Rapidly-Disintegrating Laminar Extrudates: Preliminary Experiments upon an Age Appropriate Pediatric Formulation

B.Perissutti[1]*, G Zingone[1], L Lassiani[1], M Moneghini[1] and E Franceschinis[2]

[1]Department of Chemical and Pharmaceutical Sciences, University of Trieste Italy

[2]Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Italy

Abstract

The aim of the present investigation is to produce rapidly disintegrating laminar extrudates for delivering ibuprofen in the mouth of paediatric patients. This laminar shape is particularly convenient for drug delivering in the mouth and can be easily cut in cut in different sizes allowing for a convenient adjustment of the drug dose depending on the age of the patient. Due to the fact that in paediatric formulations, the selection of the excipients is always a challenging issue and the reduction of their amount is always highly desirable, in this study to select the most appropriate composition to achieve a rapid disintegration and simultaneously permit a high amount of ibuprofen in the system, an experimental design for mixtures was employed and the disintegration time in simulated saliva was used as experimental response. In addition, after solid state analyses to check possible insurgence of drug-excipients interactions, laminar extrudates were characterised in terms of mechanical properties and *in vitro* dissolution performances. Extrudates with the desired uniform laminar shape, constant thickness (2 mm) and a very high content of drug (82% wt) were produced. These products exhibited a short disintegration time. The dose for a patient of 6-12 years corresponded to a length of extrudate between 1-1.5 cm, perfectly compatible with a formulation orodispersible thin laminar extrudate intended for a paediatric patient (Figure 1).

Keywords: Paediatric formulation; Flexible formulation; Orodipersible formulation; Excipients; Disintegration

Introduction

The wet extrusion technology has long been known, but usually it represents an intermediate step which precedes the spheronization [1]. In this case it has been employed to prepare by wet extrusion an orodispersible ibuprofen paediatric formulation for patients aged 6-12 years, containing a dose of active ingredient of 100mg. These thin laminar extrudates are requested to accomplish various demands at the same time, such as rapid dispersion in the mouth, loading a dose of active principle in a piece of extruded compatible to a paediatric administration, the use of auxiliary components permitted for paediatric useand finally a high content of active principle and little amount of excipients (thus having less chance of toxicities or intolerance in young consumers) [2-5]. In this context, the extrusion process was chosen because it has the great advantage, compared to other technologies, to allow loading of high quantities of active principle. Moreover, the laminar shape of the extrusions that can be obtained in a single step from a rectangular die could allow an easy modulation of the ibuprofen dose depending on the age and weight of the patient simply varying the length of the extrudate. Further a laminar orodispersible extrudate have minimal impact on lifestyle and a reliable and convenient administration, as requested for an ideal formulation for children [6]. Not being commercially available orodipersibles formulation prepared by wet extrusion, as a parameter of comparison, in all steps of research, a marketed formulation Nurofen˙ comprimés fondants 200 mg, oro-dispersible tablets available on the market in Belgium, was used. Further, due to the lack of characterizations for this innovative dosage form, alternative analyses used for the evaluation of films and orodispersible tablets or sublingual tablets were adapted and proposed.

Materials and Methods

Materials

Ibuprofen EP (IBU) (Acef), Crospovidone (Kollidon CL, Basf)- PVP-CL, Povidone (Kollidon,

Table 1: Pseudo mixture Experimental matrix.

Experimental matrix				
Exp.	Random sequence	MCC X₁ (%)	PVP-CL X₂ (%)	PVP X₃ (%)
1	2	0	50	50
2	6	13,6	43,2	43,2
3	1	27,2	36,4	36,4
4	4	17,3	28,2	54,5
5	3	11	54,5	34,5
6	7	17,3	54,5	28,2
7	5	11	34,5	54,5

BASF)-PVP, Microcrystalline cellulose (AvicelPh 101, FMC)- MCC, Aspartame - E 951(Acef), Polisorbate 80 (Montanox 80, Seppic) -E433were used. Nurofen° comprimés fondants -200 mg (Reckitt Benckiser Healthcare- commercialized in Belgium) were used for comparison purposes as solid oro-dipersibile dosage for m containing ibuprofen. This formulation is indicated for children over the age of12 years and for salein Belgium. Nurofen° comprimés fondants 200 mg contains in addition to 200 mg of active ingredient the following inactive ingredients: ethyl cellulose, precipitated silica, hypromellose, mannitol, aspartame (E951), Croscarmellose sodium, magnesium stearate, flavor (lemonor other). The total weight of the tablet is 700 mg, thus excipients represent 71.4% by weight.

