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Pharmacokinetics of Ibuprofen Following a Single Administration of a Suspension Containing Enteric-coated Microcapsules

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Summary

The relative bioavailability of ibuprofen (CAS 15687-27-1) was investigated following a single administration of a suspension containing enteric-coated microcapsules (A) in comparison to a rapid-release film-coated tablet (B) and a sustained-release tablet (C). The study was carried out in a three-way crossover design in 9 healthy male volunteers. Each formulation contained 800 mg ibuprofen. Plasma concentrations of ibuprofen were determined with a specific HPLC method. A mean relative bioavailability of 0.96 (B) and 1.01 (C) was determined for the test formulation. Since the corresponding 90 % confidence intervals were within the recommended limits, bioequivalence for the extent of bioavailability of the test formulation can be concluded. Differences in pharmacokinetics were observed for the rate-dependent parameters. For the test formulation, the highest mean maximum plasma concentration (54.3 μg/ml) was measured with a corresponding t_{max} of 1.9 h. For the reference formulations, mean peak plasma concentrations of 45.2 μg/ml after 2.6 h (B) and 25.7 μg/ml after 5.6 h (C) were observed. Despite the enteric coating of the microcapsules, a very short lagtime of 0.03 h was determined for the suspension. For the other rapid release formulation (B), the lagtime was in a similar magnitude (0.11 h), while the absorption from the sustained-release tablet was clearly decelerated (t_{lag} = 0.97 h). In comparison to the other rapid-release formulation (B), significant higher amounts of the drug were absorbed from the test formulation (A) within the first hour.

Zusammenfassung

Pharmakokinetik von Ibuprofen nach Einmalgabe einer Suspension magensaftresistent befilmter Mikrokapseln

Die relative Bioverfügbarkeit von Ibuprofen (CAS 15687-27-1) wurde nach Einmalgabe einer Suspension von magensaftresistenten Mikrokapseln (A) im Vergleich zu einer schnellfreisetzenden Filmtablette (B) und einer Retardtablette (C) untersucht. Die Studie wurde in einem 3fach-Crossover-Design an 9 gesunden männlichen Probanden durchgeführt. Die applizierte Dosis pro Formulierung war 800 mg Ibuprofen. Die Ibuprofenkonzentrationen im Plasma wurden mit einer spezifischen HPLC-Methode bestimmt.

Für die Testformulierung wurde eine mittlere Bioverfügbarkeit von 0.96 (B) und 1.01 (C) bestimmt. Da die errechneten 90 % Konfidenzintervalle innerhalb der geforderten Grenzen liegen, ist die Testformulierung beim Ausmaß der Bioverfügbarkeit als äquivalent zu der Referenzformulierung anzusehen. Pharmakokinetische Unterschiede der drei Formulierungen wurden bei den geschwindigkeitsabhängigen Parametern beobachtet. Für die Testformulierung wurden die höchste mittlere Plasmaspitzenkonzentration (54,3 µg/ml) nach 1,9 h gemessen. Für die Referenzformulierungen lag das mittlere C_{max} bei 45,2 µg/ml nach 2,6 h (B) und 25,7 µg/ml nach 5,6 h (C).

Trotz des magensaftresistenten Filmes der Mikrokapseln wurde nach Gabe der Suspension eine sehr kurze Lagtime von 0,03 h gemessen. Für die andere schnellfreisetzende Formulierung (B) lag dieser Parameter in einer ähnlichen Größenordnung (0,11 h), während die Resorption nach Gabe der Retardtablette deutlich verlangsamt war (t_{lag} = 0,97 h). Im Vergleich der beiden schnellfreisetzenden Formulierungen wurden in der ersten Stunde signifikant höhere Arzneistoffmengen nach der Applikation der Testformulierung (A) resorbiert.

Key words: *Anti-inflammatories, non-steroidal · CAS 15687-27-1 · Ibuprofen, clinical pharmacokinetics, enteric-coated microcapsules*

1. Introduction

Ibuprofen (CAS 15687-27-1) is an arylpropionic acid derivative with anti-inflammatory, analgesic and antipyretic activity. It is widely used in the treatment of osteoarthritis, rheumatoid arthritis and mild to moderate pain [1]. Approved oral formulations contain ibuprofen in doses from 200 mg up to 800 mg. The drug tastes bitter and irritates the mucosal membrane of the mouth and the throat. Therefore, ibuprofen is usually administered in film-coated or sustained-release formulations. Tablets containing 800 mg of the drug are rather large and are not convenient to swallow for some patients [2]. Predisintegration of the ibuprofen tablets could resolve this problem, but then the drug significantly irritates the gastric and duodenal mucosa [3]. Hence, it would be preferable to have a formulation which avoids mucosal or gastroduodenal irritation and simplifies drug intake. This was the objective of the development of enteric-coated ibuprofen microcapsules by a simple coacervation process using hydroxypropyl methylcellulose phtalate as a polymer [4].

