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Matrix mini-tablets based on starch/microcrystalline wax mixtures

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Abstract

Matrix mini-tablets based on a combination of microcrystalline waxes and starch derivatives were prepared using ibuprofen as a model drug. The production of mini-tablets was preferred over the production of pellets, as up-scaling of the pelletisation process seemed problematic. Prior to tabletting, melt granulation in a hot stage screw extruder and milling were required. The in vitro drug release was varied using microcrystalline waxes with a different melting range, the slowest drug release being obtained with a formulation containing a microcrystalline wax with a melting range between 68 and 72°C. Generally speaking increasing the wax concentration resulted in a slower drug release. In vitro drug release profiles were also modified using different starches and mixtures of starches. Increasing the ibuprofen concentration to 70% resulted in a faster drug release rate.

Keywords: Sustained release matrix; Mini-tablet; Multiple unit dosage form; Melt extrusion; Ibuprofen

1. Introduction

Mini-tablets (micro tablets) are tablets with a diameter equal to or smaller than 2–3 mm (Lennartz and Mielck, 1998). These mini-tablets can be filled into hard gelatin capsules for the production of a sustained release multiple unit dosage form which has definite advantages over single unit dosage forms. These advantages are: less risk of dose dumping, less inter- and intra- subject variability, high degree of dispersion in the digestive tract thus minimizing the risks of high local drug concentrations (Bechgaard and Nielsen, 1978; Follonier and Doelker, 1992). Mini-tablets also offer an alternative for pellets because of their relative ease of manufacturing and because dosage forms of equal dimensions and weight with smooth regular surface are produced in a reproducible and continuous way. Mini-tablets are very suitable for coating in order to sustain the drug release but the coating process is expensive, time consuming and sometimes associated with reproducibility problems of release during storage. So the development of mini-matrices to

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control the drug release has gained a lot of interest. Several papers have already been published describing matrix mini-tablets based on hydrophilic (Colombo et al., 1985; Feely and Davis, 1989; Bongiovanni et al., 1992; Østberg et al., 1994; Clancy and Cumming, 1998; Rouge et al., 1997, 1998; Sujja-areevath et al., 1998) as well as hydrophobic materials (Önay-Başaran and Olsen, 1985; Önay-Başaran et al., 1985; Ratsimbazafy et al., 1996). The aim of the present work was the preparation of matrix mini-tablets based on a combination of microcrystalline wax and a starch derivative in order to sustain the drug release. Formulations based on these components have already been described (Zhou et al., 1996) as flexible matrix systems when producing pellets by a melt pelletisation process, but upscaling of this production process proved problematic.

2. Materials and methods

2.1. Materials

Ibuprofen (diameter: 25 μm) (Knoll Pharmaceuticals, Nottingham, UK) was selected as the model drug. Three microcrystalline waxes: Paracera® M (melting range: 68–72°C), Paracera® P (melting range: 58–62°C) (Paramelt BV, Heerhugewaard, Nederland) and IGI® 2291 (melting range: 49–52°C) (IGI Europe, Brussels, Belgium) were used as hydrophobic materials. In order to make a homogenous powder mixture the wax pellets were molten and spray congealed in order to obtain a powder with a mean average particle size of 200 μm. The waxes were further processed with pregelatinized starches (Drum Dried Corn Starch – DDCS; Drum Dried Waxy Maize Starch-DDWM) and maltodextrins (Waxy Maltodextrin – WMD, DE 10, Potato Maltodextrin – PMD, DE 3). All starch derivatives were supplied by Eridania-Béghin Say-Cerestar (Vilvoorde, Belgium). Triacetin which acted as a lubricant during extrusion and tabletting was purchased from Vel (Leuven, Belgium).

2.2. Methods

2.2.1. Composition of the mixtures

During the formulation study the ibuprofen concentration was kept constant at 60% (w/w), while the microcrystalline wax concentration varied between 15 and 20% (w/w). The remaining part of the formulation consisted of a starch derivative and triacetin. The triacetin concentration varied between 1 and 4% (w/w).