Methods

Powder mixture composition and experimental design: The mixtures to be subjected to wet extrusion process were designed using experimental design for mixtures [7], using the soft ware NEMRODW [8]. To reduce systematic errors, the extrusion tests were performedinrandomorder. The mixture subjected to extrusion consists of five powder components (drug, microcrystalline cellulose, crospovidone, povidone) of which the active ingredient and the sweetener, which together accounted for 89% (w/w), were maintained in a constant quantity, while the proportions of the remaining three (together accounting 11% w/w) were varied to obtains even different pseudo-mixtures. The limits of each component in the pseudo-mixtures were defined during the preliminary trials obtaining the following values: for microcrystalline cellulose $0 \leq X_1 \leq 3$, for crospovidone $3 \leq X_2 \leq 6$, for povidone $3 \leq X_3 \leq 6$ (%w/win the mixture). For the palatability of the final formulation as partame was included in the fixed amount of 7% in the different mixtures with the rationale that for every 100 mg of ibuprofen are required 8.5 mg of aspartame

Figure 1: Convenient adjustment of the drug dose depending on the age of the patient.
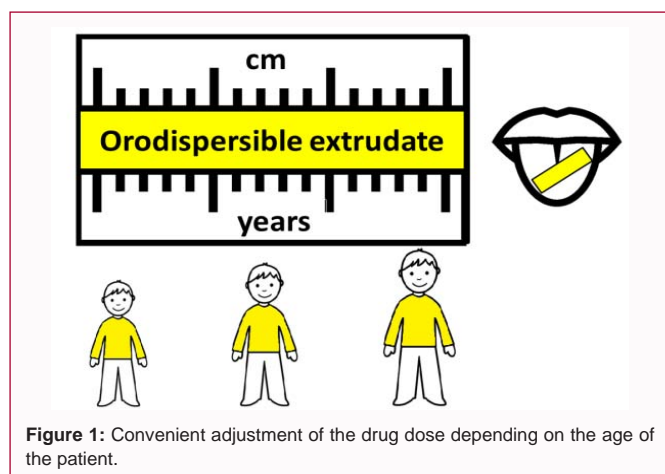
for palatability of the final formulation, as in the marketed formulation chosen as a comparison (Nurofen° comprimés fondants 200 mg). The experimental matrix is given in Table 1 and the experimental design space is depicted in Figure 2.

Wet Masses Preparation

One hundred batches of powders (active ingredient, sweetener and the three auxiliary excipients) were dry blended in a food mixer for 10 runs including 30 sec (mixing) and 1 minute (repose). The composition of the mixtures was in accordance to the proportions reported in Table 1, obtaining seven pseudo-mixtures. The mixtures were then wetted with 32% (w/w) of deionized water added with 1% of wetting agent while mixing. The kneading was carried out for further 10 minutes. The level of wetting was defined during the experimental tests. Evaluation of the content uniformity of the final extrudate established that the mixing had been successful. As wetting agent polysorbate 80 was selected from excipients acceptable in pediatric formulations and used at a low percentage, in consideration of the objective of reducing the toxicity of the final dosage form intended for a pediatric use. For clarity, Table 2 shows the composition of the final 7 mixtures. The dry mixtures were wetted with 32% demineralized water plus 1 % of polysorbate 80 (w/w). Once produced, the mixtures were packaged in sealed bags and allowed to equilibrate for 24 h at room temperature, away from light and heat sources.

