965 texture analyzer (Instron, UK). Two experimental setups were employed to mimic the in-use conditions (i.e., the peeling of the ODF from the primary packaging material by the patient or the caregiver, protocol A) or to discriminate the impact of the excipients on the ODF adhesion to the primary packaging material, protocol B.

Protocol A: about 0.5 cm of the film was carefully separated from the primary packaging material, and an adhesive tape leader (0.3 cm) was attached to the film and the packaging material separately. The prepared specimens were stored at 25±0.1 °C for

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3 15 min and then positioned horizontally to the instrument's clamps with the free ends of
4 the tape leaders of the film and packaging material inserted into the upper and lower
5 grips respectively. Five specimens each were freely pulled at a peel speed of 300
6 mm/min. F1 and F11 were tested with this setup.
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12 *Protocol B:* Double-faced adhesive tape was used to fix the backside of the primary
13 packing material of the film onto a stainless-steel standard plate. Each film was folded
14 about 0.5 cm from the primary packaging, and a tape leader was placed on about 0.3 cm
15 of the exposed film with the adhesive side of the tape attached to one end of the film
16 (bottom). The film was smoothed with a 2 Kg roller to and pro twice. The remaining
17 part of the tape leader was folded on itself to form a double thickness leader, and the tip
18 of the tape was then attached to the film (top). Each specimen was placed on the
19 instrument with the stainless-steel plate fixed to the lower grip at 180° angle and the
20 free end of the tape leader being placed into the upper grip. Five specimens each were
21 pulled from the plate at a peel speed of 300 mm/min. Formulations; F1, F2, F6, F11,
22 F12, and F13 were tested.
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37 The static peel force was calculated as the arithmetic mean of all values of the linear
38 portion of the curve. The dynamic peel values were calculated by dividing the registered
39 forces by the width of the film and are expressed in newton per millimeter (N/mm). The
40 results are expressed as the mean $\pm$ standard deviation of five specimens.
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49 **Disintegration test**

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51 The disintegration test was carried out according to specifications of the monograph on
52 the "Disintegration of tablets and capsules" reported in the Ph. Eur. The results
53 complied with the Ph. Eur. requirements for orodispersible tablets if the disintegration
54 time was lower than 3 min.
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In vitro dissolution test

The in vitro dissolution test was conducted using Ph. Eur. basket dissolution apparatus SR8 PLUS dissolution test station (Hanson Research, Chatsworth, USA). The dissolution media were 500 mL freshly deionized water and SSF maintained at 37 ± 1 °C and stirred at 25 ± 1 rpm [10]. DNA loaded ODF samples (2×3 cm) were used. DNA concentrations were assayed spectrophotometrically at 275 nm (UV–Vis spectrometer, Lambda 25, Perkin Elmer, Italy) after 1, 2, 3, 6, 9, 12, 18 and 24 min, and the calibration curves were in the range of 10–100 µg/mL ($R^2 = 0.999$). The results were expressed as the mean and standard deviation values of three replicas for each tested formulation. The dissolution results were expressed as the time required for releasing 80% of the DNA (t_{80}).

Accelerated stability study

Accelerated stability study was performed on formulations F2, and F13 (Table 1). Samples were stored at 40 ± 2 °C and $75 \pm 5\%$ relative humidity (Mettler Climate Chamber ICH110, GmbH, Germany). At each sampling point (i.e., 0, 1, 3 and 6 month), ODF were visually inspected, and the *in vitro* dissolution in SSF performed, and drug content and possible impurities assayed as previously described.

Statistical analysis

The performances of the ODF were compared by paired t-test and analysis of the variance (one-way ANOVA) followed by Bonferroni post-hoc analyses (IMB SPSS V25). The level of significance was taken as $p < 0.05$. Outliers were rejected, according to Dixon's t-test.

Results and Discussion

ODF characterization

The adopted experimental condition permitted to obtain DNA loaded ODF without significant visual defects; the further addition of TiO₂ made their appearance completely homogenous and whitish (insert D in Figure 1). The range of ODF thickness was suitable for the patient's handling (Table 1). The residual water content observed was acceptable for this type of formulation [12], despite the differences related to the measurement method (Table 1). Indeed, LOD was determined by a thermobalance that measures the evaporation of adsorbed water on the surface, while the Karl-Fisher titration measures both the surface unbound and bound water. All formulations disintegrated within 80 s complying the Ph. Eur. specifications.

