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Development and Evaluation of Fluoxetine Fast Dissolving Films: An Alternative for Noncompliance in Pediatric Patients

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Abstract: The most used pharmaceutical formulations for children are syrups, suppositories, soft chewable capsules, and mini-tablets. Administrating them might create an administration discomfort. This study aimed to develop and evaluate orodispersible films (ODFs) for pediatric patients in which the fluoxetine (FX) is formulated in the polymeric matrix. Six FX fast dissolving films (10 mg FX/ODF), FX1, FX2, FX3, FX4, FX5, and FX6, were prepared by solvent casting technique. In the composition of the ODFs, the concentration of the hydroxypropyl methylcellulose and the concentration of the propylene glycol were varied. Each formulation of fluoxetine ODF was evaluated by determining the tensile strength, folding endurance, disintegration, behavior in the controlled humidity and temperature conditions, and adhesiveness. All the obtained results were compared with the results obtained for six ODFs prepared without FX. The disintegration time of the FX ODFs was of maximum 88 s for FX2. Via the in vitro releasing study of the FX from the ODFs it was noticed that FX1 and FX2 allow a better release of the drug 99.98 ± 3.81% and 97.67 ± 3.85% being released within 15 min. From the obtained results it was also confirmed that FX ODFs were found to follow first-order release kinetic.

Keywords: fluoxetine; orodispersible film; pediatric; HPMC; kinetic

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1. Introduction

Currently, the most pharmaceutical formulations used for children are syrups, suppositories, soft chewable capsules, and mini-tablets [1]. Administrating them might create an administration discomfort. Taking into consideration the disadvantages of the conventional pharmaceutical forms and aiming to increase the bioavailability of an active pharmaceutical ingredient (API), orodispersible systems can bring multiple advantages. ODFs were developed based on the transdermal patch technologies being composed of a flexible polymer agent that once attached to the patient's tongue hydrates and adheres to the application place [2]. ODFs are defined as polymeric matrixes that contain an active ingredient that dissolves in a very short period [3,4]. The oral route represents for most of the patients the preferred route for administration of the conventional pharmaceutical formulations due to the main advantages such as convenience in administration and the noninvasive property. However, for some categories of patients such as children, difficulties at swallowing tablets and capsules may occur. Even though oral administration is the most accepted method for the administration of pharmaceutical ingredients, due to some pathologies such as dysphagia, the deglutition becomes painful [5,6]. Dysphagia leads to symptoms manifested by tablet or capsules swallowing difficulties, the lack of swallowing, or even medication refusal [7]. The pediatric category manifests often the

fear of choking by administrating solid pharmaceutical formulations; also, a subjective opinion regarding the form, size, or surface texture might influence the decision of taking a solid pharmaceutical formulation. Orodispersible systems represent a new approach of the oral release of the active pharmaceutical ingredients (APIs), by which an increased acceptance rate is assured in virtue of fast dissolution the possibility of self-administrating, without water. After the APIs are dissolved or dispersed in the saliva, they are absorbed through the sublingual mucosa or they are ingested with the saliva, generating a systemic effect [8,9]. Reported to the composition of an ODF, the drug can be incorporated until 25% of the film mass [10], a quantity that establishes the limits at a maximum of 25 mg API/ODF. An increased quantity of an active ingredient might lead to the recrystallization phenomenon which included changes regarding the mechanical properties [11]. Additionally, it is recommended an active ingredient with a molecular mass lower than 300 in order to favor the penetration through the mucosa, to be water-soluble and, partially ionized at the buccal pH. Developing and obtaining ODF can be realized through multiple procedures, such as solvent casting methods, hot-melt extrusion, and electrospinning [12].

The most often used technique to obtain ODF is the solvent casting method which implies the following steps: (1) preparing the casting solution through dissolving or suspending the API in the polymer together with the plasticizer solution, and volatile solvents (water and/or alcohol); (2) degassing (sonication) of the mixture obtained; (3) transferring the corresponding volume in an adequate form; (4) solvent evaporation from the poured dispersion to form a film by drying it in an oven; (5) cutting the ODF in unitary films, to contain the pre-established dose of the API; (6) conditioning in sealed sachets [13].

Among the ODFs, advantages compared to the conventional pharmaceutical formulations are as follows: the administration without water; the large contact surface offers a fast disintegration and dissolution in the oral cavity; the small dimension of the ODFs improves the transport, handling, and storage of the final product; they present better stability in time, as a result of the solid form of presentation compared to liquid pharmaceutical formulations; assure an accurate administrated dose compared to the liquid formulations; the API can be absorbed through the buccal mucosa and can enter directly in the systemic circulation, avoiding the first-pass effect; assure a fast therapeutic action and increase the efficacy and the drug safety profile; provides new business opportunities for the manufacturing companies through the possibility to differentiate the products from the generics with the same API. These pharmaceutical formulations with fast dissolution are presenting also disadvantages such as: taste masking necessity of the API's unpleasant taste, significantly perceived at the contact with the tasted buds; the APIs can be incorporated in small doses; the uniformity of dosage represents a technical challenge; APIs that are unstable at the buccal pH cannot be administrated; the substances that are irritative for the oral mucosa cannot be administrated; the package has to assure the mechanical integrity of the ODFs that are fragile as well as their protection from environmental factors, especially water [14].

This study aimed to develop and evaluate ODFs suitable for pediatric patients containing fluoxetine. Fluoxetine is an API used to treat depression.