Extrusion Procedure

The laminar extrudates were prepared using a vertical lab scale ram extruder (Thalassia°, Trieste, Italy) described into details in a previous work [9]. Briefly, the movement of the stainless steel ram in this extruder is promoted by an oleo dynamic cylinder driven by an electric pump (max pressure 150 bar). The cylindrical nickel plated brass barrel, acting as a powder reservoir, has a capacity of 66 cm³ and an internal diameter of 25 mm. The die attached at the end of the barrel can be changed on demand: in this case a die with flat entry and rectangular shape (2 mm x 8 mm cross section) was used. The extruder chamber, thermo stated at 25°C, was loaded with 50 g of each mixture. The mass was forced through the die using a constant ram velocity. The obtained laminar extrudates were collected during the steady-state flow stage and deposited in trays covered with baking paper, and finally dried (in static oven) at 35°C until constant weight was achieved (4h).These drying parameters, chosen based on previous experience and according to the data of literature [10] did not influence the solid state characteristics of the blends, as assessed by DSC and PXRD analyses. Then, the laminar extrudates were sliced up in unities of length (1.5 cm) suitable to have 100 mg drug content and stored in well-closed bags for 7 days before characterizations.
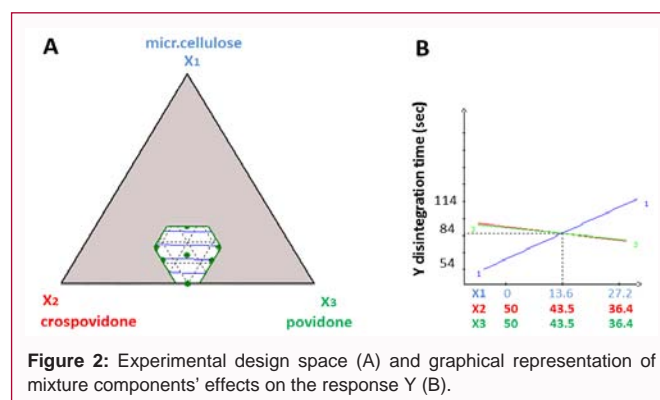

Figure 2: Experimental design space (A) and graphical representation of mixture components' effects on the response Y (B).

Table 2: Composition of the wet masses (100 g powder plus 32 g water and 1 g surfactant).

Exp.	Components in variable amounts(*)				Component in fixed amounts		
	MCC	PVP-CL	PVP	IBU	Aspartame	H_2O	Surfactant
1	0	5.5	5.5	82	7	32	1
2	1	4.7	4.7	82	7	32	1
3	3	4	4	82	7	32	1
4	1.9	3.1	6	82	7	32	1
5	1.2	6	3.8	82	7	32	1
6	1.9	6	3.1	82	7	32	1
7	1.2	3.8	6	82	7	32	1

Wettability Measurements

In order to assess the effect of the addition of surfactant on the Wettability of the active substance ibuprofen, which represents 82% w/w of the formulations and therefore is by far the predominant component, the contact angle was measured. This evaluation was carried out according to the drop method on compressed non-disintegrating disks, using deionized water as a wetting liquid. Two types of compacts were subjected to this test: tablets of ibuprofen wetted by a) deionized water (32% w/w) and b) deionized water (32% w/w) plus 1% of polysorbate 80. Disks were prepared compressing the mixtures in a manual press Perkin Elmer, imparting a force of 5 tons for 1 minute. After compression, the tablets were dried at 40°C using the same procedure as the extrudates. The flat tablets produced were then analyzed with the Drop Shape Analysis System (Krüss DSA 30), using as a wetting solution 5 ml of purified water. The contact angle measurement, performed in triplicate was performed after 10 seconds.

Characterisations of the Laminar Extrudates

Solid state analyses

Thermal analyses were conducted using a differential scanning calorimeter DSC Mettler TA 4000 (Greifensee, Switzerland) connected to a cell Mettler DSC20 calorimeter, equipped software STARe software version 9.30. The analysis was conducted on fragments of extruded, on the raw materials and physical mixtures prepared in the same weight ratios of the systems obtained by extrusion. The samples were subjected to a dynamic heating speed of 10°C / min in a temperature range between 25 and 200°C in air atmosphere. Furthermore, a STOE D500 diffractometer (Siemens, Monaco) was employed, analysing samples in the range of angle 2θ from 5 to 35 ˚ 2θ with a step of 0.05 degrees of 2θ, and counting time of 2 seconds. The current used was 20 mA and the voltage of 40 kV. The following samples were analysed: raw materials, laminar extrudates previously ground in an agate mortar, and corresponding physical mixtures.

Thickness and breaking load measurements

In order to simulate the pressure exerted on the formulation by the tongue, the tensile strength of laminar extruded was determined in transversal direction by using a Hardness Tester Model TBH 30 Erweka (Heusenstamm, Germany). For each formulation 10 extruded samples were analysed. At the same test, 10 reference commercial tablets were analysed, impressing the breaking load again in transversal direction of the tablet. The same device was used to measure extrudate and tablet thickness (mean ± SD, n=10).