The formulation components influenced the tensile properties of ODF. As an example, Figure 2 shows the stress-strain curves for the placebo films (F1 and F10) and the DNA loaded ODF (F2), DNA ODF with all TMA (F6), and DNA, TMA and TiO₂ loaded ODF (F13). At low strain values, the tensile profile of all ODF appeared linear, indicating elastic deformation. Afterward, the behavior was mainly dominated by the type of loaded excipients. Indeed, the tensile strength (σ), which is an index of the maximum force reached by each film before plastic deformation, markedly increased in drug-loaded ODF independently of the presence of TMA. The deformation became plastic with the strain increase; the neck formation was also observed in all formulations, even though it was more prominent in the placebo ODF. Hence, it was evident that the σ and elasticity were predominantly influenced by the loading of DNA and partly by TiO₂, rather than TMA. Table 2 summarizes the quantitative results of the tensile measurements.

As already mentioned, the loading of DNA into ODF increased the σ values (F1 versus F2) ($p \leq 0.03$). This trend was also maintained in the DNA loaded ODF containing TMA, as a single component or in combination (F1 versus F3, F4, F5, and F6) ($p \leq 0.01$). However, the overall contribution of TMA on the tensile properties was limited since the σ values measured for F2 and F6 did not significantly change, even when the nano-sized TiO_2 was added in F13. This finding markedly differs from those reported for ODF with the same composition obtained by solvent-casting, where the addition of TMA increased the plasticity compared to the placebo formulation [10].

Adding only DNA (F2) or a combination with all TMA (F6) (**Table 2**), the ϵ values decreased with respect to placebo ODF (F1) about 9- and 14-folds, respectively ($p < 0.0001$). In parallel, a decrease in the film elasticity (Y) in both F2 and F6 was observed in comparison to F1 ($p < 0.01$). The increase of the Y -value was also measured comparing F1 to formulations containing DNA and a specific TMA (i.e., F3, F4, and F5). Moreover, lower Y was measured when TMA were added individually to the placebo ODF (F2 versus F7, F8, and F9). This trend shows that the observed increase in Y was predominantly due to the presence of DNA.

Finally, the ODF toughness, measured as the tensile energy to break (TBE), increased by loading DNA (F1 versus F2, $p < 0.01$) and decreased after also adding TMA (F2 versus F6, $p < 0.0001$). A similar result was also observed comparing the TBE valued of F2 with those of placebo ODF loaded by a specific TMA or combination thereof (F2 versus F7, F8, F9, and F10, $p \leq 0.02$). Moreover, no significant differences in TBE were evident comparing the value registered for F6 to those obtained by F7, F8, and F9.

These results demonstrated that the decrease in the film toughness could be mainly attributed to the TMA.

As expected, TiO_2 decreased DNA loaded film's elasticity, as evidenced by an increase in the Y value (F2 versus F12, $p < 0.05$; and F2 versus F13, $p = 0.004$). This data agrees with previous data concerning not only TiO_2 [12] but also other nanosized materials such as poly-(vinyl acetate) nanoparticles [14, 15] and quercetin nanocrystals [16]. In all these cases, such materials increased the stiffness of maltodextrin made ODF, suggesting that the size of particulate can be used to tune the tensile properties of ODF. In order to deeply understand the influences of TiO_2 on the film mechanical properties, the force required to peel-off the ODF from the primary packaging material, on which the ODF was printed, was studied.

When the real condition for the ODF peeling was simulated (method A, **Table 2**), F1 was characterized by high static and dynamic peel forces required to detach the ODF from the packaging material compared to F11. Moreover, F1 shows an erratic detachment pattern indicating high intimate contact between the ODF and the packaging material so that more energy was required to separate them. In contrast, a linear curve was obtained with low static and dynamic peel forces and a steady detachment pattern when TiO_2 was added in F11 (**Figure 3**).

The anti-sticking role of the TiO_2 loaded ODF on the packaging material was then deepened by using method B. The data in **Table 2** showed that when pressure was applied on the ODF/packaging material and the detachment angle fixed, the anti-sticking effect of TiO_2 was maintained. Indeed, F11, F12, and F13 were characterized by lower static and dynamic peeling forces, as indicated by the maximum (static) peel force and the dynamic peel force ($p \leq 0.01$), in comparison to formulations F1, F2, and F6, respectively. Moreover, the presence of DNA in the ODF synergized the effect of TiO_2 on the two peeling forces (F11 versus F12 and F13, $p \leq 0.01$). In other words, the

presence of TiO₂ favored the peeling from the primary packaging, an indication of ODF handling without damage.