The influence of the drug concentration on the drug release profile was studied on mini-tablets containing ibuprofen in concentrations varying between 40 and 70% (w/w). The remaining part of the formulation consisted of Paracera® P, triacetin and WMD. The maltodextrin/wax ratio was kept constant at 1.5/1 for the formulations containing 40–70% ibuprofen. Table 1 gives an overview of all the formulation compositions evaluated during this study.

2.2.2. Preparation of the granules

Formulations containing ibuprofen, microcrystalline wax, a starch derivative and triacetin were mixed in a planetary mixer (Kenwood Chef, Hampshire, UK) followed by melt extrusion. The melt extrusion was performed on a MP19TC-25 laboratory scale co-rotating twin screw extruder of APV Baker (Newcastle-under-Lyme, UK). The machine was equipped with a control panel (allowing control of barrel temperatures, screw speed and powder feed rate) and twin screws having 2 mixing sections, a 3 mm cylindrical die and a twin screw powder feeder. The extrusion parameters were set at a screw speed of 100 rpm and a powder feed rate of about 700 g/h. The temperature profile of the extrusion barrel depended on the melting range of the microcrystalline wax used. Therefore different temperature profiles were necessary during extrusion: 58-56-56-53–53°C from the powder feeder towards the die for Paracera® P and IGI® 2291 based formulations, while a higher temperature profile: 64-62-62-59-58°C was used for Paracera® M formulations. The extrudates (diameter 3 mm) were milled using a Kenwood® mill (Kenwood Chef, Hampshire, UK), followed by sieving on a Retsch VE 1000 shaker (Retsch, Haan, Germany)

using 250, 500 and 710 μm sieves. The granules with a size fraction of 250–500 μm were withheld for further analysis and compression tests. As the narrow diameter of the compression die (2 mm) required granules with excellent flow properties, the flow rate through a funnel, the Carr Index (compressibility index) and the Hausner ratio were determined. Using the glass funnel specified in the Ph. Eur III the flow rate (g/s) was calculated from the time needed for the entire sample (40 g of granules) to empty from the funnel. Bulk density was calculated from the amount of granules poured into a 100 ml graduated cylinder up to a total volume of 50 ml while for the tap density determination the cylinder was tapped until no measurable change in the volume was observed. Based on bulk and tap density both the Carr Index (%) ((tapped − bulk) × 100/tapped) and Hausner ratio (tapped/bulk) were calculated.

2.2.3. Production of mini-tablets

The granules (250–500 μm) were compressed using an eccentric tabletting machine (Korsch, EK 0, Frankfurt, Germany) equipped with a standard filling shoe. Punch holders were equipped with flat punches 2 mm in diameter. The mean compaction pressure was 156 ± 16 MPa for each mini-tablet. Each mini-tablet weighed approximately 7.5 mg.

2.2.4. Drug release measurements

A modified paddle method (USP XXIII) was used in which the mini-tablets (60 mg mini-tablets corresponding to 36 mg ibuprofen) were kept in a spherical basket positioned at the bottom of the dissolution vessel. The dissolution of the mini-tablets containing ibuprofen was performed in 900 ml phosphate buffer (pH 7.2). Sink conditions were achieved in simulated intestinal fluid (pH 7.2), as the solubility of ibuprofen is 27.1 mg/ml at 37°C (Adeyeye and Price, 1994). The temperature of the medium was kept at 37 ± 0.5°C, while the rotational speed of the paddles was set at 100 rpm. Samples of 5 ml were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24 h, replaced by fresh medium and spectrophotometrically analysed for ibuprofen at 221 nm by means of a Perkin Elmer Lambda 12 UV-VIS double beam spectrophotometer (Zaventem, Belgium). The dissolution on the mini-tablets was simultaneously performed in six dissolution vessels, each vessel containing eight mini-tablets.