Disintegration Tests

The disintegration test (observed response Y) was conducted in a modified USP disintegration test, using 10 ml of pH 6.8 buffer as a medium (simulated saliva), since the classical EP method (employing 900 mL of disaggregation medium) is not adequate to simulate the mouth cavity environment and to test orodispersibleformulations. In short, the method used consisted of a beaker glass of 25 ml containing 5 ml of phosphate buffer, subjected to the same agitation and heating (temperature-controlled bath at 37°C) of the USP disintegrating apparatus (Erweka ZT3, Eusenstamm, Germany). The extrudates were observed during the analyses, and their time of disaggregation was counted using a stopwatch. The analysis was repeated six times for each sample, always using as a comparison specialty commercial Nurofen® comprimés fondants 200 mg.

Attempts to impart the extruded during the disintegration test at a pressure similar to that exerted by the tongue were unsuccessful, since the calibrated weight (100 g) cylinder, positioned over the laminar extrudate, excluded the monitoring of the disintegration time.

Stimulated Wetting Test

To evaluate the ability of hydration over time of the extruded samples, simulating their behavior when in direct contact with saliva, extruded samples of about 1-1.5 cm (equal to 100 mg of ibuprofen) from each mixture were cut, carefully weighed, and subjected to the method reported in the literature [11-13]. In short, the fragments of extruded were placed in a tray covered by a layer of absorbent paper (size 11x7 cm) impregnated with phosphate buffer (acting as a tongue), and on the top covered with two layers of absorbent paper impregnated of phosphate buffer (simulating the palate). At fixed times (15, 30, 45, 60, 75, 90, 105, 120 seconds) fragments were collected and weighed by calculating the percentage of hydration at various times with the following formula (eq.1):

$$W = \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \times 100 \qquad \text{(eq. 1)}$$

For every time point the three samples of each mixture were tested.

In vitro Drug Dissolution

The in vitro ibuprofen dissolution studies were performed using the method proposed for sublingual tablets by Rachid et al. [12]. The dissolution medium consisted in 5 ml of pH 6.8 phosphate buffer (prepared with 4.33 g of K_2HPO_4 and 3.39 g KH_2PO_4), thermostated at 37° C. Samples of extruded containing 100 mg of ibuprofen (suitable dose for children aged 6-12 years) and approximately 1- 1.5 cm in length, were placed on the filter (porosity 0.45 uM) and covered with buffer solution. At each time point, the vacuum pump (KNF Laboport - Neueberg) was activated to allow the removal (in the tube below the vacuum filter) of the solution containing the drug dissolved. The times selected, by virtue of the presence of orodispersible formulation in the mouth, were the following: 15, 30, 45, 60, 90, 120 seconds (6 time points). The analysis was conducted in threefold repetition: for each distinct time point 3pieces of laminar extrudates of the same mixture were taken. The dissolution medium was then filtered and assayed spectrophotometrically (after appropriate dilution with phosphate buffer thermostated at 37°C, if necessary) at 223 nm (Spettrofotometer Biochrom Libra S12, Cambridge, UK). For comparison, dosage units of oro-dispersible Nurofen® comprimés

Table 3: Characterization results of the laminar extrudates and reference formulation.