Solid state characterization

A DSC study was carried out to determine the solid state of DNa. In agreement with literature data, DSC trace of pure DNa showed two endothermal events with a sharp peak at about 56 °C and a broad one at 76 °C (**Figure 4**) which correspond to the dehydration of DNa tetrahydrated [17]. The first endotherm was due to the loss of less bound water); the second endotherm represented a composite heat effect due to the fusion of the solvate crystals and the evaporation of the main portion of bound water [17]. The mass loss determined by TGA and the enthalpy ($\Delta H = 380$ J/g) associated to these events confirmed to the loss of four water molecules. Then, a sharp endothermic melting peak at about 270 °C was followed by complex endo–exo phenomena mainly due to decomposition [18]

MDX 6 presents glass transition temperature (T_g) at about 103 °C [19] and the mixing with plasticizer(s), i.e. water or glycerol, caused a massive drop in its value [20].

Regarding the placebo ODF, due to the hydrophilic nature of all components, a wide endothermic attributed to water evaporation was evident at temperature lower than 100 °C (**Figure 3**). Upon loading DNa, in the same temperature range a sharp peak at about 69 °C probably due to loss of hydration water of the crystalline drug (**Figure 3**).

Unfortunately, the extensive decomposition of ODF undergone up to 130 °C due to the ODF degradation, prevented further characterization. In any case, the collected data evidenced that the preparation method did not change the diclofenac solid state.

Drug content and in vitro dissolution properties

DNa, 25 mg equivalent of diclofenac, was successfully loaded in the ODF (**Table 3**), and the drug content complied with the pharmacopeia limits. Nevertheless, heating at 95 °C, as required by the preparation protocol, caused the formation of the impurity A of DNa [Ph. Eur. Monograph on Diclofenac sodium (01/2017:1002)], which, in any cases, represented less than 0.2 %w/w (**Table 4**) for F2 and F13. The dissolution profiles of formulations F2, F6 and F13 were superimposable in deionized water (**Figure 5A**), and pH 5.7 SSF (**Figure 5B**), with $t_{80\%}$ approximately 3 min in all three formulations. Based on these results, F2 and F13 were considered suitable for an accelerated stability study.

Accelerated stability study

After six months of storage of the ODF in accelerated conditions, the physical appearance was unaffected: ODF were non-sticky and remained easy to handle without fractures. The drug content and the impurity A of DNa remained within the acceptable range over time according to the Ph. Eur. specifications (**Table 4**). The *in vitro* dissolution profiles of DNa loaded in F2 or F13 were superimposable over time (**Figures 6A and 6B**), confirming the t_{80} detected at time 0 within 3 min. Moreover, in all cases, the complete drug release was achieved in less than 10 min.

The overall results confirmed that hot-melt printing is a versatile method for the extemporaneous preparation of ODF made of maltodextrins. Indeed, the formulation space given by such a technology permits to load in the ODF with different TMA to mitigate the unpleasant taste of drugs, like DNa, without altering the ODF technological properties. However, this is not a rule of thumb, as several authors reported that the addition of TMA may influence ODF tensile properties and this aspect is evident in ODF prepared by solvent casting, regardless of the matrix-former excipient used in the

preparation. As an example, an irregular pattern of tensile strength was reported for hydroxypropyl methylcellulose-corn starch-based films loaded with donepezil hydrochloride and different TMA (i.e., aspartame, sucralose, saccharin sodium, and pineapple flavor) [21]. A significant alteration of tensile properties was also reported in the case of ODF made of maltodextrins and loaded by nicotine [6]. On the contrary, the TMA effect on the tensile properties seems lower for the ODF obtained by hot-melt printing than for those with the same formula but prepared by the casting technique [10]. This feature can be attributed to the absence of solvent(s) in the proposed printing technology, which permits to obtain ODF with a slightly higher thickness.

Regarding the presence of TiO_2 , which was selected as a color additive to enhance ODF aesthetic appearance, this excipient significantly improved the film mechanical properties. The addition of 0.1% is sufficient to reinforce the ODF, as demonstrated by the significant increase of the tensile strength (F1 versus F11, **Table 2**). This effect has already been described when TiO_2 was loaded as a functional filler in pharmaceuticals and foods [22-24]. Interestingly, TiO_2 also exhibits anti-sticking properties; the peel forces required to detach the ODF from the primary packaging material was significantly reduced (**Table 2**). Thus, TiO_2 could be considered a functional excipient to control the ODF tackiness and, therefore, avoid failures during patient handling.