The release data were evalutated according to the equation of Ritger and Peppas (1987) fitting the data from the initial 60% of drug release to Eq. 1.

$$\log M_t/M_\infty = \log k + n \log t \quad (1)$$

Table 1
Overview of the formulations used[a]

Formulation	IBP	Microcrystalline wax	Starch derivative	Triacetin
1	60	15 P	22.5 WMD	2.5
2	60	15 M	22.5 WMD	2.5
3	60	15 IGI 2291	22.5 WMD	2.5
4	60	15 P	24 WMD	1
5	60	15 P	21 WMD	4
6	60	20 P	17.5 WMD	2.5
7	60	15 P	22.5 PMD	2.5
8	60	15 P	22.5 DDWM	2.5
9	60	15 P	22.5 DDCS	2.5
10	60	15 P	4.5 DDCS, 18 WMD (1/4)	2.5
11	60	15 P	6.75 DDCS, 15.75 WMD (1/2.3)	2.5
12	60	15 P	9 DDCS, 13.5 WMD (1/1.5)	2.5
13	40	23 P	34.5 WMD	2.5
14	70	11 P	16.5 WMD	2.5

[a] All concentrations are given in percentage (w/w). IBP, ibuprofen; P, Paracera® P; M, Paracera® M.

Where M_t/M_∞ is the fractional release of the drug at time t, k is a constant incorporating structural and geometric characteristics, and n is the release exponent indicative of the drug release mechanism. A value of $n = 0.45$ indicates Fickian diffusion, $0.45 < n < 1.00$ anomalous diffusion and $n = 1.00$ zero order drug release.

2.2.5. Friability

Ten grams of mini-tablets together with 200 glass beads (diameter: 4 mm) were placed in a friabilator, equipped with an abrasion wheel (Pharma Test, Hainburg, Duitsland). After rotating for 10 min the size fraction < 250 μm was removed, weighed and expressed as a percentage of the initial weight of the mini-tablets.

2.2.6. Porosimetric analysis

The pore size of the mini-tablets before dissolution was determined using a mercury porosimeter (Autopore III 9410 System, Micromeritics, Zaventem, Belgium). A calibrated powder penetrometer with a 5 ml sample volume and a 1.131 ml stem volume was filled with mini-tablets and the mercury intrusion into the pores was measured over a pressure range of 0.5–60 000 psia, allowing pore size determination between 0.003 and 360 μm. From these data the porosity (%) of the mini-tablets was calculated.

2.2.7. X-ray diffractometry

The powder X-ray diffraction patterns were determined using a Siemens D 5000 Bragg-Brentano $\theta/2\theta$ diffractometer with CuK_α radiation ($\lambda = 1.54°$), voltage 40 kV, current 50 mA at a scanning rate of 1°/min for 2θ. The samples were placed in a holder and scanned over a range of $2\theta = 2–50°$. A narrow range of $2\theta = 20–23°$ and a scanning rate of 0.0625°/min for 2θ were used for measuring the peak intensities of ibuprofen and Paracera® P.

3. Results and discussion

Matrix pellets based on a combination of microcrystalline wax, starch and ibuprofen in a high shear mixer (GRAL 10, Collette, Wommelgem, Belgium) were succesfully developed on a small scale (Zhou et al., 1996). The up-scaling study resulted in a broader particle size distribution of the pellets leading to low yield values for a defined particle size range. Melt extrusion was considered as an alternative in order to form these microcrystalline wax/starch matrices. Brittle, sharkskinned extrudates were obtained and needed further handling. The extrudates were milled and sieved in order to obtain granules which could be compressed to mini-tablets.

3.1. Physical and technological properties of the granules and mini-tablets

Flow measurements of the 250–500 μm granule fraction were performed as good flowability is a prerequisite to obtain mini-tablets with an acceptable weight variation. For all the formulations the flow rate of the 250–500 μm granule fraction was between 6 and 9 g/s. According to literature data excellent flow properties are seen for powders with a Carr Index between 5 and 15% and a Hausner ratio below 1.25 (Wells, 1997). All the formulations tested (granule fraction between 250 and 500 μm) had a Carr Index ranging between 7.5 and 12% while their Hausner ratio was below 1.20. The excellent flow properties were also proved by the narrow weight distribution of the mini-tablets, as all formulations had coefficient of variation values of less than 5% relative to their mean weight. This, combined with the low friability (less than 1%) (Table 2) of all formulations demonstrated the suitability of these mixtures to produce mini-tablets.

