Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 335–341
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Fast dispersible/slow releasing ibuprofen tablets

Adamo Fini [a,*], Valentina Bergamante [b], Gian Carlo Ceschel [b], Celestino Ronchi [b], Carlos Alberto Fonseca de Moraes [c]

[a] *Dipartimento SMETEC, University of Bologna, Bologna, Italy*
[b] *MonteResearch, Milano, Italy*
[c] *EMS, Hortolandia, Brazil*

Received 26 July 2007; accepted in revised form 20 November 2007
Available online 28 November 2007

Abstract

Eight formulations were developed containing ibuprofen in the form of orally disintegrating tablets. To prevent bitter taste and side effects of the drug, the drug was associated with Phospholipon 80H, a saturated lecithin, by wet granulation. The granules were then coated using different film forming agents (Kollicoat SR 30, Amprac 01, Kollidon 90F, Eudragit RD 100) obtaining four lots 1–4. Coated granules were then formulated with a sweetener (Aspartame), a mannitol-based diluent (Pearlitol SD 200) and Kollidon CL (1-4K) or Explotab (1-4E) were added as superdisintegrants and compacted under low compression force. The eight lots of tablets, 1-4K and 1-4E, were assessed if suitable as oral disintegrating tablets by determination of a range of technological parameters. Wetting and disintegregation time matched with the requirements of EP IV Ed., for almost all these formulations. Dissolution profiles suggested that the combined action of the hydrophobic lecithin and the coating delay the release of the drug from tablets with respect to when it is free or in the form of simple granules. By an appropriate combination of excipients it was thus possible to obtain orally disintegrating tablets and a delayed release of ibuprofen using simple and conventional techniques.

Keywords: Orally disintegrating tablets; Ibuprofen; Lecithin; Taste masking; Slow release; Gastroprotection; Fast dispersing tablets

1. Introduction

Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, orally disintegrating tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration [1–3], since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and travelling patients. The advantages of this new type of solid dosage form are widely recognized, since the term "oro-dispersible tablet" appears in the European Pharmacopoeia (Suppl. 4.1, IV Ed.) defined as "*uncovered tablet for buccal cavity, where it disperses before ingestion*". These tablets display a fast and spontaneous de-aggregation in the mouth, soon after the contact with saliva, though they can be handled or extracted from the package without alteration. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption [4,5]. To fulfil these requirements, tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid de-aggregation of the matrix. Different technological techniques, such as freeze drying or moulding or direct compression [6–8], are currently employed to prepare the formulations of this type present on the pharmaceutical market.

* Corresponding author. Dipartimento SMETEC, University of Bologna, Via San Donato, 15, 40127 Bologna, Italy. Tel.: +39 051 2095655; fax: +39 051 2095652.
E-mail address: adamo.fini@unibo.it (A. Fini).

0939-6411/$ - see front matter © 2008 Published by Elsevier B.V.
doi:10.1016/j.ejpb.2007.11.011

In this paper a simple compression technology was employed for preparing fast disintegrating tablets containing ibuprofen. Traditional compression in fact involves a limited number of process steps and low costs, resulting in fully automated production and packaging lines; it also allows the presence of high doses of both active agent and excipients [9]. Since too high mechanical resistance of the tablet does not usually favour rapid de-aggregation, to combine these two opposite prerequisites into the same formulation we coupled mechanical resistance of the final tablet, to be inserted and taken from usual blister packs, together with the presence of a (super)disaggregant agent to improve oral dispersibility.

Ibuprofen is widely available as *over the counter* formulations throughout Europe for a number of non-serious, self-limiting conditions involving mild to moderate fever and pain. This drug is sometimes associated with a "peppery" taste that limits its use as an effective analgesic and antipyretic drug, e.g. in children. Formulations where ibuprofen was associated with hydroxypropyl beta cyclodextrin, for the entrapment of ibuprofen to reduce its bitter taste, and sweeteners to mask the sour taste and make it more palatable, have been described [10,11]. Moreover, previous results showed that ibuprofen (and its salts) irritates the throat much more than the mouth, and that its quality in the throat is characterized primarily as sting/prick, itch and tickle (often leading to cough) [12].

In addition to its bitter and irritating taste, ibuprofen displays significant risks of gastrointestinal side effects, when chronically administered in the elderly. The developed formulations aimed also to minimize the gastrolesivity of the drug and to improve its palatability by a close association with a lecithin, as excipient, and the presence of sweet-taste additives, such as aspartame and mannitol. Fast dispersibility of the tablet, guaranteed by the presence of a superdisaggregant, and slow release of the drug were tested by the measurement of a number of technological parameters.