Finally, despite DNA is classified in the BSC Class II [25], all the studied formulations allowed a fast *in vitro* drug release in both media (i.e., deionized water and pH 5.7 SSF); t_{80} was attained within 3 min, and a complete drug release was achieved in less than 10 min in all cases. Thus, ODF formulations can be described as ‘rapidly dissolving’ dosage form according to the EMA guidelines for new drug products [26].

It should also be mentioned that even if DNA is a thermosensitive drug, its degradation during the printing procedures is minimal, since the impurity A was the only one detected

and remained below the maximum limit set by the Ph. Eur. ($< 0.2\%$). Most importantly, the DNA degradation pattern, namely additional impurities or significant changes of preparation-related ones, was not modified over time. Moreover, the *in vitro* dissolution profiles for the selected formulations were superimposable during the accelerated stability study period.

This data suggests that the period of stability of ODF produced by the hot-melt approach could be compliant with the requirements for compounding in pharmacy settings. Indeed, pharmacy preparations are assumed by the patients in a shorter time than industrially prepared medicinal products: their expiration period is within six months from the preparation.

Tuning the area (1 cm^2 and 2 cm^2 or 6 cm^2) of the optimized formulation (Formulation F13, **Table 3**), it would be possible to make available personalized dosage forms to manage acute migraines [27] and pain [28, 29] in pediatric patients. This aspect could be of interest for children, since to the best of our knowledge, there is no commercially available pediatric dosage form (e.g., syrup or suspension) of DNA due to its stability issues. Moreover, the high acceptability of ODF as a drug delivery platform has already been demonstrated in infants and children and caregivers [3] since they are a non-invasive and easy to administer, combining the advantages of liquid (e.g., immediate drug release) with those of solid dosage forms (e.g., API stability) [1]. All the formulation components are within the regulatory framework for acceptable daily intake (ADI) [30, 31]. For example, TiO_2 is a color additive approved by the Food and Drug Administration (FDA) for use in drugs for humans [31]. Furthermore, the amount incorporated (i.e., 0.1%) in the formulation, which is enough to enhance its aesthetic appearance, is far below the ADI recommended by both the FDA and the EU report on Dietary Food Additive Intake [30, 31].

Conclusions

Within the current regulatory frameworks for stability and critical quality attributes of ODF in compliance with the EMA and ICH guidelines [32], the feasibility of loading diclofenac sodium and the combination of TMA in the printed ODF without affecting the drug stability was demonstrated. The tensile properties were mainly dominated by the loaded drug, and not significantly affected by the TMA. Moreover, TiO_2 , which improved the ODF aesthetic appearance, also favored the ODF detachment from the primary packaging material. Therefore, hot melt printing can be proposed to prepare palatable ODF loaded by a bitter thermosensitive drug. The technology could be advantageously used in hospital pharmacy settings to allow a precise personalization of dose.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Table captions

Table 1. Compositions (% w/w) of the placebo and diclofenac sodium (DNa) ODF and their main features (n.d.: not determined).

Table 2. Tensile properties (mean $\pm$ SD, n=5) and static and dynamic peel forces of ODF from the primary packaging material (mean $\pm$ SD, n=5) of prepared ODF. n.d.: not determined.

Table 3. Drug contents and different dose strengths in ODF with different area.

Table 4. Diclofenac content (%) and impurity A (%) in formulation F2 and F13 during the accelerated stability study.

Figure captions

Figure 1. Schematic representation of ODF preparation according to ram-extrusion. A paste of the various excipients (**insert A**) was prepared in a mortar and transferred into the extruding chamber heated (**insert B**). The melt was extruded to print the ODF on aluminum primary packaging foil (**insert C**). The printed ODF of the desired dimensions were sealed without further manipulations (**insert D**).

Figure 2. Stress-strain curves of the placebo ODF (F1, black dotted line), DNA loaded ODF (F2, green solid-line), DNA plus TMA loaded ODF (F6, red solid-line), TMA only loaded ODF (F10, blue solid-line), and), DNA plus TMA and TiO₂ (F13, purple solid-line).

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Figure 6. *In vitro* dissolution profiles of DNa loaded ODF (F2) (A), DNa plus TMA+TiO₂ loaded ODF (F13) (B) in pH 5.7 SSF at time 0, 1, 3 and 6-month stability tests.

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Table 1 - Compositions (% w/w) of the placebo and diclofenac sodium (DNa) loaded ODF and their main features (LOD: loss on drying; MC: moisture content; n.d.: not determined).