The porosity of the mini-tablets varied from 12.3 to 16.1% (Table 2). These results indicate that the initial porosity is independent on the composition of the mini-tablets, and therefore not responsible for the difference in drug release profile.

3.2. X-ray diffraction

The results of powder X-ray diffraction are shown in Figs. 1 and 2. The diffraction patterns for ibuprofen (IBP) (Fig. 1a), Paracera® P (P) (Fig. 1b), a physical mixture of IBP and P (Fig.

Table 2
Characterisation of the mini-tablets

Formulation	Friability (%)	Porosity (%)	Release characteristics		
			n	k	R^2
1	0.2	12.8	0.50	26.70	0.9997
2	[b]	[b]	0.44	24.87	0.997
3	[b]	[b]	0.60	34.09	0.9974
4	0.1	12.3	0.48	24.83	0.9996
5	0.2	14.2	0.51	28.93	0.9996
6	0.3	12.7	0.47	24.59	0.9987
7	0.2	14.3	0.52	22.52	0.9995
8	0.2	12.6	0.73	20.77	0.9983
9	0.3	15.2	[a]	[a]	[a]
10	0.2	12.3	0.58	28.19	0.9999
11	0.6	12.7	0.71	33.83	0.9976
12	0.5	12.9	0.85	46.62	0.9994
13	0.3	14.1	0.53	24.47	0.9995
14	0.5	16.1	0.53	34.33	0.9971

[a] The equation could not be applied.
[b] No data available.