2. Materials and methods

2.1. Materials

All the materials used in the present research were commercial samples. *Active agent*: ibuprofen (Welding GmbH, Hamburg, Germany); *protective agents*: Phospholipon 80H (*hydrogenated phosphatidylcholine, 60%*) (Phospholipid, Koln, Germany); Lipoid *S75* (*phosphatidylcholine, 71%; phosphatidylethanolamine, 7.6%*) (Lipoid, Ludwigshafen, Germany); *film forming agents*: Kollicoat SR 30D (*30% w/w aqueous dispersion polyvinyl acetate 27%, Povidon 2.5%, SDS 0.3%*) (Eigenmann & Veronelli, Rho, Italy), Amprac 01 (*pregelatinised starch acetate*) (Rofarma, Gaggiano, Italy), Kollidon 90F (*water soluble high PM PVP polymer, with a water content around 19% w/w*) (Basf, Ludwigshafen, Germany), Eudragit RD 100 (*copolymers of acrylate and methacrylates esters with quaternary ammonium groups in combination with 10% sodium carboxymethylcellulose*) (Rofarma, Gaggiano, Italy); de-aggregating agents: Explotab (*sodium starch glycolate*) (Loxer, Monaco, France), Kollidon CL (*crospovidone*) (Basf, Ludwigshafen, Germany). Aspartame (ACEF, Fiorenzuola d'Arda, Italy), Pearlitol SD200 (*spray dried mannitol*) (Faravelli, Milan, Italy); *lubricant*: magnesium stearate (Faravelli, Milan, Italy) were of pharmaceutical grade, according to EP IV Ed.

2.2. Preparation of the tablets

The preparation of the tablets was carried out according to three different steps.

2.2.1. Granulation

Each phosphatidylcholine (Phospholipon 80H; Lipoid S75) was mixed with ibuprofen in the weight ratio 1:4. The mixture was kneaded in the presence of an amount of water sufficient to homogenize the mass using a laboratory kneader (LK5 Erweka Italia, Seveso, Italy) which was then extruded through a steel grid (2.8 mm) (wet granulator Mod. FGS, Erweka Italia, Seveso, Italy). The final granulate was dried at 45 °C (Drier Mod FD 600 F8/5, Vismara, Milano, Italy) up to a humidity content 3–5% and sieved, selecting particle size $\leqslant$600 μm. The two materials were identified as A (Phospholipon 80H) and B (Lipoid S75).

2.2.2. Film formation

This and the following steps were carried out only with lot A (see Section 3).

Four commercial coating materials (Kollicoat SR 30D, Amprac 01, Kollidon 90F, Eudragit RD 100) were sprayed as aqueous suspension on the granulate particles. The aqueous coating processes were preferred, since they represent an alternative to organic solvent-based film coating for environmental, economic and safety reasons, and all the materials proposed match these needs quite well.

A 20% *w/w* suspension was prepared in water containing each of the four film forming agents that differ in the nature and concentration of the four filming materials (Kollidon R 30D – 2%; Amprac 01 – 2.8%; Kollidon 90F – 0.7%; Eudragit RD 100 – 1.5%, respectively). Each suspension was sprayed onto granules, previously prepared and the filmed granules were simply indicated as 1, 2, 3 and 4, according to the film agent (in order). The whole process was carried out on a "pan" (Mod. VNF 50, Nicomac). Starting from these intermediate formulations we prepared the final tablets.

2.2.3. Compression

Filmed granules were mixed with appropriate amounts of diluent (spray dried mannitol, size < 200 μ), disaggregating agent and lubricant (magnesium stearate). The addition of 10% *w/w* of a disaggregating agent (Kollidon CL-K and Explotab-E) generated two new series of tablets (1K, 2K,