Sample	Thickness (mm) (mean ± SD, *n*= 10)	Hardness (N) (*n*= 10)	Percent drug content (mean ± SD, *n*= 3)	Loading efficiency (%) (mean ± SD, *n* = 3)	Disintegration time (sec) (mean±SD, *n* = 6)
1	1.85 ± 0.18	<10 N	89.3 ± 5.5	111.3 ± 3.0	115 ± 21
2	1.9± 0.13	<10 N	86.02 ± 6.0	113 ± 7.0	73 ± 17
3	2.03±0.16	<10 N	93.9 ± 7.0	114.5 ± 8.2	187 ± 24
4	1.9± 0.13	<10 N	96.7 ± 4.0	118 ± 4.5	85 ± 8
5	2.3±0.12	<10 N	91 ± 8.4	111 ± 10.3	88 ± 10
6	1.93±0.13	<10 N	86.6 ± 5.0	95.3 ± 4.0	32 ± 7
7	2.19±0.16	<10 N	95.5 ± 1.3	116.5 ± 1.6	21 ± 4
Reference formulation		<10 N	n.d.	n.d.	39 ± 12
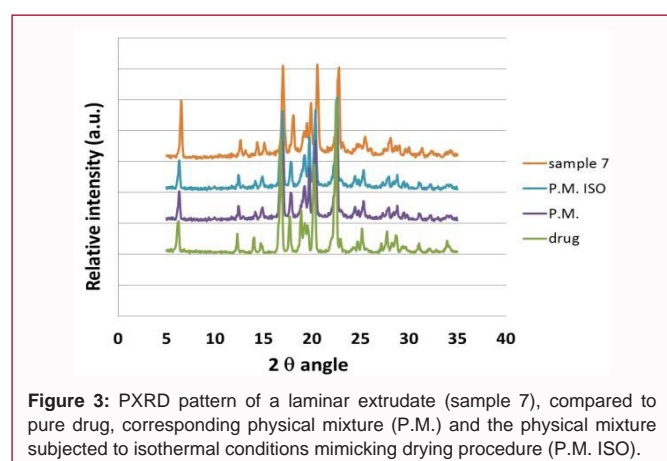
Figure 3: PXRD pattern of a laminar extrudate (sample 7), compared to pure drug, corresponding physical mixture (P.M.) and the physical mixture subjected to isothermal conditions mimicking drying procedure (P.M. ISO).

fondants 200 mg were therefore divided into halves (to get the same dose of active ingredient) and subjected to the same analysis. Given the small number of samples (3 repetitions for each time point) statistical analysis of the data were not carried out.

Results and Discussion

The objective of this study was to obtain by wet extrusion an orodispersible dosage form containing ibuprofen intended to patients aged between 6 and 12 years. Not being orodispersible extrudates available on the market, as a comparison parameter, in every step of the research, the marketed formulation Nurofen® comprimés fondants 200 mg (from now on "reference") was used.

The extrusion was preferred over other techniques because innovative and because it allows to incorporate high amounts of active principle up to a maximum of 90% in the final product [1]. Furthermore, this technology enables to obtain, through appropriate selection of the die, a shape suitable to administration in the mouth. In this research it was chosen a rectangular die allowing to obtain a thin laminar shape of extrudates, having thickness of 2 mm, width of 8 mm and length that can be chosen according to the desired dose (and, in this case, to the patient's age). The small thickness of the extrudatespresumably consents an easy dispersion in the mouth. In order to reduce as much as possible the amount of other ingredients in the final dosage form, thus limiting the possibility of adverse reactions by the same auxiliary components, it would be highly desired that such formulations provide a high drug loading. Furthermore, due to the goal of rapid dispersions in the mouth, such formulations must contemplate the presence of disintegrating excipients that favour the disintegration of the solid form in the mouth cavity. Finally, in this preliminary study, for the palatability of

the final formulation, being an orodipersible formulation and ibuprofen a well- known bad tasting drug [14-16], Aspartamewasincluded in the fixed amount of 7% in the different mixtures with the rationale that for every 100 mg of ibuprofen is required 8.5 mg of aspartame, as in the marketed formulation chosen as a comparison. In view of its well-known toxicity [17] the idea is to replace it in a subesquent study. First preliminary tests were carried out in order to define the optimal quantity and composition of the binder solution, usually ranging about 32-40% w/w [1]. The powder masses were composed of ibuprofen and microcrystalline cellulose, the most classical diluent/binder for wet extrusion [1]. During such preliminary tests it was noted that with a 37-40% water content, the masses showed insufficient consistency and irregular shape as they flowed out of the die at very low pressures, while masses containing less than 32% water were not sufficiently plastic to be extruded (the extrusion process required higher pressures than those permitted from the apparatus) or togive origin to regular extrudates (e.g. sharkskin defects, surface cracks or fractures). Then several disintegrants, such as cross linked cross carmellose sodium (AcdiSol® FMC, Bruxelles, B), Soy polysaccharides (Emcosoy® STS IP, JRS Pharma Rosenberg, DE), sodium starch glicolate (Explotab®, JRS Pharma, Rosenberg, DE) and crospovidone were tested in association with high percentages of ibuprofen (superior to 80%). In the selection of such excipients the disintegrant ability and attitude to wet extrusion process of classical synthetic excipients (such as crospovidone) was compared with that of other ingredients of natural or semi-synthetic origin, that are commonly preferred in formulations for children by paediatricians and from the market. At the end of such screening, however, only crospovidone resulted capable of forming extrudates having regular shape and smooth surface, while permitting a rapid disintegration in water. During preliminary trials the following limits of the 3 above mentioned excipients in the pseudo-mixtures were defined: for microcrystalline cellulose $0 \leq X_1 \leq 3$, for crospovidone $3 \leq X_2 \leq 6$, for povidone $3 \leq X_3 \leq 6$ (% w/win the mixture). It is interesting to note that the presence of microcrystalline cellulose was found not mandatory for the extrusion process, opening the possibility to further reduce the number of included excipients, and to prevent delay of disintegration due to the presence of microcrystalline cellulose. Also during preliminary trials, the addition of 1% surfactant in the binder solution was found to be necessary to achieve a rapidly disintegrating product. This was due to the fact that ibuprofen, which represents 82% w/w of the formulations and therefore is by far the predominant component, is a hydrophobic powder [18]. The addition of 1% polysorbatein the binder solution determined a remarkable reduction of mean contact angle: pure ibuprofen was 77.05±7.09°, whilst after addition of 1% polisorbate 80 the value diminished to