In a clinical randomized trial of pediatric depression, published by Graham J. Emslie and colab., it was concluded that fluoxetine is the only antidepressant that has shown to be effective [15].

Figure 1 shows the physical and chemical properties of the fluoxetine [16–18].

On a large scale, it has been shown that fluoxetine has the same efficiency as the already existing drugs, but due to its selectivity, the side effects of the treatment are in general, gentle and transitional [19]. Fluoxetine is prescribed in cases of major episodes of depression such as obsessive-compulsive disorder and bulimia nervosa. Additionally, in the case of children, it is administrated in major or moderate episodes of depression when patients do no respond after 4–6 sessions of psychotherapy [20]. According to the indications of the "Guidance on the Use of Antidepressants in Children and Adolescents" (2014) fluoxetine is considered the first-choice antidepressant to children over 8 years [21].

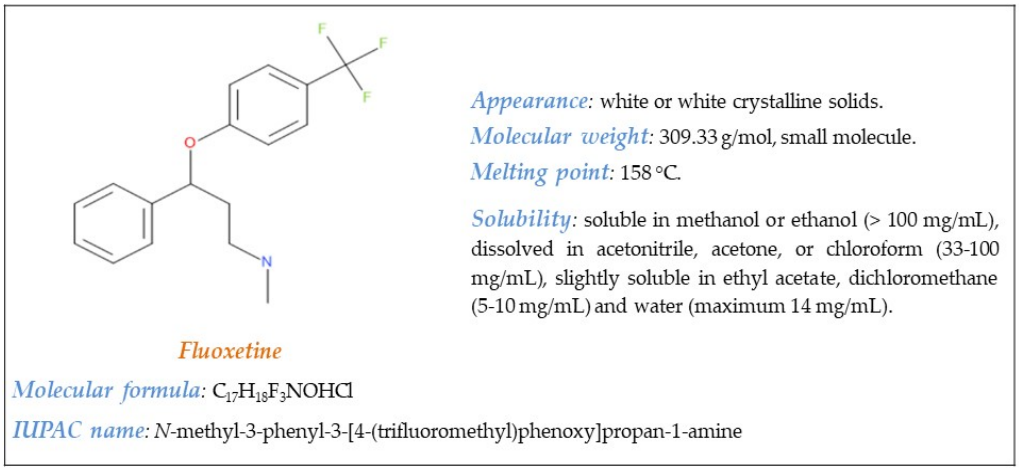


Figure 1. Physical and chemical properties of fluoxetine.

In the present days, medicines containing fluoxetine are available on the pharmaceutical market under few formulations as follows: 10 mg capsules, 20 mg capsules and 20 mg dispersible tablets. "U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients" recommended for the children aged between 8 and 17 years an initial dose of fluoxetine of 10 mg once a day [22].

Thereby, the development of new formulation such as ODFs containing fluoxetine can represent an innovation in the pharmaceutical field. As only concentrations of 10 mg fluoxetine capsules and 20 mg fluoxetine dispersible tablets are approved by the authorities, and this study focuses on increasing pediatric patient compliance and reducing the risk of choking, the challenge of this experimental study is to obtain ODFs containing 10 mg fluoxetine suitable for children which present good mechanical and pharmacotechnical properties.

2. Materials and Methods

2.1. Materials

Fluoxetine (FX) was purchased from Solmag, Italy; hydroxypropyl methylcellulose E5 Premium LV (HPMC) was purchased from Dow Chemical Co., Midland, TX, USA; polyvinylpyrrolidone K30 (PVP) was purchased from BASF Pharma, Ludwigshafen, Germany; propylene glycol (PG) was purchased from Scharlau Chemie, Barcelona, Spain; maltodextrin (MDX) was purchased from JRS Pharma, Rosenberg, Germany and Tween 80 (TW) was purchased from Sigma Aldrich, Milano, Italy. All other reagents were of analytical grade.

2.2. Methods

2.2.1. Orodispersible Films Preparation

Usually, ODFs are prepared by means of solvent casting method. Through this method, the mixture that contains the drug, the film-forming polymer, the plasticizer and other excipients is allowed to evaporate forming a solid film. The other methods used to develop ODFs are hot-melt-extrusion where the use of solvents is avoided and electrospinning.

Six formulations of orodispersible films without FX (Table 1) were prepared by a solvent casting technique (Figure 2). As film-forming ingredients, HPMC, PVP, and MDX were used in different weight ratios (10:3:1 for formulations FO1 and FO2, 8:3:1 for formulations FO3 and FO4, and 12:3:1 for formulations FO5 and FO6). PG was used as a plasticizer in different concentrations (10% *w/w* or 12% *w/w*). TW was used in all the formulations in a concentration of 1% *w/w* as a surfactant that facilitates disintegration of the orodispersible films.

Table 1. Orodispersible films without FX.