Table 1
Percentage composition of the eight formulations of the A series

Component (%)	Function	1K	2K	3K	4K	1E	2E	3E	4E
Granules									
Ibuprofen	Active agent	29	29	29	29	29	29	29	29
Phospholipon 80H	Protection	7	7	7	7	7	7	7	7
Kollicoat SR 30 D (1)	Coating	2	–	–	–	2	–	–	–
Amprac 01 (2)	Coating	–	2.8	–	–	–	2.8	–	–
Kollidon 90F (3)	Coating	–	–	0.7	–	–	–	0.7	–
Eudragit RD100 (4)	Coating	–	–	–	1.5	–	–	–	1.5
Tablets									
Aspartame	Sweetener	5	5	5	5	5	5	5	5
Kollidon CL (K)	De-aggregant	10	10	10	10	–	–	–	–
Explotab (E)	De-aggregant	–	–	–	–	10	10	10	10
Pearlitol SD200	Diluent	46	45.2	47.3	46.5	46.0	45.2	47.3	46.5
Magnesium Stearate	Lubricant	1	1	1	1	1	1	1	1

3K, 4K; and 1E, 2E, 3E, 4E) of total weight 700 mg and whose complete composition is shown in Table 1.

The powder mixture was accurately blended with the Turbula® Shaker-Mixer T2F (Glen Mills Inc., USA) for 30 min and the final mixture was compressed on an alternative compressor, using a 13 mm punch at 7 kPa to prepare the final form for the de-aggregation and releasing tests, which are oro-dispersible tablets.

2.3. Technological parameters

The eight formulations thus prepared were assessed for a variety of technological parameters. Granules were tested for residual humidity, flowing time and Carr's index. After being checked for weight and hardness, the tablets were also tested for crushing strength, friability, disintegration time and dissolution rate. The results obtained are reported in Table 2.

2.3.1. Carr's index

Carr's "percent compressibility" was calculated using the equation $([p_{tap} - p_{bul}]/p_{tap}) \times 100$. The bulk and tap densities were determined as follows. A known quantity of each sample (25 g) was poured through a funnel into a 100-mL tarred graduated cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density. For tap density, the cylinder was tapped from a height of 2.5 cm 50 times on a wooden bench top to attain a constant volume reading from the cylinder.

2.3.2. Crushing test

The crushing strength of six tablets at each compression force level was determined using an Erweka hardness tester (Type TBH 30, Erweka, Heusenstamm, Germany). Hardness and friability tests were carried out according to EP IV Ed. for uncoated tablets.

2.3.3. Wetting and de-aggregation time

A sample of the final tablet was placed in a Petri dish (10 cm in diameter) containing 10 ml water at room temperature. The wetting time is that necessary for the complete wetting of the tablet. Results of this test, carried out in triplicate, are shown in Table 2 for the different samples.

The de-aggregation test was performed according to the methods described in EP IV Ed. Suppl. 4.1 (dispersible tablets) and the de-aggregation time is the time required to

Table 2
Technological parameters of the eight formulations prepared for granules and tablets

Formulation	1K	2K	3K	4K	1E	2E	3E	4E
Parameter of the granules								
Residual humidity (% ±0.2)	2.6	2.9	3.1	2.9	2.9	3.2	2.9	2.7
Flowing time (s ± 1)	9	8	7	8	10	10	7	8
Apparent density (mg/ml ± 0.03)	0.49	0.52	0.54	0.50	0.48	0.53	0.52	0.49
Packed density (da/di ± 0.02)	0.55	0.57	0.59	0.56	0.56	0.58	0.57	0.57
Carr's index (% ± 0.05)	10.90	8.77	8.47	10.71	14.28	8.62	8.77	14.03
Parameter of the tablets								
Mean mass (mg ± 0.4)	710.5	709.3	712.4	707.5	708.4	711.4	709.6	712.3
Hardness (kp ±0.1)	7.2	7.6	7.5	7.4	7.3	6.8	7.8	7.5
Friability (% ±0.03)	0.48	0.60	0.57	0.50	0.89	1.13	0.85	0.91
Wetting time (s ±3)	33	35	37	34	136	149	>180	>180
De-aggregation time (s ±5)	32	37	70	33	139	140	>180	>180
% Released after 30 min (±5)			36	27	49	72		
% Released after 60 min (±5)			66	50	79	87		

transform a tablet into small fragments, when immersed in water at room temperature, without stirring.

2.4. Dissolution test

A dissolution test was performed at 37 °C using the paddle method at 100 rpm with 500 ml phosphate buffer (pH 6.8) as a dissolution medium. At predetermined intervals, 5 ml of the medium was sampled and filtered. The filtrate was analyzed by ultraviolet/visible variable wavelength spectrophotometer at 220 nm (UV/vis Spectrophotometer model Jasco V-530).