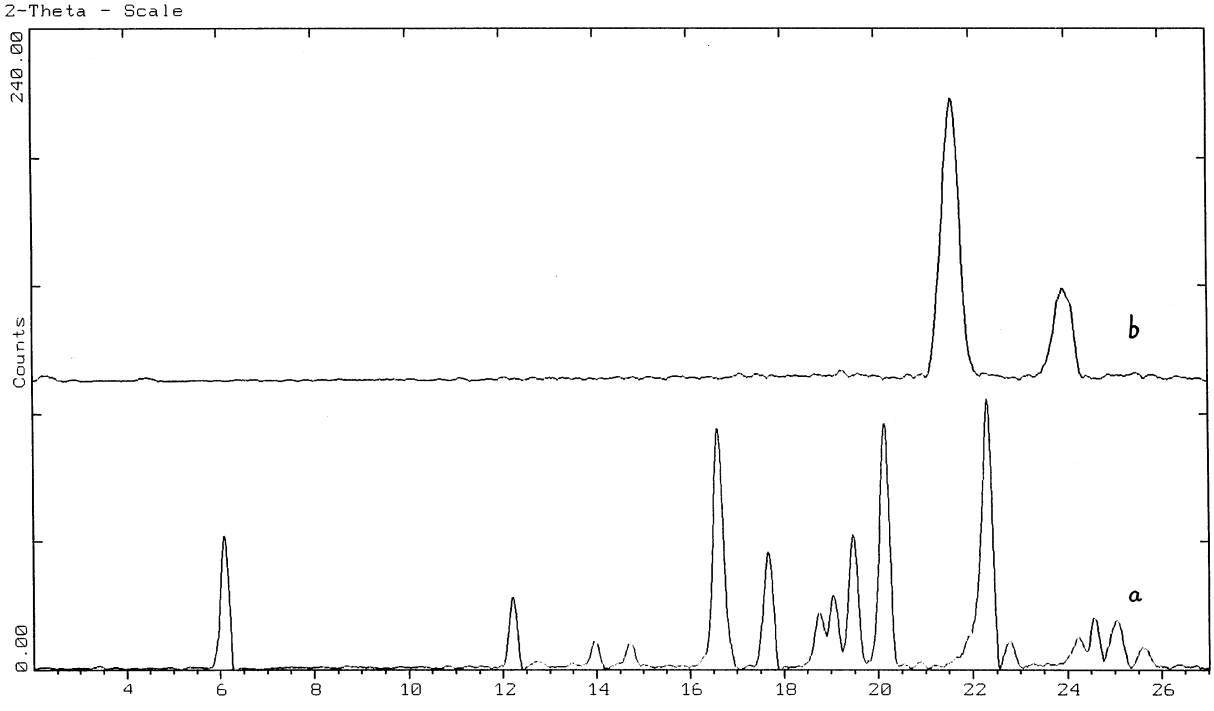

Fig. 1. X-ray diffractograms of (a) ibuprofen and (b) Paracera® P.

2a, ratio 4/1 IBP/P), a 'solidified melt' of IBP and P (Fig. 2b, ratio 4/1 IBP/P) and mini-tablet formulation 1 (Fig. 2c, ratio 4/1 IBP/P) were recorded. The diffractogram of pure ibuprofen with numerous distinctive peaks showed that the drug is highly crystalline in nature. Besides, peaks of high intensity were also present in the diffractogram of Paracera® P. X-ray diffraction analysis demonstrated that major diffraction peaks of ibuprofen were present in the physical mixture, in the 'solidified melt' and in the mini-tablet formulation (Fig. 2). The 2θ angles of the physical mixture, 'solidified melt' and the mini-tablet formulation reflected no changes. Peak characteristics, particularly the relative intensity of ibuprofen to Paracera® P peaks showed no differences in the physical mixture, the 'solidified melt' and the mini-tablet formulation. This was confirmed by calculating the ratio ((IBP/IBP + P) × 100) of one ibuprofen (IBP) and Paracera® P (P) peak surface area at $2\theta = 22.4°$ and $2\theta = 21.4°$, respectively. No differences in ratio ((IBP/IBP + P) × 100) were seen when the physical mixture (47.5 ± 3.1, $n = 3$), the 'solidified melt' (48.3 ± 0.6, $n = 3$) and mini-tablet formulation '1' with 4/1 IBP/P ratio (47.6 ± 0.5, $n = 3$) were compared. Similar results were obtained for the formulation containing 60% ibuprofen and 20% Paracera® P (3/1 IBP/P). The diffraction patterns with the characteristic ibuprofen peaks and the approximately same values for the ratio's suggested that no drug dissolved in the microcrystalline wax of the mini-tablet formulation.

3.3. Effects of composition of the mini-tablets on drug release

3.3.1. Influence of wax type, wax and triacetin concentration on drug release

IGI® 2291-, Paracera® P- and Paracera® M-matrix mini-tablets showed differences in their $t_{50\%}$ dissolution times (Fig. 3). The $t_{50\%}$ for the IGI® 2291-formulation was 2 h, while for the Paracera® P and M formulation it was 4 and 6 h, respectively. After 8 h of dissolution testing, the drug release was