Composition % (*w*/*w*)	FO1	FO2	FO3	FO4	FO5	FO6
HPMC	10	10	8	8	12	12
PVP	3	3	3	3	3	3
MDX	1	1	1	1	1	1
PG	10	12	10	12	10	12
TW	1	1	1	1	1	1
Water	75	73	77	75	73	71

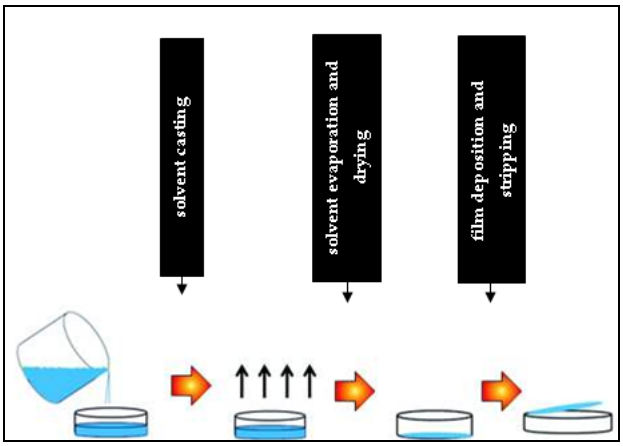


Figure 2. Solvent casting technique.

TW was dissolved in water and mixed with the corresponding amount of PG. The hydrophilic film polymer (HPMC) was briefly dispersed to the mixture under continuous stirring (300 rpm, Heidolph RYR1 homogenizer, Germany) for 1 h. In the obtained polymeric dispersion PVP and MDX were added. The resulting dispersion was degassed for one hour using an ultrasound bath (Ultrasonic bath, MRC laboratory instruments, UK), and then was poured in glasses with 2 cm diameter (to obtain ODFs corresponding to 10 mg FX *w*/*w*). The homogeneous dispersion was kept in an oven at 40 °C and RH ≈ 30% for solvent evaporation to obtain ODFs. The resulting films were wrapped in aluminum foil and kept at ambient conditions for further characterization.

In the same conditions six formulations of orodispersible films with FX were prepared, but initial the drug was dispersed in hot water (Table 2).

Table 2. Orodispersible films with FX.

Composition % (*w*/*w*)	FX1	FX2	FX3	FX4	FX5	FX6
FX	3	3	3	3	3	3
HPMC	10	10	8	8	12	12
PVP	3	3	3	3	3	3
MDX	1	1	1	1	1	1
PG	10	12	10	12	10	12
TW	1	1	1	1	1	1
Water	72	70	74	72	70	68

2.2.2. Physical Appearance

The physical appearance of the ODFs was appreciated by visual evaluation, on a white background, in terms of clarity and texture.

2.2.3. Thickness

The thickness determination of the ODF represents a critical parameter because it can influence the disintegration time and also the speed of releasing of the API from

the polymeric matrix. An increased thickness might lead to a decreased quantity of API released [23]. ODF thickness was measured in five different points of each sample using a digital micrometer (Mitutoyo, Germany, accuracy ± 1 µm). The results were expressed as average of the obtained values.

2.2.4. Weight Uniformity

According to the 10th European Pharmacopoeia in force, the determinations are made using 20 ODFs if the average mass is less than 80 mg, and for 18 of the ODFs, a deviation of ±10% is admitted whilst for two of the orodispersible films a deviation of ±20% is admitted. If the average mass is between 80 and 250 mg the deviation admitted for 18 ODFs is ±7.5%, while for two ODFs 15% is admitted. If the weight of the ODFs is higher than 250 mg, for 18 ODFs a deviation of 5% is permitted while for two of them 10% is admitted [21,24]. Thereby, the uniformity of mass was realized by weighing 20 ODFs from each formulation, and the results obtained were analyzed using their average mass.

2.2.5. Tensile Strength

Tensile strength was determined by using a manufactured laboratory instrument type designed with two clamps to hold the sample (circular ODFs with 2 cm diameter): one clamp was fixed to a support and the other was movable. Weights of ten grams were attached successive to the movable clamp until the breaking or cracking of the analyzed sample occurred [25,26]. Taking into account the weight that caused the breaking of the analyzed sample, the tensile strength was calculated using the following equation [27]:

$$TS\ (N{\cdot}\mathrm{mm}^{-2}) = (M{\cdot}g)/(W{\cdot}T), \quad (1)$$

where

M—the weight at which the sample cracked;
g—gravitational acceleration (9.81 $N{\cdot}kg^{-1}$);
W—sample width (mm);
T—sample thickness (mm).

2.2.6. Folding Endurance

The folding endurance was measured manually for the prepared ODFs. The value of folding endurance is expressed as the number of times the film (circular ODFs with 2 cm diameter) could be folded at the same place (middle line) until it broke or cracked [27,28].

2.2.7. Disintegration Behavior

The disintegration time represents the time needed for the film to dissolve or decompose into fine particles [29–31]. The disintegration test was realized by adding the samples (circular ODFs with 2 cm diameter) in a beaker containing 10 mL of distilled water at 37 °C. The results obtained represent the average disintegration time for three samples of each analyzed formulation.

2.2.8. Orodispersible Films Behavior in the Controlled Humidity and Temperature Conditions

The behavior in the controlled humidity and temperature conditions of the ODFs was evaluated by weighing three samples (circular ODFs with 2 cm diameter) of each formulation and maintaining them sealed in a glass vessel for 11 weeks (RH ≈ 40%; 25 °C ± 0.2 °C). The results obtained were based on the eventual weight modification of the ODFs in time.