Form.	ODF compositions (% w/w)							Thickness (μm)	Weight (mg)	LOD (%)	MC (%)	Dist. Time (s)	DNa content (%)
	MDX6	GLY	DNa	Mint	Licorice-mint	Sucralose	TiO ₂						
F1	80.00	20.00	-	-	-	-	-	220 $\pm$ 27	333 $\pm$ 26	3.3 $\pm$ 1.1	9.6 $\pm$ 0.1	38 $\pm$ 2	-
F2	70.40	17.60	12.00	-	-	-	-	252 $\pm$ 14	246 $\pm$ 5	3.7 $\pm$ 1.3	8.0 $\pm$ 0.1	46 $\pm$ 1	10.95 $\pm$ 0.14
F3	66.10	16.50	12.00	5.40	-	-	-	254 $\pm$ 13	251 $\pm$ 8	4.3 $\pm$ 0.8	n.d.	62 $\pm$ 3	12.19 $\pm$ 0.14
F4	68.20	17.10	12.00	-	2.70	-	-	259 $\pm$ 16	219 $\pm$ 6	3.7 $\pm$ 0.4	n.d.	72 $\pm$ 1	12.01 $\pm$ 0.47
F5	69.60	17.40	12.00	-	-	1.00	-	345 $\pm$ 11	295 $\pm$ 28	5.0 $\pm$ 0.3	n.d.	65 $\pm$ 4	14.75 $\pm$ 0.36
F6	63.10	15.80	12.00	5.40	2.70	1.00	-	292 $\pm$ 9	216 $\pm$ 3	4.2 $\pm$ 1.7	8.3 $\pm$ 0.0	56 $\pm$ 1	12.48 $\pm$ 0.21
F7	75.70	18.90	-	5.40	-	-	-	298 $\pm$ 9	258 $\pm$ 9	4.4 $\pm$ 0.4	n.d.	64 $\pm$ 5	-
F8	77.80	19.50	-	-	2.70	-	-	287 $\pm$ 9	238 $\pm$ 19	5.6 $\pm$ 0.4	n.d.	78 $\pm$ 2	-
F9	79.20	19.80	-	-	-	1.00	-	323 $\pm$ 18	246 $\pm$ 2	4.7 $\pm$ 1.2	n.d.	61 $\pm$ 1	-
F10	72.70	18.20	-	5.40	2.70	1.00	-	318 $\pm$ 17	200 $\pm$ 7	3.3 $\pm$ 0.5	8.1 $\pm$ 0.0	50 $\pm$ 1	-
F11	79.90	20.00	-	-	-	-	0.10	223 $\pm$ 4	190 $\pm$ 4	4.9 $\pm$ 0.1	8.4 $\pm$ 0.2	45 $\pm$ 8	-
F12	70.30	17.6	12.00	-	-	-	0.10	289 $\pm$ 9	249 $\pm$ 9	4.0 $\pm$ 0.4	8.8 $\pm$ 0.1	35 $\pm$ 6	12.45 $\pm$ 0.09
F13	63.00	15.80	12.00	5.40	2.70	1.00	0.10	271 $\pm$ 9	225 $\pm$ 1	3.8 $\pm$ 0.3	15.1 $\pm$ 0.4	72 $\pm$ 2	11.73 $\pm$ 0.71

Table 2 - Tensile properties (mean $\pm$ SD, n=5) and static and dynamic peel forces of ODF from the primary packaging material (mean $\pm$ SD, n=5) of prepared ODF. n.d.: not determined.