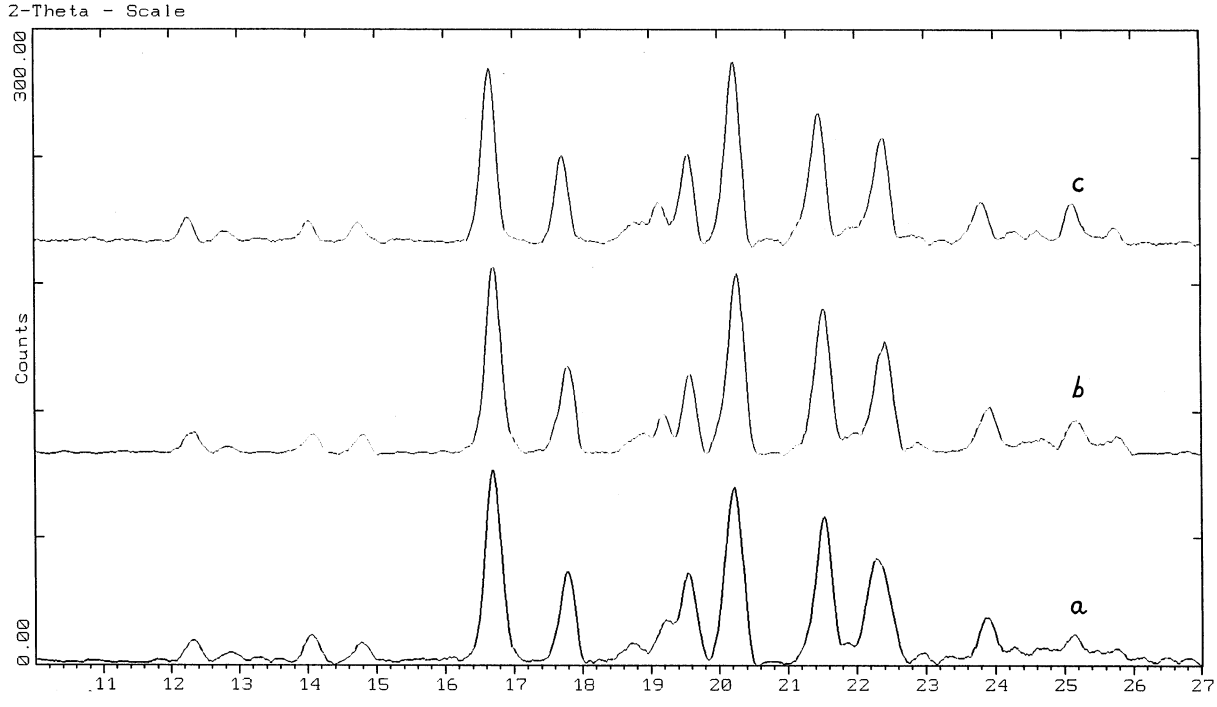

Fig. 2. X-ray diffractograms of (a) physical mixture of ibuprofen (IBP) and Paracera® P (P) ratio 4/1 (b) 'solidified melt' of IBP and P ratio 4/1 (c) mini-tablet formulation '1' ratio 4/1 IBP/P.

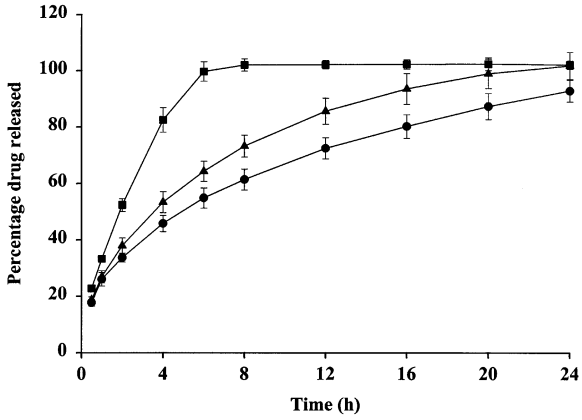

Fig. 3. Dissolution profiles of matrix mini-tablets containing 60% ibuprofen, 22.5% WMD, 2.5% triacetin and 15% microcrystalline wax. (●) Paracera® M, (▲) Paracera® P, (■) IGI® 2291.

100% for IGI® 2291 mini-tablets, whereas formulations containing 15% Paracera® P and M released 73 and 61% of ibuprofen, respectively. The amount of drug released was correlated with the melting range of the waxes (49–52°C for IGI® 2291, 58–62°C for Paracera® P and 68–72°C for Paracera® M): the higher the melting range, the less drug was released after 8 h. Similar results were obtained by Adeyeye and Price (1994) and Zhou et al. (1996). The faster drug release rate of the IGI-formulation correlated with a higher n-value (calculated using Eq. 1); indicating that its drug release was less diffusion controlled and that other factors such as erosion become more important. Increasing the amount of wax in the formulation showed a slower drug release profile. Increasing the Paracera® P content from 15 to 20% decreased the ibuprofen release from 85 to 74% after 12 h (Fig. 4). Formulation 6 was manufactured twice on two different days and no differences in dissolution profile was seen. Triacetin which facilitated hot melt extrusion and compression due to its lubrication and anti-sticking effect also affected the drug release profile (Fig. 4). The formulation containing 1% triacetin released 78% ibuprofen after 12 h, while the formulation containing 4% triacetin released 92% after 12 h. Table 2 indicates that drug release mechanism of these formulations was mainly diffusion controlled ($n = \pm 0.5$).