2.2.9. Adhesiveness Capacity

The adhesiveness capacity of the ODF was determined by attaching the sample to a plate of a modified balance device. The sample was moistened for one minute by adding

two drops of distilled water. On both plates of the balance, a weight of 50 g was added. After one minute, weights were placed on the other pan until the ODF detached from the pan. The adhesiveness capacity was determined by the vertical tensile force determined by the weight that caused the detachment of two plates between which was the ODF analyzed sample (circular ODFs with 2 cm diameter). An average of three determinations were undertaken [32,33]. The detachment force was expressed in dynes/cm^2 and was calculated based on the Equation (2):

$$F = m \cdot g / A, \quad (2)$$

where

m—the applied mass that was needed for detachment;
g—gravitational acceleration (9.81 N·kg^{-1});
A—ODFs films surface (surface: 3.14 cm^2).

2.2.10. ODF Fluoxetine Dosing

Standard calibration curve of FX: a stock solution of 0.1% (1000 µg/mL) of FX was prepared, in phosphate buffer with a pH of 6.8. The stock solution was diluted as follows 0.5:10, 1:10, 1.5:10, 2:10, 2.5:10, 3:10, 4:10, and 6:10, corresponding to 50, 100, 150, 200, 250, 300, 400, and 600 µg·mL^{-1} FX. The resulting solutions were analyzed at 275 nm, spectrophotometrically.

The FX content was determined spectrophotometrically using a Shimadzu UV-1800 spectrophotometer on three samples of ODF dissolved in 10 mL of phosphate buffer with a pH of 6.8. After sample filtration, a dilution of 1:10 was made, and the resulting solution was analyzed at 275 nm.

2.2.11. Fluoxetine In Vitro Release

The prepared ODFs (circular ODFs with 2 cm diameter and 10 mg FX concentration: FX1, FX2, FX3, FX4, FX5, FX6) were examined based on the basket apparatus Erweka DT, Germany (comparable with apparatus 1, described by Ph.Eur. 10.0). The in vitro release experiments were done using 100 mL degassed phosphate buffer pH 6.8 dissolution media, which simulates the pH of the human saliva. The temperature of the dissolution media was set at 37 + 0.2 °C. The basket agitator, which contains the sample of the ODF corresponding to 10 mg FX, was adjusted at a stirring rate of 50 rpm. For each in vitro experiment, 5 mL sample was withdrawn at different time intervals: 2, 5, 8, 10, 15, 20, 30 min and replaced with an equal volume of fresh phosphate buffer pH 6.8. The samples were analyzed spectrophotometrically at 275 nm. The obtained release profiles were analyzed through a kinetic point of view (software: DDSolver Add-in Program, Microsoft Excel) [34–38].

2.2.12. Statistical Analysis

For statistical analysis GraphPad Prism 6 software was used, running the following tests: descriptive statistics; two-way ANOVA followed by Tukey's multiple comparisons test; Pearson correlation (r); area under the curve (AUC). The statistically significant difference was set at $p < 0.05$, for a CI of 95%.

3. Results

3.1. Physical Appearance

ODFs are based on a typical composition: API, hydrophilic polymers, plasticizers (to provide elasticity of the films), fillers, colors and flavors. To develop ODFs, either a single polymer or combinations of several polymers are used. The most used polymers for ODFs preparation are natural polymers (examples: starch, gelatin, sodium alginate, maltodextrin) and synthetic polymers (examples: hydroxypropyl methylcellulose, sodium carboxy methylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone) [38,39]. For example, a study published by ElMeshad A.N. and El Hagrasy A.S. presents blends of two

polymers that were used successfully (HPMC E15 and maltodextrin) to obtain ODFs with mosapride citrate [40].

In this study, transparent ODFs with an uniform aspect and a fine texture were obtained. The orodispersible film morphology was not influenced by the presence of FX (Figure 3).

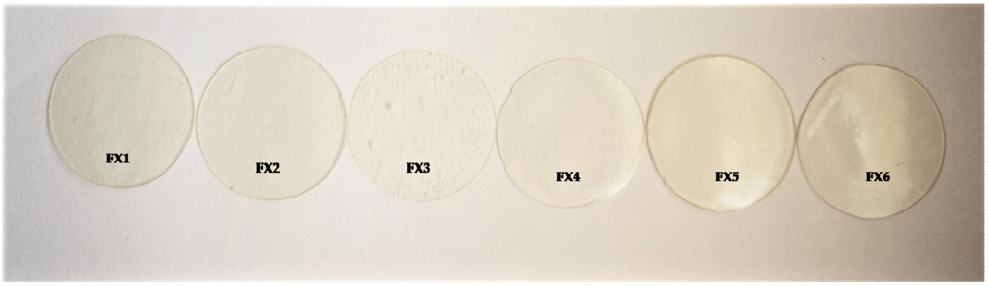


Figure 3. The physical appearance of the prepared orodispersible films with FX.

3.2. Thickness and Weight Uniformity

The ODFs thickness proved to be a parameter directly depending on the formulation variables (Table 3). As may have been expected, it can be observed that the ODF thickness increases as the HPMC concentration tends to grow: FO3, FO4 (8% HPMC) > FO1, FO2 (10%) > FO5, FO6 (12% HPMC).

Table 3. Thickness and weight of the orodispersible films.

Formula	FO1	FO2	FO3	FO4	FO5	FO6
Thickness (mm) ± SD	0.41 ± 0.01	0.35 ± 0.03	0.19 ± 0.02	0.33 ± 0.08	0.45 ± 0.05	0.42 ± 0.02
Weight (mg) ± SD	120 ± 13	110 ± 16	80 ± 10	130 ± 12	130 ± 5	160 ± 4
Formula	**FX1**	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**
Thickness (mm) ± SD	0.44 ± 0.02	0.47 ± 0.05	0.25 ± 0.01	0.40 ± 0.01	0.48 ± 0.01	0.43 ± 0.01
Weight (mg) ± SD	140 ± 8	180 ± 6	100 ± 10	140 ± 5	180 ± 7	170 ± 5

The FX presence in the ODFs led to a small increase in thickness, but the variation of these parameters followed the same behavior as the one manifested in the orodispersible films without API.