2.5. Differential scanning calorimetry (DSC) and thermogravimetric analysis

Thermal analyses were carried out using a Perkin-Elmer DSC 7 (Perkin-Elmer Italia S.p.A, Monza, Italy), with a scanning rate of 10 °C/min in the temperature range 30–200 °C; thermogravimetric analyses were performed with a Mettler-Toledo automatic thermal analyzer system TGA/SDTA (851/SF/1100). Open alumina crucibles were used for analysis in the temperature range 30–300 °C at 10 °C/min scanning rate under nitrogen stream (Mettler-Toledo S.p.A. – Novate Milanese, Milan, Italy).

2.6. HPLC analysis

Distribution uniformity of the drug inside the different size fraction of the granules or after preparation of the tablets was assessed by means of HPLC. A Dionex P580 system equipped with a variable-wavelength UV detector UVD170S was used for this purpose. *Experimental conditions:* Column C18; mobile phase: methanol–acetonitrile–water phase (85:15:5 v/v); flow rate 1.0 ml/min; detection UV-detector; wavelength 220 nm; injection volume 20 μl. Powdered samples were dissolved in the mobile phase at four concentrations of the drug and examined for a linear response (0.2, 0.5, 1 and 2 mg/ml): the limit of quantification was found to be 0.05 mg/ml.

2.7. Statistical analysis

All data were statistically analyzed by analysis of variance (ANOVA): results were quoted as significant where $P < 0.05$.

3. Results and discussion

3.1. Wet granulation of the system drug/lecithin

As previously stated, the problem with the oral administration of ibuprofen-based formulations is not simply taste masking, but direct contact with the throat mucosae and its gastrolesivity also need to be prevented. In this respect the use of ibuprofen pre-associated with lecithin is widely documented in the literature: zwitterionic phospholipids tend to form inclusion complexes with non-steroid anti-inflammatory drugs [13], reducing direct contact between the drug and the gastrointestinal mucosa [14], thereby conserving the defensive hydrophobic properties of the tissue [15–18]. In the case of present formulations, two different commercial phospholipid mixtures were employed differing in the nature of acyl moieties: Lipoid S75 is formed from highly purified, unsaturated soybean (S) lecithin, marketed by Lipoid, and containing 75% phosphatidylcholine. Phospholipon 80H contains minimum 60% phosphatidylcholine but, unlike Lipoid S75, is fully hydrogenated.

Association between the drug and the protective agent was obtained by means of a wet granulation in the presence of water at room temperature: the paste obtained after prolonged mechanical kneading was then granulated, collecting, after drying, a size fraction $\leqslant 600$ μm. At this stage the nature of lecithin was found critical, since Lipoid S75, which is formed from brown agglomerates, having a rubber consistency, does not leave a solid material at drying, but remains as a soft paste, unsuitable for further processes. Unsaturation can be the origin of its non-crystalline state already at room temperature and of its appearance as a soft paste, rather than a powder. Phospholipon 80H, on the contrary, is originally a powder and demonstrated better behaviour during and after granulation, providing an easily handled final material.

As a consequence, after employing both lecithins in the granulation step, granules obtained using Lipoid S75 were not further considered and additional tests were carried out with the Phospholipon 80H/ibuprofen association.

3.2. Film formation

In present formulations, taste-masking was obtained in two parallel ways: coating the granulated particles with different film-forming agents, also to control the release, and adding a diluent with a slight sweet taste in the subsequent step together with a sweetener.

Four commercial coating materials (Kollicoat SR 30D, Amprac 01, Kollidon 90F, Eudragit RD 100), in different percentages (2%, 2.8%, 0.7% and 1.5%, respectively), according to their coating ability were sprayed as aqueous suspension on the granulate particles (samples 1–4, in order).

Kollicoat SR 30D is an aqueous dispersion composed of 27% polyvinyl acetate (PVAc), 2.5% povidone, and 0.3% sodium lauryl sulfate: the formed PVAc film possesses high flexibility, rendering the film-coated pellets compressible without rupture [19,20].

Pregelatinised starch acetate (Amprac 01) can form films of good mechanical properties, remarkable crack resistance and consequently a high tensile strength; thermal analysis outlines its affinity for water and this fact plays a positive role, since residual water can act as a plasticizer lowering the T_g [21].