51.55±5.35 (mean± SD, n = 3). Extrudates with the desired uniform laminar shape, constant thickness (2 mm) and a very high content of drug (82% wt) were produced with all the compositions (Table 3). The thickness varies very little from the dimensions of the die, demonstrating the absence of phenomena of expansion after the exit from the die or deformation while drying or over storage. The recorded values are affected by the composition of the mixture and are reproducible within batches with the same composition. The dimensions are compatible with the objective of administration in the mouth and promising for the purposes of dispersion in the mouth itself. The dose for a patient of 6-12 years (100 mg) corresponded to a length of extrudate between 1-1.5 cm, perfectly compatible with a formulation orodispersible thin laminar extrudate intended for a paediatric patient. At the end of the selection of the excipients, the physical compatibility between the drug and excipients was check for any interactions that could occur between components during the various processing steps. Extruded samples were analysed by DSC and PXRD, in comparison with the same physical mixtures having ratios by weight active principle/excipients and with the individual raw materials. Again, due to comparative purposes the physical mixture was subjected to an isothermal heating simulating drying conditions and then analysed by DSC and PXRD. The results of the PXRD (Figure 3) and DSC analyses (data not shown for brevity) agreed to attest the absence of interactions and significant changes in the solid state of the active ingredient by simply mixing, or as a result of the process drying or extrusion. As it can be seen from disintegration tests, the addition of surfactant permitted to the laminar system (having a very high content of drug) to be homogeneously wetted, thus reaching crospovidone particles and allowing for rapid disintegration. The most rapid systems disintegrated in less than 30 sec. The laminar extrudates disintegrated with different disintegration times, depending on their composition, and the disintegration time was in some cases comparable to that of the marketed formulation (around 30 sec). This result is particularly significant when taking into account that these extrudates contain a very high amount of active ingredient, whereas the reference contains the 28.6% of drug. The effect of varying percentage of individual components in mixtures on the disintegration time in pH 6.8 buffer were evaluated graphically by use of the program NEMRODW, considering the disintegration time as experimental response (Figure 2). Disintegration time decreased as the amount of crospovidone increased, and as the amount of cellulose diminished. To go into more details, from the graphical evaluation of the effect on the disintegration time of the percentage of the individual components on mixtures wetted with 1% polysorbate 80 the following considerations can be drawn: the higher the content of povidone and crospovidone in mixtures, extrudates break up in less time, while increasing the proportion of microcrystalline cellulose in mixtures there has been a slowdown in disintegration, as expected from a diluent/binder insoluble in water [19]. Looking at the slope of the three lines, each corresponding to the percentage of a component, a greater influence of the percentage of microcrystalline cellulose than the other two excipients may be observed. The composition of the extruded demonstrating the best disintegration time in the group was: in addition to the fixed amounts of 82% of API and 7% of aspartame, 6% of crospovidone (limit of experimental plan) and1.9% of microcrystalline cellulose and 3.1% of PVP. By assessing the disintegration time in light of the other performed characterizations (results reported in Table 3), it can be seen how the disintegration is not dependent on the thickness nor the hardness of the extrudates. No correlation between the above
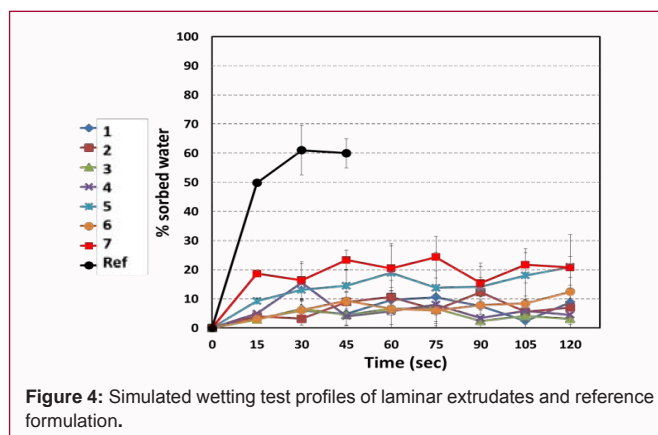