3.3. Tensile Strength

The tensile strength of the ODFs was generally higher in the case of the orodispersible films that contained FX (Figure 4). Exceptions from this behaviour were formulations based on 8% HPMC and 10% PG in which the presence of FX decreases the mechanical resistance of the ODF FX3 (the values of tensile strength were 0.41 $N \cdot mm^{-2}$ for FO3 vs. 0.33 $N \cdot mm^{-2}$ for FX3). Additionally, from Figure 4 it can be noticed that in the case of both types of ODFs with API and without API, the highest resistance was obtained in the case of the films that contained 12% and 10% PG (FO5: 0.44 $N^* \cdot mm^{-2}$ and FX5: 0.57 $N \cdot mm^{-2}$). Once the HPMC quantity decreases and the PG concentration increases, the ODFs mechanical resistance decreased, highlighting the fact that an increased concentration of HPMC offers increased mechanical properties to the ODFs.

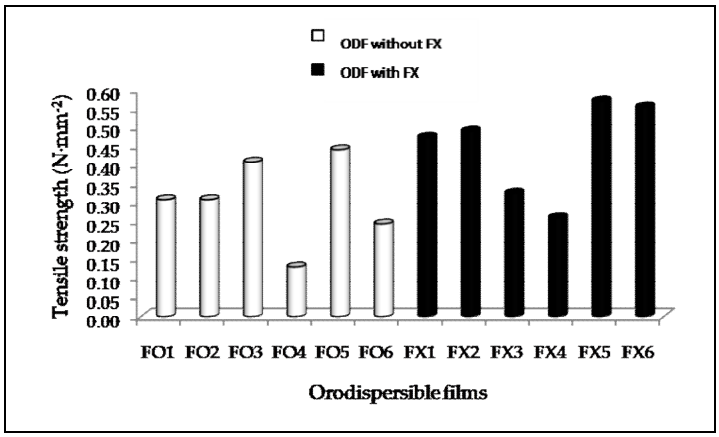


Figure 4. Tensile strength of the orodispersible films.

3.4. Folding Endurance

Analyzing the results presented in Table 4, it can be observed that the ODF resisted several fold higher than 40, which makes them easy to handle and easy to be transported. Still, differences in their behavior can be observed. On the other hand, it can be stated that the presence of fluoxetine in the ODF has a positive influence over the parameter mentioned before. Additionally, it can be noticed that the folding endurance increases directly proportional with the growth of the HPMC concentration in the ODF as it follows FO3, FO4 > FO1, FO2 > FO5, FO6 and, FX3, FX4 > FX1, FX2 > FX5, FX6. As well, the PG influences the folding endurance. A concentration of PG higher than 12% determined a smaller folding endurance in comparison with the one registered in the case of the ODFs with 10% PG.

Table 4. Folding endurance of the orodispersible films.

Formula	**FO1**	**FO2**	**FO3**	**FO4**	**FO5**	**FO6**
Folding endurance (x)	65 x	50 x	45 x	40 x	70 x	50 x
Formula	**FX1**	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**
Folding endurance (x)	70 x	60 x	50 x	48 x	77 x	60 x

3.5. Disintegration Behavior

According to the results provided in Table 5, it can be noticed that the ODFs that did not contain FX disintegrated between 110 s (FO1) and 175 s (FO5), whilst the ODFs with FX disintegrated 2–3 times faster, between 48 s (FX3) and 88 s in the case of FX2. Even all the FX ODFs presented disintegration times that fitted in the official provisions, the disintegration times might vary due to the ratio in which the polymers are in the obtained ODFs, decreasing as follows: FX1, FX2 (HPMC:PVP:MDX—8:3:1 *w/w*) < FX5, FX6 (HPMC:PVP:MDX—12:3:1% *w/w*) < FX3, FX4 (HPMC:PVP:MDX—8:3:1 *w/w*). It can be seen that a decrease in HPMC concentration produced ODFs with a rapid disintegration, which is in accordance with the study published by Kai Bin Liew and his collaborators [41]. Additionally, in the case of FX ODFs using the same content of polymers small differences in the disintegration behavior can be noticed, probably as a result of the plasticizer content used. Decrease in PG produced ODFs with shorter disintegration time. A PG content higher than 12% increased the disintegration time compared to the formulations with 10%.

Table 5. Disintegration time of the orodispersible films.

Formula	FO1	FO2	FO3	FO4	FO5	FO6
Disintegration time (seconds) ± SD	110 ± 3	170 ± 2	140 ± 5	170 ± 4	175 ± 3	170 ± 3
Formula	**FX1**	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**
Disintegration time (seconds) ± SD	87 ± 5	88 ± 2	48 ± 3	54 ± 3	65 ± 4	69 ± 5

3.6. Orodispersible Films Behavior in the Controlled Humidity and Temperature Conditions

By exposing the ODFs to a humidity of 40% and a controlled temperature of (25 ± 0.2 °C) their weight remained unmodified after 11 weeks. These results suggest that if the films are kept sealed and in adequate conditions, they will not absorb water neither will dry by volatilization. After 11 days, we can assume that by sealing the ODFs in airtight sachets a stable moisture content is ensured.