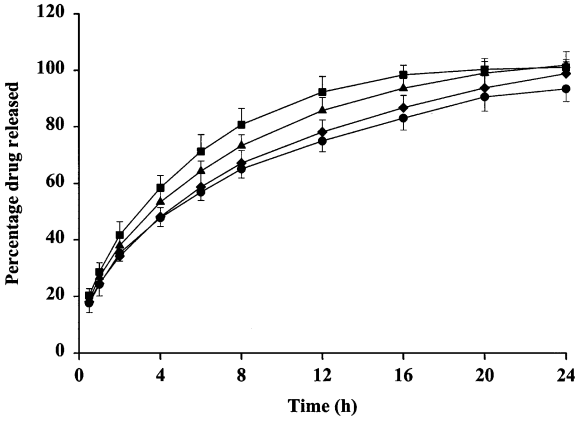

Fig. 4. Dissolution profiles of matrix mini-tablets containing 60% ibuprofen, Paracera® P, WMD and triacetin. (■)15% Paracera® P, 21% WMD, 4% triacetin, (▲)15% Paracera® P, 22.5% WMD, 2.5% triacetin, (◆)15% Paracera® P, 24% WMD, 1% triacetin, (●) 20% Paracera® P, 17.5% WMD, 2.5% triacetin.

3.4. Influence of the starch derivative

Substituting WMD for PMD had little effect on the drug release profile. The $t_{50\%}$ changed from 4 h for the WMD formulation to 5 h in case of the PMD formulation (Fig. 5). Incorporating DDWM in the formulation accelerated the ibuprofen release. The total amount of drug was

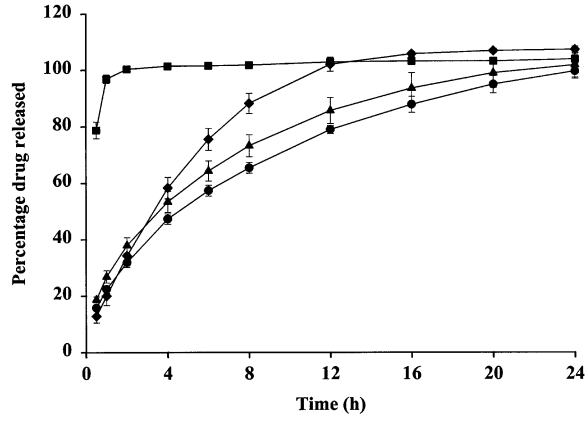

Fig. 5. Dissolution profiles of matrix mini-tablets containing 60% ibuprofen, 15% Paracera® P, 2.5% triacetin and 22.5% starch derivative. (■) DDCS, (◆) DDWM, (▲) WMD, (●) PMD.

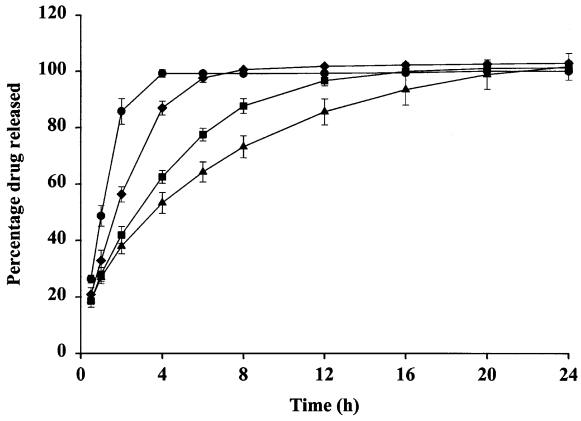

Fig. 6. Dissolution profiles of matrix mini-tablets containing 60% ibuprofen, 15% Paracera® P, 2.5% triacetin and 22.5% starch mixture. (▲) 22.5% WMD, (■) 4.5% DDCS – 18% WMD, (◆) 6.75% DDCS – 15.75% WMD, (●) 9% DDCS – 13.5% WMD.