Figure 4: Simulated wetting test profiles of laminar extrudates and reference formulation.
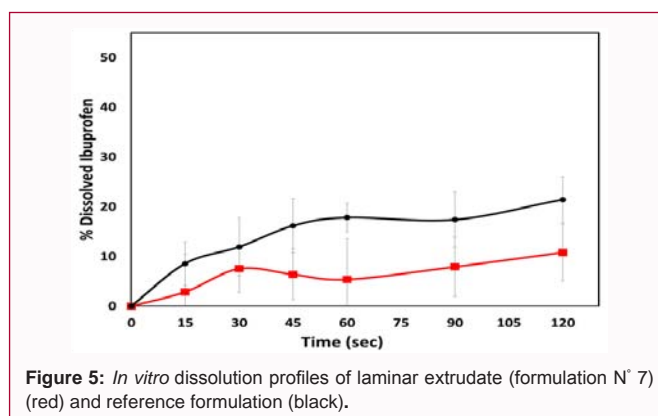

Figure 5: *In vitro* dissolution profiles of laminar extrudate (formulation N° 7) (red) and reference formulation (black).

properties and disintegration was noticed. In fact, while the disintegration varies significantly from sample to sample, the thickness and the breaking load (less than 10 N in all cases) are quite similar. The composition of the extrudates appears therefore primarily responsible for the different performance. In order to assess the ability of such dosage forms hydrate when in contact with small amounts of water, a method proposed in the literature and in the case of laminar extruded [11], sublingual [12] and orodispersible preparations [13] was used. The results of this test are reported in Figure 4, where it can be observed thatwater absorption varies between 3 and 25%. The samples that showed a greater absorption of water corresponded to samples with lower disintegration time. Such amount of water absorbed (3-25%) are perfectly compatible with the small amounts of hydrophilic colloids, able to swell and absorb water present in the extruded and are always able to determine the fragmentation extrudate in the mouth. As expected, the commercial sample containing rather large amounts of hydrophilic agents, e.g. croscarmellose sodium, absorbed much greater amounts of water. The correspondence between simulated wetting time and disintegration time proved that this was due to the time required for water to diffuse through the whole extrudate, rather than the hardness of the extrudates, that was found in all case very scarce (Table 3). Finally, in order to evaluate the release of active ingredient from the formulation in the short time of stay in the mouth, and then predict whether the active ingredient can be dissolved in the saliva and be available for absorption, *in vitro* dissolution test was carried out. Although it was not a goal of the research, the absorption of a certain percentage of the dose of active principle before swallowing would allow a quick pharmacological onset and would partly bypass the gastro-intestinal tract. In addition, knowledge of drug dissolution in

the saliva is an important finding to design the subsequent study of taste-masking formulation of the extrudate. Sample 7 showing the shortest disintegration time in each set was selected cut in fragments having a content of 100 mg of active and subjected to *in vitro* dissolution test according to the method proposed by Rachid et al. [12]. Reference tablets, divided in halves (to have the same content of active principle), were also tested in analogous conditions. The results (Figure 5) proved that a certain amount of ibuprofen (about 5%) is released, and hence available for absorption, from the extrudates in less than 2 minutes (average time of permanence of a orodispersible formulation in the mouth) thanks to the hydrophilic components of the formulation and the presence of the surfactant, despite the poor solubility of the active principle.