3.7. Adhesiveness Capacity

According to the results found in Table 6, it can be observed that FX influenced the ODFs mucoadhesive capacity causing decreased values of the detachment force of a maximum of 14%. On the other hand, a concentration of HPMC of 12% in the ODFs caused an increased detachment force in formulations FO5 and FO6, and FX5, FX6, respectively, compared to the other proposed formulations. This might be explained by the good bioadhesive properties of the polymer. Additionally, the PG concentration of 10 or 12% caused a slightly decreased detachment force between the prepared formulation with the same content of the polymer. Medicine administration to non-cooperative patients, like children, can be facilitated by the adhesion of ODFs to the oral cavity, therefore preventing the medicine to be split out. On the other hand, adhesion properties of an ODF can decrease the risk of aspiration and also decrease the risk of choking.

Table 6. Adhesiveness (stickiness) of the orodispersible films.

Formula	FO1	FO2	FO3	FO4	FO5	FO6
Adhesiveness (dyne·cm^{-2})	1.62×10^{-2}	1.92×10^{-2}	2.13×10^{-2}	1.92×10^{-2}	2.85×10^{-2}	2.95×10^{-2}
Formula	**FX1**	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**
Adhesiveness (dyne·cm^{-2})	1.41×10^{-2}	1.86×10^{-2}	1.84×10^{-2}	1.82×10^{-2}	2.6×10^{-2}	2.55×10^{-2}

3.8. Fluoxetine ODF Dosing

Establishing the FX concentration of the prepared ODFs (ø 2 cm) was accomplished using a spectrophotometric method. The specific wavenumber at which the absorbance was determined was 275 nm.

The results obtained are represented in Table 7.

Table 7. Fluoxetine concentration in the prepared ODFs.

Formulation	FX1	FX2	FX3	FX4	FX5	FX6
Drug content (mg/ODF) ± SD	9.90 ± 0.11	9.95 ± 0.08	10.07 ± 0.12	9.88 ± 0.05	9.97 ± 0.08	10.02 ± 0.06
Equation of the calibration curve of FX in phosphate buffer pH 6.8						
$y = 0.0019x + 0.0033$; $R^2 = 0.9992$						

3.9. Statistical Analysis to Establish the Influence of Composition Variables on the ODFs Characteristics

Experimental data calculated as average on each of the two main types of formulations were analyzed by comparison between ODFs with fluoxetine (FX) versus ODFs without FX (FO) to evaluate the variance on the film characteristics determined by the presence of FX in the film's matrices. The results (Table 8) show statistically significant influences of the formulation variables: FX (3%) and matrix type with the two formulation variables (HPMC ± 2% and/or PG ± 2%).

Table 8. The results of descriptive statistical analysis and variance of the two formulations types FX versus FO.

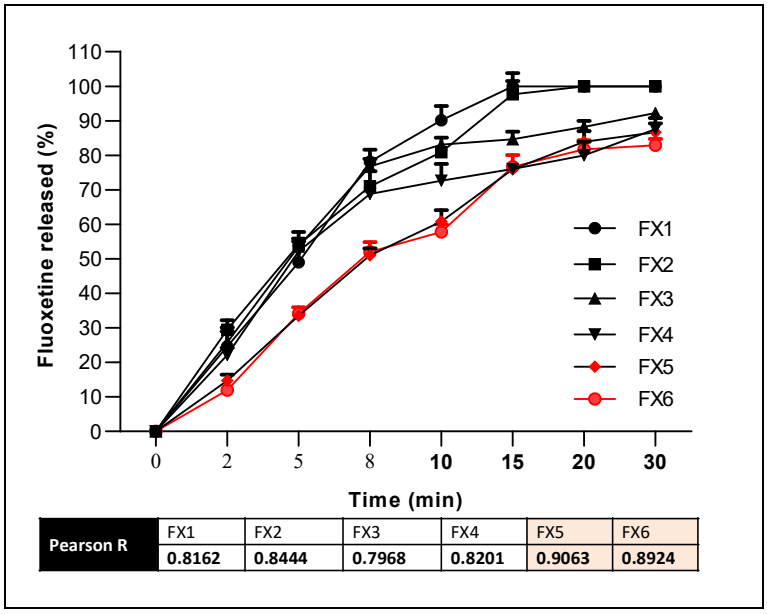
Parameter	**Thickness (mm)**		**Weight (mg)**		**Tensile Strength ($N \cdot mm^{-2}$)**		**Disintegration Time (s)**		**Adhesiveness ($dyne \cdot cm^{-2}$)**	
Matrix type	**FO**	**FX**	**FO**	**FX**	**FO**	**FX**	**FO**	**FX**	**FO**	**FX**
Descriptive Statistics (n = 6; n—number of samples F1–F6)										
Mean	0.3583	0.4117	121.70	151.70	0.3075	0.4463	155.80	68.50	0.02232	0.02013
SD	0.0939	0.0842	26.39	31.25	0.1126	0.1254	25.77	16.53	0.00544	0.00466
Std. Error of Mean	0.0383	0.0344	10.78	12.76	0.0460	0.0512	10.52	6.747	0.00222	0.00190
Coefficient of variation (%)	26.20	20.46	21.69	20.61	36.62	28.10	16.54	24.13	24.36	23.16
Influence of formulation factors FX vs. FO (% of total variation; two-way ANOVA, $\alpha = 0.05$)										
Fluoxetine 3%	**8.55 *** $p < 0.0001$		**22.67 *** $p < 0.0001$		**28.93 *** $p < 0.0001$		**82.60 *** $p < 0.0001$		**5.24 *** $p < 0.0001$	
HPMC ± 2%/PG ± 2%	**75.88 *** $p < 0.0001$		**57.67 *** $p < 0.0001$		**50.95 *** $p < 0.0001$		**6.61 *** $p < 0.0001$		**92.56 *** $p < 0.0001$	
Interaction	**3.88 *** p = 0.0035		**12.60 *** $p < 0.0001$		**20.12 *** $p < 0.0001$		**10.31 *** $p < 0.0001$		**1.44 *** $p < 0.0001$	