Form.	σ (MPa)	Y (MPa)	ϵ (%)	TBE (MJ/m ³)	Static peel force (N/mm)		Dynamic peel force (N/mm)	
					Method A	Method B	Method A	Method B
F1	0.17 $\pm$ 0.03	2.06 $\pm$ 0.65	850 $\pm$ 56	0.48 $\pm$ 0.08	0.038 $\pm$ 0.011	0.19 $\pm$ 0.05	0.015 $\pm$ 0.003	0.13 $\pm$ 0.03
F2	2.21 $\pm$ 0.54	47.38 $\pm$ 24.97	91 $\pm$ 12	1.45 $\pm$ 0.27	n.d.	0.07 $\pm$ 0.01	n.d.	0.05 $\pm$ 0.01
F3	2.29 $\pm$ 0.60	71.22 $\pm$ 27.90	103 $\pm$ 15	1.52 $\pm$ 0.33	n.d.	n.d.	n.d.	n.d.
F4	1.62 $\pm$ 0.59	44.24 $\pm$ 19.10	114 $\pm$ 33	0.97 $\pm$ 0.19	n.d.	n.d.	n.d.	n.d.
F5	1.39 $\pm$ 0.17	49.02 $\pm$ 12.33	103 $\pm$ 28	1.14 $\pm$ 0.22	n.d.	n.d.	n.d.	n.d.
F6	1.82 $\pm$ 0.76	77.80 $\pm$ 48.21	53 $\pm$ 18	0.57 $\pm$ 0.37	n.d.	0.05 $\pm$ 0.00	n.d.	0.02 $\pm$ 0.01
F7	0.38 $\pm$ 0.05	7.80 $\pm$ 1.64	256 $\pm$ 47	0.67 $\pm$ 0.18	n.d.	n.d.	n.d.	n.d.
F8	0.43 $\pm$ 0.08	7.30 $\pm$ 2.84	272 $\pm$ 53	0.68 $\pm$ 0.13	n.d.	n.d.	n.d.	n.d.
F9	0.28 $\pm$ 0.04	4.26 $\pm$ 1.04	375 $\pm$ 75	0.45 $\pm$ 0.08	n.d.	n.d.	n.d.	n.d.
F10	0.96 $\pm$ 0.10	25.04 $\pm$ 5.79	105 $\pm$ 7	0.69 $\pm$ 0.09	n.d.	n.d.	n.d.	n.d.
F11	1.33 $\pm$ 0.28	33.70 $\pm$ 11.70	144 $\pm$ 35	1.27 $\pm$ 0.11	0.020 $\pm$ 0.001	0.13 $\pm$ 0.03	0.009 $\pm$ 0.003	0.08 $\pm$ 0.01
F12	2.06 $\pm$ 0.31	87.16 $\pm$ 17.50	103 $\pm$ 1	1.52 $\pm$ 0.33	n.d.	0.04 $\pm$ 0.01	n.d.	0.02 $\pm$ 0.00
F13	2.25 $\pm$ 0.40	101.71 $\pm$ 15.52	49 $\pm$ 7	0.64 $\pm$ 0.10	n.d.	0.03 $\pm$ 0.00	n.d.	0.02 $\pm$ 0.00

Table 3 - Drug contents and different dose strengths in ODF with different area.

ODF area (cm ²)	F13 Drug Content	
	<i>DNa (mg)</i>	<i>DNa (%)</i>
1	3.90±0.01	11.44±0.53
2	9.43±0.42	11.13±0.17
6	25.66±1.51	11.73±0.71

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Table 4 - Diclofenac content (%) and impurity A (%) in formulation F2 and F13 during the accelerated stability study.

Time (months)	F2		F13	
	<i>DNa (%)</i>	<i>Impurity A (%)</i>	<i>DNa (%)</i>	<i>Impurity A (%)</i>
0	10.43±0.09	0.17±0.00	11.73±0.71	0.11±0.06
1	10.72±0.26	0.15±0.05	11.19±0.12	0.18±0.03
3	10.17±0.05	0.16±0.01	11.00±0.08	0.18±0.01
6	11.03±0.24	0.11±0.04	11.13±0.17	0.14±0.01