Kollidon 90F is a water soluble high PM PVP polymer, with a water content around 19% *w*/*w*; it is widely known

that high molecular weight povidone can be used in flexible film formation, with an appreciable amount of elongation on stress. Its concentration in the spray solution for coating was the lowest one, since a higher concentration gives rise to high viscosity, increasing the spray time significantly. The resulting films have a very high flexibility, no tackiness and a smooth surface.

Eudragit RD 100 is a powder for pH independent fast disintegrating films: it contains copolymers of acrylate and methacrylate esters with quaternary ammonium groups (Eudragit®RL 100) in combination with 10% sodium carboxymethylcellulose [22].

Size distribution analysis of the granulated particles obtained after this process suggests that amidon (Amprac 01) and PVP (Kollidon 90F) also promote aggregation, since about 90% of the granule particle size is $\geqslant$600 μm (50% >800 μm), while Eudragit R 100 and Kollicoat SR 30D allow a more homogeneous size distribution.

The composition of the coated granules is shown in Table 1.

3.3. Tablets

Filmed granules represented a suitable material for formulating oral disaggregating tablets by means of a traditional technology. The percent composition of the formulations, adjusted by varying the content of the excipients ready to be compacted, is shown in Table 1. Attention was also paid to patients with possible dental caries or weight problems with the use of an acariogenic sweetener, such as aspartame, lacking in calories; and the taste was also improved by the use of Pearlitol, spray dried mannitol, with a narrow particle size distribution, exhibiting low hygroscopicity, excellent chemical stability, direct compressibility and rapid dissolution; moreover its negative heat of solution imparts a cooling effect added to the fresh feel in the mouth during disaggregation. Prior compression the powders were accurately blended. Uniform distribution of the active agent was assessed by HPLC, according to a method developed for analysis of anti-inflammatory drugs in the presence of phospholipid derivatives: the content of ibuprofen was found inside the ±2% of the theoretical value [23].

No special equipment was adopted to compact the physical mixtures into tablets. Operative parameters could be easily modulated in order to give the final tablets a satisfactory de-aggregation time, but also the necessary mechanical resistance for processing and handling both for the packaging and also for extraction from the container, before administration. Since fast disaggregating tablets are less hard than conventional ones, due to a lower compression employed (hardness is usually <3 kPa), these tablets can therefore be fragile and need individual packaging. Hardness values of present tablets were preset in the range 6.8–7.5 kPa. Friability of the tablets, lower than 1% in most cases, indicates that the developed formulations can be processed and handled without excessive care. To obviate the difference in hardness, we added a disaggregant agent to the formulations. In fact, a fast disaggregating tablet must disintegrate in the saliva, harder tablets (like present ones: 7 kPa vs 3 kPa) need a de-aggregating agent of a superior ability. In this case Kollidon CL, cross-linked PVP – series K – or Explotab, sodium starch glycolate – series E were employed.

Some technological parameters of the final tablets are shown in Table 2.

3.4. De-aggregation and wetting time

Disintegration time, which is affected by the hardness of the tablets, is related to the nature of the disintegrant agent that allows the tablet to break up into smaller fragments upon contact with physiological fluids. Kollidon CL is completely insoluble in all commonly used solvents: as it swells in contact with water in a very predictable manner, it is mainly used as a superdisintegrant. In contrast to other compounds the capability of swelling is reversible. Explotab is the sodium salt of carboxymethyl ether of starch: practically insoluble in organic solvents, it absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules. The content of superdisintegrant agents, employed in formulations of this type, usually ranges between 10% and 30% *w*/*w*: the present formulations all contain 10% of each superdisintegrant. This parameter appears to be the main factor responsible for the difference in disintegrating time, as shown in Table 2. It has in fact been reported [24] that the main factor influencing the disintegration time of a tablet, in the presence of Kollidon CL, is the compression force rather than the disintegrant concentration; while with Explotab, whatever the compression force, the disintegrant concentration leads to an increase of the disintegration time.

On the basis of the de-aggregation time of the tablets, according to the EP IV Ed., almost all the formulations developed can be defined "fast dispersible": the limit for de-aggregation is in fact suggested as within 3 min. Exceptions are represented by samples 3E and 4E, whose de-aggregation time is higher than that required by EP IV. However E-series formulations proved unsuitable for use as oral dispersible tablets, since they were found to swell and the volume increase appeared inappropriate for the oral cavity.

Tablets of K series demonstrated to be "more quickly dispersible" with respect to those of the E series: the time values in fact are quite different for the two disaggregating agents and the ratio is about 3–4:1, Kollidon CL being more efficient.