released within 12 h. The disintegrating properties of DDCS previously recorded by Zhou et al. (1996) were confirmed (Fig. 5), the formulation containing DDCS failed to form matrix mini-tablets as they released over 95% of the drug within 1 h. Substituting a part of the WMD fraction by DDCS (20, 30 and 40% of WMD was replaced by DDCS) revealed the matrix system flexibility (Fig. 6). The slowest drug release was obtained with a formulation without DDCS, while the fastest drug release was seen with the tablet containing the highest DDCS concentration. All formulations (except formulation 2) showed a non-Fickian diffusion release mechanism ($0.45 < n < 1.00$) (Table 2). A combined mechanism of diffusion and erosion might be responsible for this phenomenon. Again, the higher n-value of the formulation containing 22.5% DDWM (formulation 8) might indicate that its drug release is less diffusion controlled and that erosion is an important factor during dissolution. This was confirmed by visual inspection of the mini-tablets after 24 h of dissolution testing as only an erodated core of the matrix mini-tablets could be recovered. The mini-tablets consisting of 22.5% DDCS (formulation 9) could not be recovered after dissolution, as they completely disintegrated within the first hours of the dissolution test. Hence Eq. 1 could not be applied to calculate its drug release mechanism. The increase of n ($n = 0.58$, 0.71 and 0.85 for formulation 10, 11 and 12, respectively) (Table 2) seen when part of the WMD fraction was substituted for DDCS correlated well with an increased drug release rate (formulation 10, 11 and 12 released 62, 86 and 100% ibuprofen, respectively after 4 h of dissolution testing). Considering the disintegrating properties of DDCS, an increased suspectibility to erosion (due to swelling of the matrices) might be responsible for these findings.

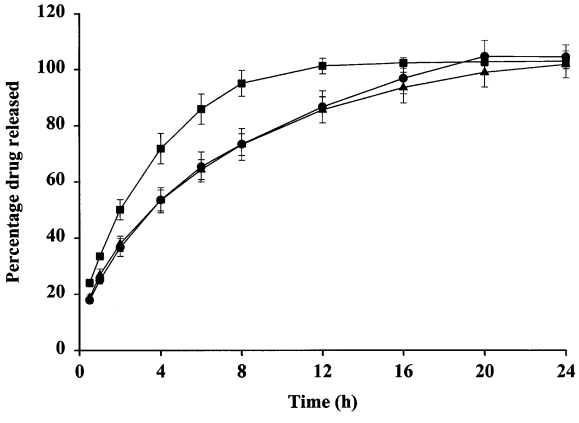

Fig. 7. Dissolution profiles of matrix mini-tablets containing ibuprofen, Paracera® P, 2.5% triacetin and WMD. (▲) 60% ibuprofen, (●) 40% ibuprofen, (■)70% ibuprofen.

3.5. Influence of drug load

Fig. 7 reveals no difference in drug release profile between the 40 and 60% ibuprofen formulation when the maltodextrin/wax ratio was kept constant. The high WMD concentration (34.5%) in the 40% formulation is probably responsible for the drug release pattern seen, since the higher concentration (23%) of microcrystalline wax should suppose (as previously stated) a slower drug release compared with the 60% formulation. The 70% ibuprofen formulation resulted in a faster drug release probably due to the high drug load and a lower concentration of matrix forming materials compared with the 40 and 60% formulation.

4. Conclusions

The production of mini-tablets is a new developing area which shows some advantages compared to pellets even from a technological viewpoint since semi-continuous processing is possible. The matrix mini-tablets based on a combination of starch and microcrystalline wax offer a flexible system able to sustain the drug release even at high drug loadings. The drug release can easily be varied by modifying one of the components of the formulation.

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