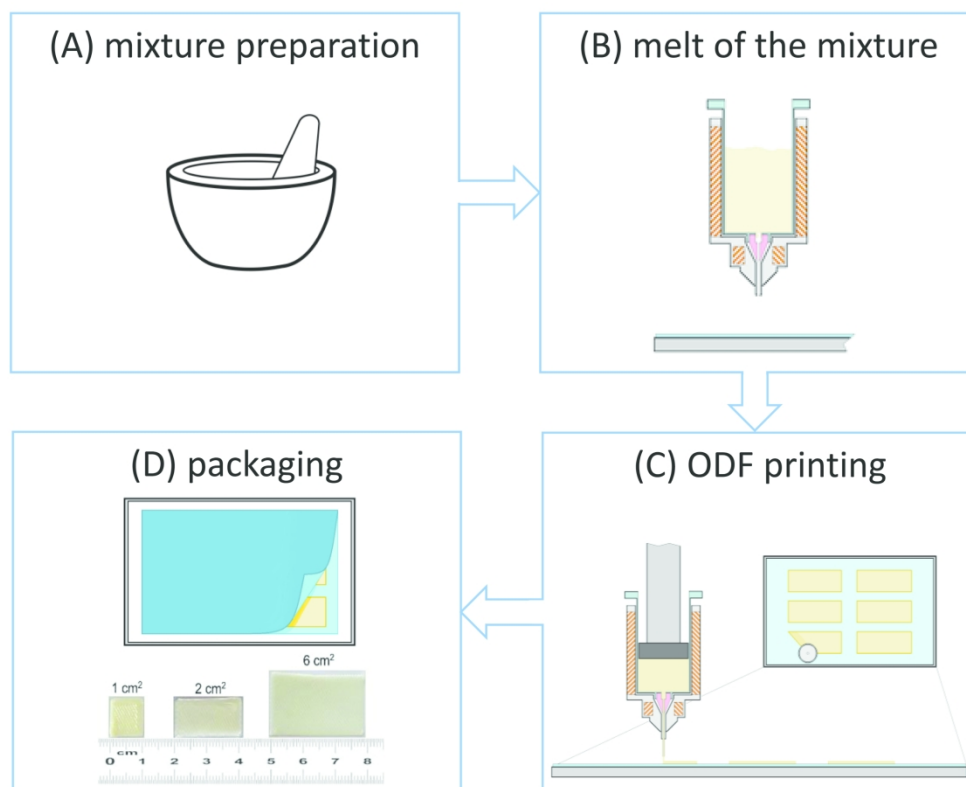


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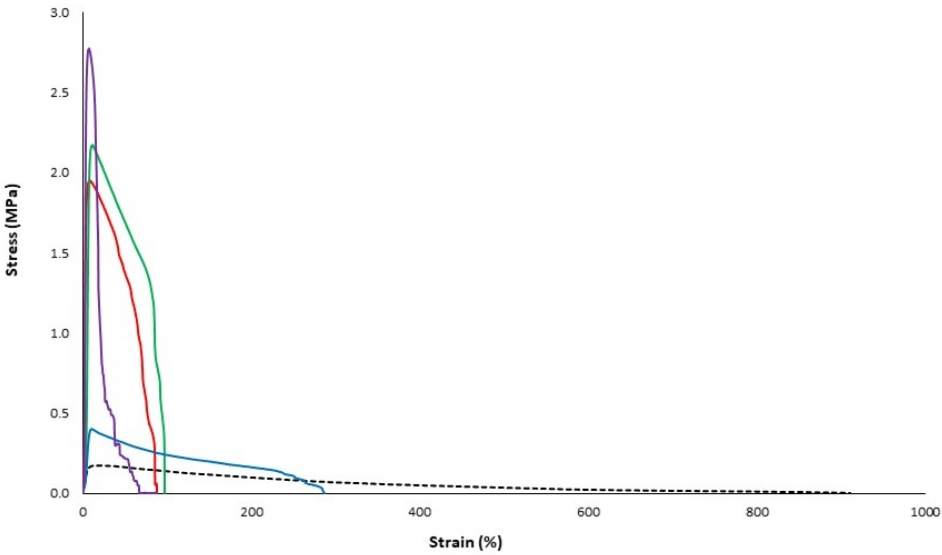


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238x139mm (96 x 96 DPI)