3.5. Thermal analysis

Thermal analyses were carried out on simple components and the binary physical mixtures of drug/excipient to check purity and to show any possible interactions. The Phospholipon 80H thermogram contains two endo-

therms (62 and 80 °C), suggesting the complex composition of the material: the baseline is not constant and shows a drift to high temperature. Ibuprofen presents a narrow and symmetric melting endotherm, peaking at 75 °C. The thermal behaviour of the mixtures is more complex, since the melting endotherm of the drug is found at temperature very close to the peak of the lecithins: mixture at higher drug/lecithin weight ratios (2:1 and 4:1) made it possible to exclude any interaction: thermogram of the mixtures is simply the sum of those of the single components. Due to the drift of the baseline, we decided not to report thermogram profiles in a figure. The preliminary drug/lecithin association prevented interactions between ibuprofen and the PVP of the coating (when present), as previously observed [25], that could improve dissolution of the drug. PVP stabilizes indomethacin in its amorphous state, when formulated in the form of solid dispersion, through an interaction that inhibits dimers representing the common solid state structure for acidic drugs. This modification was reported to favour depression of the melting point of the system, improving dissolution and thus release of the active agent and this situation can be hypothesized to be common also for other acidic drugs, such as ibuprofen.

Thermogravimetric analysis revealed that all granulates contained <3% of residual humidity that did not affect the further steps of the preparation.

3.6. Release

Oral dispersible tablets are designed to disaggregate in the oral cavity and usually release and allow the active agent to dissolve remarkably fast in the saliva. Association between drug and lecithin, as in present case, introduces a control of the release: differences between uncoated granules, where the drug is associated only with a hydrophobic lecithin, and free drug were observed in preliminary tests. While the granules take more than 1 h to dissolve, the free drug reaches complete dissolution in few minutes. The control of the release is even more important for tablets, where ibuprofen release is affected not only by the association with lecithin, but also by the coating film.

The release of ibuprofen from all the formulations of the K series (containing Kollidon CL as superdisaggregant) is <60–70% after 1 h: the association with lecithin delays the release, with respect to pure ibuprofen, despite the favourable pH of the dissolution medium; and also could limit the contact of the drug with mouth mucosae besides preventing dumping as a possible side effect.

Fig. 1 compares dissolution profiles of two formulations of the E series (those having acceptable disaggregating time, that is 2E and 4E) with the formulations 3K and 4K.

Experimental data were interpolated by the equation: $M_t/M_\infty = kt^n$, where M_t is the mass released at time t; M_∞ is the starting mass at $t = 0$; k is the kinetic constant and n is the release exponent, indicative of the mechanism of release. Kinetic constants are higher for the samples 1E and 2E ($5.06 \times 10^{-2}\,\mathrm{min}^{-n}$ and $10.15 \times 10^{-2}\,\mathrm{min}^{-n}$, respectively) than those for samples 3K and 4K ($4.38 \times 10^{-2}\,\mathrm{min}^{-n}$ and $3.63 \times 10^{-2}\,\mathrm{min}^{-n}$, respectively). The presence of the superdisaggregant Kollidon CL in the series K produced tablets dissolving more slowly with respect to the E series, containing Explotab. These tablets can be defined as "fast dispersible/slow dissolving". It emerged also that the release appears governed by simultaneous diffusion/erosion, since n values are higher than 0.5 (1E: 0.88; 3K: 0.67; 4K: 0.73) with the exception of the E2 samples, where the release is linearly related to the square root of time ($n = 0.5$) and diffusion appears the dominant mechanism of the release.

Finally it is interesting to note that, despite the presence of two PVPs (Kollidon 90F and Kollidon CL) as film forming agents and superdisaggregant in the tablets, the sample 3K displays slow dissolution. It was in fact reported [25] that a close association between an acidic drug and PVP