* statistically significant; ns—statistically non-significant.

Regarding the size of the variance that can be attributed to FX of the total variance, it was found that the largest variance determines the disintegration time (82.60%) and the smallest on the film thickness (8.55%) and adhesiveness (5.24%); while the types of matrices determine the smallest variance on the disintegration time (6.61%) and the largest on the adhesiveness (92.56%) and thickness of the film (75.88%). The interactions of FX with the film matrix type add the smallest variance to adhesiveness (1.4%) and the largest to tensile strength (20.12%).

3.10. Drug Release Study

The FX ODFs in vitro drug release was realized in a dissolution media similar to the saliva, at the pH of 6.8 for 30 min. Figure 5 shows the releasing profiles of the drug from the six proposed ODFs. From the results obtained it can be noticed that the FX release is depending on the formulation variables, decreasing in the following order: FX1, FX2 (HPMC 10%) < FX3, FX4 (HPMC 8%) < FX5, FX6 (HPMC 12%). An increased concentration of the polymer HPMC in FX5 and FX6, resulted in a lower concentration of FX released after 30 min of 86.63 ± 2.59%, and 82.95 ± 1.80%, respectively, compared to the other ODFs obtained. The decreased concentration of HPMC in the FX3 and FX4 formulations favored a 6% higher release of the drug after 30 min. On the other hand, it can be noticed that FX1 and FX2 allow the release of the API of 99.98 ± 3.81% and 97.67 ± 3.85%, respectively, after 15 min, a fact that makes them eligible for future studies regarding their optimization. PG concentration might influence the amount of drug released, a higher concentration of PG causing a decrease with 2–5% FX released from the analyzed ODFs.

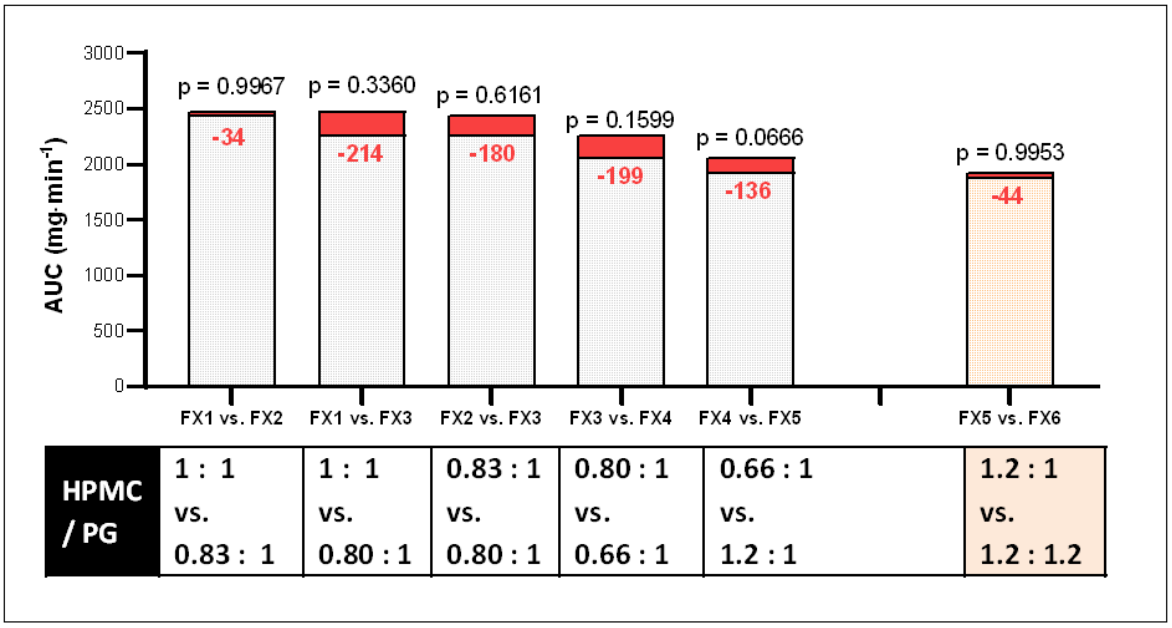


Pearson R	FX1	FX2	FX3	FX4	FX5	FX6
	0.8162	0.8444	0.7968	0.8201	0.9063	0.8924

Figure 5. Dissolution profiles and correlation coefficients—Pearson r.

The results obtained are comparable with the ones published by Lu Zhang et al. in 2018, in which it has been demonstrated that over 80% of the selected API (fenofibrate) was released after 20 min [23].