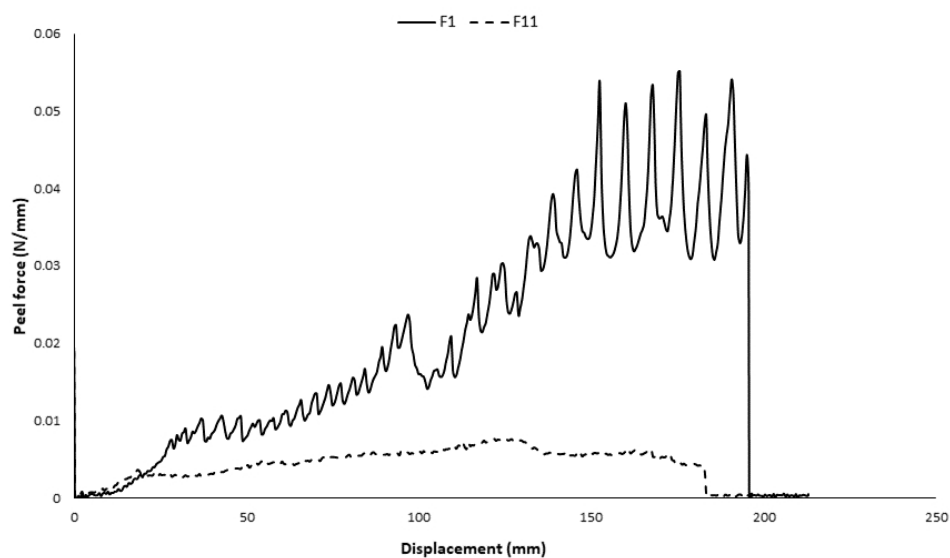


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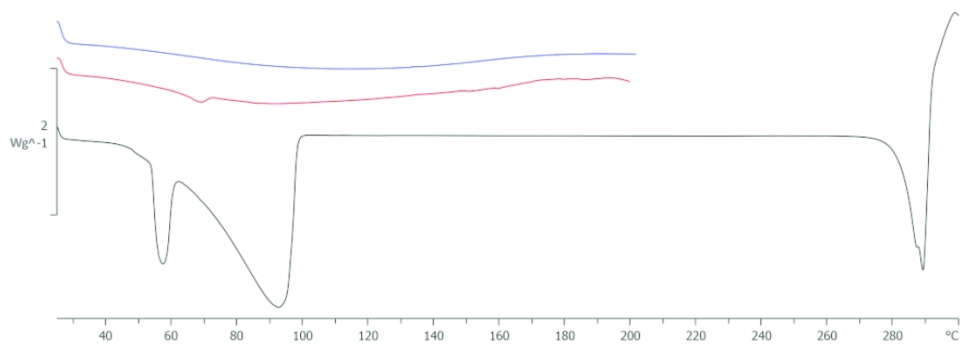


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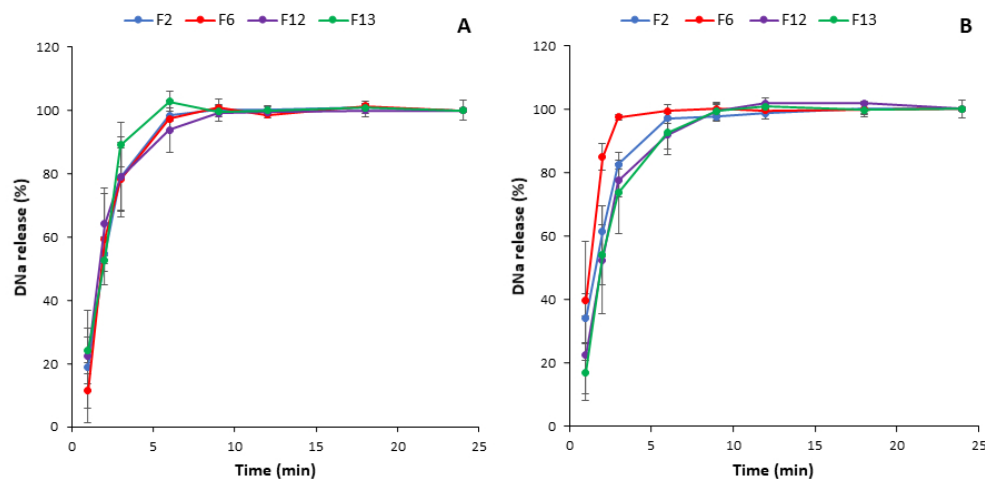


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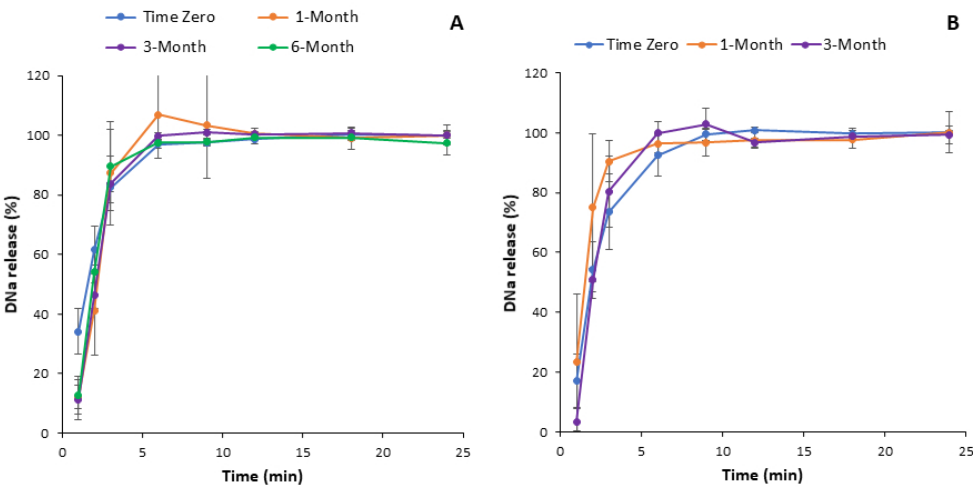


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