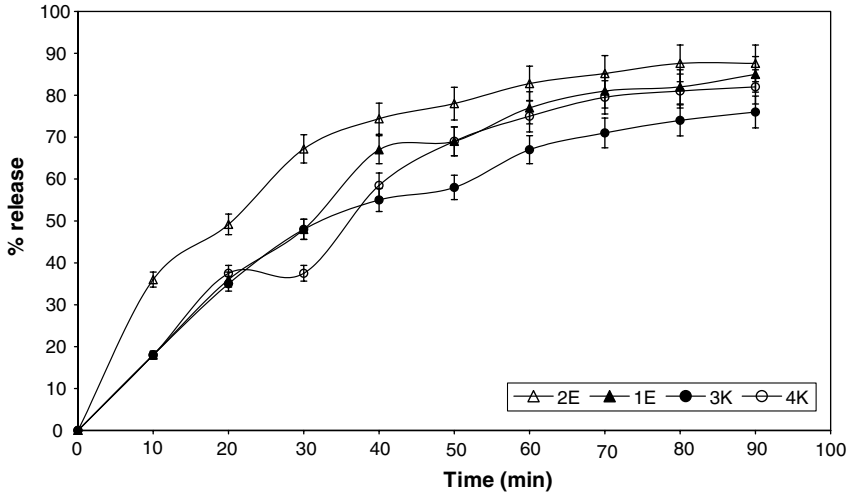

Fig. 1. Comparison of ibuprofen release profiles for tablets of different composition: 1E ▲: Kollicoat-SR + Explotab; 2E △: Amprac 0.1 + Explotab; 3K ●: Kollidon 90 F + Kollidon CL; 4K ○: Eudragit RD 100 + Kollidon CL.

enables the formation of a state suitable to improve the dissolution rate: in the present case the preliminary granulation of the drug with lecithin prevented any contact between the drug and PVP, when present in the coating film, preventing this dissolution promotion mechanism.

4. Conclusions

Rapid-disintegrant tablets transform into easy-to-swallow suspension on contact with the saliva, after ingested in mouth. These are particularly useful for pediatric or geriatric patients, can be taken without liquids and facilitate treatment of emergent pain, irrespective of the place and situation where it may arise.

The developed formulations have suitable characteristics that distinguish them from common solid dosage forms, such as rapid de-aggregation, combining advantages of both liquid and conventional tablet formulations, ease of swallowing and possible taste-masking components for an acceptable taste in the mouth. The presence of a superdisaggregant makes it possible to produce sufficiently hard tablets that still disaggregate within seconds and most of the developed tablets can be considered as "fast dispersible". They can also be programmed not only for oral dispersibility, but also for delayed release, with dissolution of the drug taking place far from the buccal district. Finally these tablets can be prepared by means of a conventional tabletting technique and are designed to exert a control of the side effects of the drug at gastric level.

Formulations containing Kollidon CL as superdisintegrant can represent examples of fast dispersible/slow releasing tablets that offer an alternative to traditional tablets for orally dispersible ibuprofen tablets.

Acknowledgements

This paper was supported by PRIN Funds. The text was revised by a native English speaker.