Conclusion

Rapidly–disintegrating laminar extrudates, easy to be cut in different lengths allowing for a convenient adjustment of the drug dose, can be a viable and age appropriate formulation to deliver ibuprofen in children. These systems offer several advantages, including the easy administration without need of water, the use of very little amounts of excipients (18% by wt) per each drug dose, the easy dose adjustment depending on the age of the patient.

References

1. Fielden KE, Newton JM. Extrusion and Extruders, In Swarbrick J, Boylan J. (Eds.) Encyclopedia of Pharmaceutical Technology, Marcel Dekker. New York. 1992.

2. Mc Nally GP, Railkar A, M Drug. Delivery Challenges for the Pediatric Patient: Novel Forms for Consideration, in: Pediatric drug development: concepts and applications. Oxford, Wiley-Blackwell. 2009.

3. Fabiano V, Mameli C, Zuccotti V. Paediatric Pharmacology: Remember the Excipients. Pharmacol Res. 2011; 63, 362-365.

4. Bowles A, Keane J, Ernest T, Clapham D, Tuleu C. Specific aspect of Gastro-Intestinal Transit in Children for Drug Delivery Design. Int J Pharm. 2010; 395, 37-43.

5. Breitkreutz J, Wessel T, Boos J. Dosage forms for peroraldrug administration to children. Paediat Perin Drug Ther. 1999; 3: 25-33.

6. Nunn T, Williams J. Formulation of medicines for children. Brit J Clin Pharmacol. 2005; 59: 674–676.

7. Voinovich D, Campisi B, e Phan-Tan-Luu P. Experimental Design for mixture studies. Comprehensive Chemometrics: Chemical and Biochemical Data Analysis. 2009; 391-452.

8. Mathieu D, Nony J, Phan-Tan-Luu R. Nemrodw: New Efficient Methodology for Research using Optimal Design (NEMRODW) Software, LPRAI, Marseille, France. 2015.

9. Grassi M, Voinovich D, Franceschinis E, Perissutti B, Filipovic-Grcic J. Theoretical and experimental study on theophylline release from stearic acid cylindrical delivery systems. J Control Rel. 2003; 30: 275-289.

10. Iosio T, Voinovich D, Grassi M, Pinto JF, Perissutti B, Zacchigna M, et al. Bi-layered self-emulsifying pellets prepared by co-extrusion and spheronization: Influence of formulation variables and preliminary study on the *in vivo* absorption. Eur J Pharm Biopharm. 2008; 69: 686-697.

11. Müllers KC, Wahl MA, Pinto JF. Production of Dosage Form for Oral Drug Delivery by Laminar Extrusion of Wet Masses. Eur J Pharm Biopharm. 2013; 84: 626–632.

12. Rachid O, Rawas-Qalaji M, Simons FER, Simons KJ. Dissolution testing for sublingual tablets: a novel *in vitro* method. AAPS Pharm Sci Tech. 2011; 12: 544-552.

13. BiY, Sunada H, YonezawaY, DanjoK, OtsukaA, IidaK. Preparation And Evaluation Of A Compressed Tablet Rapidly Disintegrating in the Oral Cavity. Chem Pharm Bull. 1996; 44: 2121-2127.

14. Mennella JA, Beauchamp GK. Optimizing oral medications for children. Clin Ther. 2008; 30: 2120-2132.

15. Mennella JA, Spector AC, Reed DR, Coldwell SE. The badtaste of medicines: overview of basic research on bitter taste. Clin Ther. 2013; 35: 1225-1246.

16. Walsh J, Cram A, Woertz K, Breitkreutz J, Winzenburg G, Turner R. Tuleu C. Playing hide and seek with poorly tasting paediatric medicines: Do not forget about the excipients. Adv Drug Del Rev. 2014; 73: 14-33.

17. Tuleu C, I Costello, P F Long, I K Wong, C Tuleu, V Yeung. Eds Peadiatric formulations in practice, in: Paediatric Drug Handling , London, Pharmaceutical Press. 2007; 43-75.

18. Higgins JD, Gilmor TP, Martellucci SA, Bruce RD. Ibuprofen, In: Brittain H.G. (Ed.) Analytical Profiles of Drug Substances and Excipients; San Diego, Academic Press. 2001; 27: 266-300.

19. Rowe RC, Sheskey PJ, Cook WG, Fenton ME. Eds Handbook of Pharmaceutical Excipients, Seventh edn, London. Pharmaceutical Press. 2012.