To evaluate the influence of composition variables on the FX release profile statistical analysis was conducted. The results presented in Figure 6 show the formulations with similar dissolution behaviors, with no statistically significant differences according to the adjusted p value (Tukey's multiple comparisons test; two-way ANOVA, $\alpha = 0.05$).



HPMC / PG	1 : 1 vs. 0.83 : 1	1 : 1 vs. 0.80 : 1	0.83 : 1 vs. 0.80 : 1	0.80 : 1 vs. 0.66 : 1	0.66 : 1 vs. 1.2 : 1	1.2 : 1 vs. 1.2 : 1.2

Figure 6. Formulations with similar dissolution behaviors, with no statistically significant differences.

The results presented in Figure 7 show the ODFs with statistically different dissolution profiles, according to the adjusted p value (Tukey's multiple comparisons test; two-way ANOVA, $\alpha = 0.05$).

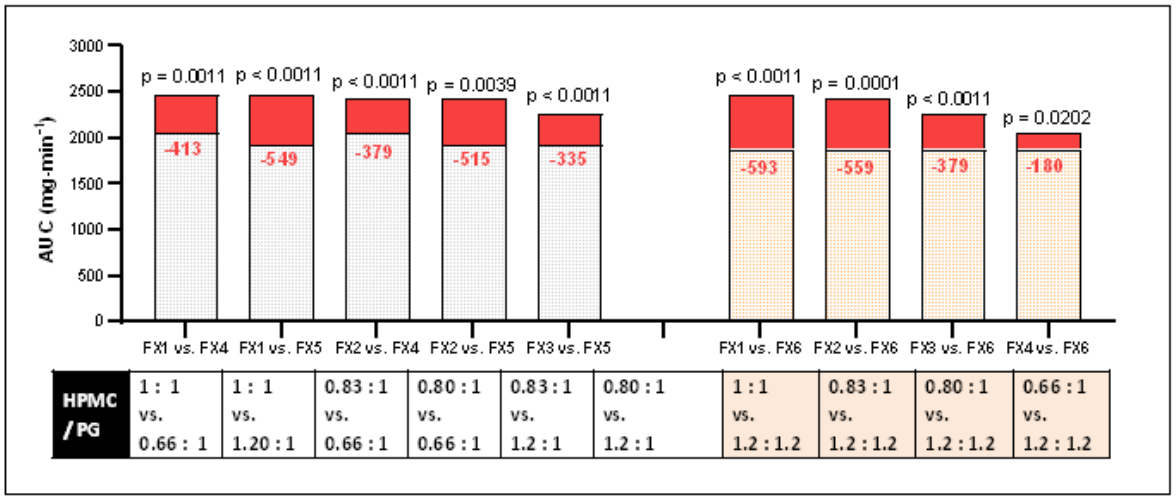


Figure 7. Formulations with statistically different dissolution profiles.

Modeling the releasing curves was realized with the help of some mathematical functions applied using the DDSolver Add-in Program, Microsoft Excel (Table 9).

Table 9. Kinetic releasing parameter of the FX from the ODFs.

Formulation	FX1	FX2	FX3	FX4	FX5	FX6
Kinetic parameters	Dissolution Data Modeling of Zero-order Model					
k_0	7.94	7.58	4.41	4.05	3.86	3.76
AIC	42.51	42.54	72.20	70.06	64.17	64.57
R^2_{adj}	0.8896	0.8660	0.1911	0.2605	0.6747	0.6475
	Dissolution Data Modeling of First-order Model					
k_1	0.17	0.16	0.16	0.12	0.09	0.08
AIC	34.54	25.24	43.57	49.42	34.63	40.80
R^2_{adj}	0.9707	0.9925	0.9774	0.9440	0.9919	0.9819

To establish the mathematical model that fits better the releasing profile of FX, the values of the Akaike informational criterion (AIC) were analyzed. AIC represents the goodness of fit indicator in which the model that fits better has the lowest AIC value. Another goodness of fit kinetic parameter used to choose the kinetic model that fits better the releasing profiles of the FX was the $R^2_{adj.}$

To explain the release kinetic for all ODFs two mathematical models were applied: Zero-order (equation: $F = k_0 * t$) and First-order (equation: $F = 100 * [1 - Exp(-k_1 * t)]$). Based on the results presented in Table 9 and analyzing the two goodness of fit indicators we can see that AIC values for First-order are lower than Zero-order and also R^2_{adj} are higher for First-order plots. The results were in accordance with those obtained by Seetha Devi A. and collaborators [26] who demonstrated that the FX releasing profiles from the studied ODFs are the best fitted by First-order kinetic which means that the API release is concentration dependent.

4. Conclusions

The difficulties in the pediatric therapy related to the children's lack of compliance in accepting the medication are well-known. Taking into consideration the actual trends regarding the identification of some new therapies, six ODFs without API and six ODFs with FX were prepared by solvent casting method. We used different blends of hydrophilic polymers as film formers and two concentrations of PG as plasticizer.

The obtained ODFs were evaluated for their physicochemical and mechanical parameters. The statistical results show statistically significant influences of the formulation

variables: FX and matrix type with the two formulation variables (HPMC concentration and/or PG concentration). Among the six ODFs with FX prepared, formulations FX1 and FX2 were found to release 99.98 ± 3.81% and 97.67 ± 3.85% of API within 15 min. From the obtained results it was also confirmed that FX ODFs were found to follow First-order release kinetics.

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