References

[1] R.K. Chang, X. Guo, B. Burnside, R. Couch, Fast-dissolving tablets, Pharm. Technol. 24 (2000) 52–58.
[2] W. Habib, R. Khankari, J. Hontz, Fast-dissolving drug delivery system, Crit. Rev. Ther. Drug Carrier Syst. 17 (2000) 61–72.
[3] T. Schettler, S. Paris, M. Pellett, S. Kidner, D. Wilkinson, Comparative pharmacokinetics of two fast-dissolving oral ibuprofen formulations and a regular release ibuprofen tablet in healthy volunteers, Clin. Drug Invest. 21 (2001) 73–78.
[4] S. Hisakadzu, B. Yunxia, Preparation, evaluation and optimization of rapidly disintegrating tablets, Powder Technol. 122 (2002) 188–198.
[5] S. Schiermeier, P.C. Schmidt, Fast dispersible ibuprofen tablets, Eur. J. Pharm. Sci. 15 (2002) 295–305.
[6] H. Seager, Drug-delivery products and the Zydis Fast-dissolving dosage form, J. Pharm. Pharmacol. 50 (1998) 375–382.
[7] H. Walid, R. Khankari, J. Hontz, Fast-dissolving drug delivery systems, Crit. Rev. Therap. Drug Carrier Syst. 17 (2000) 61–72.
[8] A.E. Clausen, A. Bernkop-Schnurch, Direct compressible polymethacrylic acid-starch compositions for site-specific drug delivery, J. Control Rel. 75 (2001) 93–102.
[9] Y.X. Bi, H. Sunada, Y. Yonezawa, K. Danjo, Evaluation of rapidly disintegrating tablets prepared by a direct compression method, Drug Dev. Ind. Pharm. 25 (1999) 571–581.
[10] A. Ito, M. Sugihara, Development of oral dosage form for elderly patients: Use of agar as base of rapidly disintegrating oral tablets, Chem. Pharm. Bull. 44 (1996) 2132–2136.
[11] M.K. Ghorab, M.C. Adeyeye, Enhanced bioavailability of process-induced fast-dissolving ibuprofen cogranulated with beta-cyclodextrin, J. Pharm. Sci. 92 (2003) 1690–1697.
[12] P.A.S. Breslin, T.N. Gingrich, B.G. Green, Ibuprofen as a chemesthetic stimulus: evidence of a novel mechanism of throat irritation, Chem. Senses 26 (2001) 55–65.
[13] L.M. Lichtenberger, J.J. Romero, W.M. De Ruijter, F. Behbod, R. Darling, A.Q. Ashraf, S.K. Sanduja, Phosphatidylcholine association increases the anti-inflammatory and analgesic activity of ibuprofen in acute and chronic rodent models of joint inflammation: relationship to alterations in bioavailability and cyclooxygenase-inhibitory potency, J. Pharmacol. Exp. Ther. 298 (2001) 279–287.
[14] B.S. Anand, J.J. Romero, S.K. Sanduja, L.M. Lichtenberger, Phospholipid association reduces the gastric mucosal toxicity of aspirin in human subjects, Am. J. Gastroenterol. 94 (1999) 1818–1822.
[15] B.S. Dunjic, J. Axelson, A. Ar'Rajab, K. Larsson, S. Bengmark, Gastroprotective capability of exogenous phosphatidylcholine in experimentally induced chronic gastric ulcers in rats, Scand. J. Gastroenterol. 28 (1993) 89–94.
[16] L.M. Licthenberger, Z.-M. Wang, J.J. Romero, C. Ulloa, J.C. Perez, M.-N. Giraud, J.C. Barreto, Non-steroidal anti-inflammatory drugs (NSAIDs) associated with zwitterionic phospholipids: Insight into the mechanism and reversal of NSAID-induced gastrointestinal injury, Nat. Med. 1 (1995) 154–158.
[17] B.S. Kurinets, L.M. Lichtenberger, Phosphatidylcholine-associated aspirin accelerates healing of gastric ulcers in rats, Digest. Dis. Sci. 43 (1998) 786–790.
[18] M.N. Giraud, C. Motta, J.J. Romero, G. Bommelaer, L.M. Lichtenberger, Interaction of indomethacin and naproxen with gastric surface-active phospholipids: a possible mechanism for the gastric toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs), Biochem. Pharmacol. 57 (1999) 247–254.
[19] K. Kolter, F. Ruchatz, Kollicoat® SR 30D – a new sustained-release excipient, in: Proc. Int. Symp. Controlled Release Bioact. Mater., vol. 26, 1999, pp. 6311. See also: Kollicoat SR 30 D, BASF Technical Bulletin, pp. 1–14.
[20] G.A. Novoa, J. Heinamaki, S. Mirza, O. Antikainen, A. Iraizoz Colarte, A. Suzarte Paz, J. Yliruusi, Physical solid-state properties and dissolution of sustained-release matrices of polyvinylacetate, Eur. J. Pharm. Biopharm. 59 (2005) 343–350.
[21] G. Bonacucina, P. Di Martino, M. Piombetti, A. Colombo, F. Roversi, G.F. Palmieri, Effect of plasticizers on properties of (Amprac 01) free films, Int. J. Pharm. 313 (2006) 72–77.
[22] C. Wu, J.W. McGinity, Influence of an enteric polymer on drug release rates of theophylline from pellets coated with Eudragit RS 30D, Pharm. Dev. Technol. 8 (2003) 103–110.
[23] V. Ioffe, T. Kalendarev, I. Rubistein, G. Zupkovitz, Reverse phase HPLC for polar lipids. Simple and selective HPLC procedures for analysis of phospholipid-based derivatives of valproic acid and various anti-inflammatory drugs, J. Pharm. Biopharm. Anal. 30 (2002) 391–403.
[24] P. Di Martino, S. Martelli, P. Wehrle, Evaluation of different fast melting disintegrants by means of a central composite design, Drug Dev. Ind. Pharm. 31 (2005) 109–121.
[25] L.S. Taylor, G. Zografi, Spectroscopic characterization of interaction between PVP and indomethacin in amorphous.