In this study, we investigated the pharmacokinetics of ibuprofen following a single administration of a suspension of the microcapsules in comparison to a film-coated and sustained-release tablet, respectively. The objectives of the study were to obtain information about the pharmacokinetics and the tolerability of suspended microencapsuled ibuprofen and the relative bioavailability in comparison to commercially available formulations.

2. Materials and methods

2.1. Study design and subjects

The study was performed according to a three-way crossover design in 9 healthy male volunteers. Their mean (± s.d.) age was 26.7 ± 6.7 years, their height was 177.9 ± 3.9 cm and their weight was 68.9 ± 5.5 kg. Two volunteers were smokers, the others non-smokers. The study was conducted in accordance with the Declaration of Helsinki (revised Hong Kong edition), the German Drug Law and the current GCP (Good Clinical Practice) guidelines. All subjects gave written informed consent. The study protocol and consent form were approved by an independent ethics committee.

The volunteers received 3 different treatments in random order: the test formulation (a suspension of enteric-coated microencapsuled ibuprofen) and the reference formulations (a rapid-release film-coated tablet and a sustained-release tablet). After an overnight fast, the tablets were administered with 200 ml water. Microencapsuled ibuprofen was suspended in 100 ml water and then immediately swallowed. The glass was rinsed with another 100 ml water which was also taken.

Blood samples (10 ml) were drawn into lithium-heparinised containers by venous puncture or through an indwelling catheter. Sampling times for the three formulations were 0 (predose), 15, 30, 45, 60, 90 min and 2, 3, 4, 6, 9, 12, 15, 18 h after the administration. Plasma was taken immediately, deep-frozen and kept at −20 °C until analysis.

2.2. Formulations

The test formulation was a granule containing 800 mg ibuprofen in enteric-coated microcapsules together with gelling agent, citric acid, saccharose and other excipients (Batch no. 007602). The microcapsules were prepared with hydroxypropyl methylcellulose phtalate by the method of Weiß et al. [4]. For administration purposes the formulation was suspended in 100 ml of water. A pH of 3.2 was measured for this suspension. The reference formulations were a rapid-release film-coated tablet (Dolo Puren® forte, Batch no. 063484) and a sustained-release tablet (Ibuprofen Klinge® 800 retard, Batch no. 058715). All formulations tested were produced by Klinge Pharma GmbH, Munich (Germany).

2.3. Drug assay

Plasma ibuprofen concentrations were measured by HPLC following liquid-liquid extraction. The internal standard was tertiary butylbenzoic acid. The lower limit of quantitation (LLQ) was 2.5 µg/ml. At this level, accuracy and precision were 2.8 % and 3.1 % (n = 9). Linearity was shown over the range of 2.5 to 75 µg/ml.

The dissolution profile was measured using a method of USP XXIII (paddle, 150 rpm, 900 ml phosphate-buffer of pH 7.2). Samples of ibuprofen from the in vitro release studies were quantitated as described earlier [5].

2.4. Data analysis

Plasma ibuprofen concentration data obtained after the three administrations were analysed using a non-compartmental approach with TOPFIT 2.0 [6]. AUC values were estimated using the linear trapezoidal rule. The residual area was determined by dividing the value of the last concentration by the terminal rate constant. Values of C_{max} and t_{max} were noted directly from the data. The lagtime (t_{lag}) was defined as the last time before the first measurable concentration. The mean residence time (MRT) was determined by dividing the area under first moment curve (AUMC) by the AUC. The cumulative fraction of the available drug absorbed following the different administrations was determined by the Wagner-Nelson method [7].

Statistical procedures were performed using SYSTAT 5.0. For AUC and C_{max}, an analysis of variance (ANOVA) was performed by the GLM procedure (general linear models) following logarithmic transformation of the data, and then the shortest 90 % confidence intervals were calculated.

3. Results

The formulations investigated were very well tolerated and no adverse events were reported. No changes were seen in the physical examination of the volunteers when comparing pre- and post-treatment status.

The in vitro release profile of the drug from the different formulations is shown in Fig. 1. At pH 7.2, the suspended enteric-coated microcapsules release about 100 % of the dose within the first 5 min. The drug is also rapidly available from the film-coated tablet. However, after 5 min only about 70 % of the dose is dissolved in the buffer. Ibuprofen was released slowly in a constant rate from the sustained-release tablet. After 60 min, only 20 % of the dose were detected in the dissolution medium. In vitro, the drug release from this formulation is completed after 480 min.

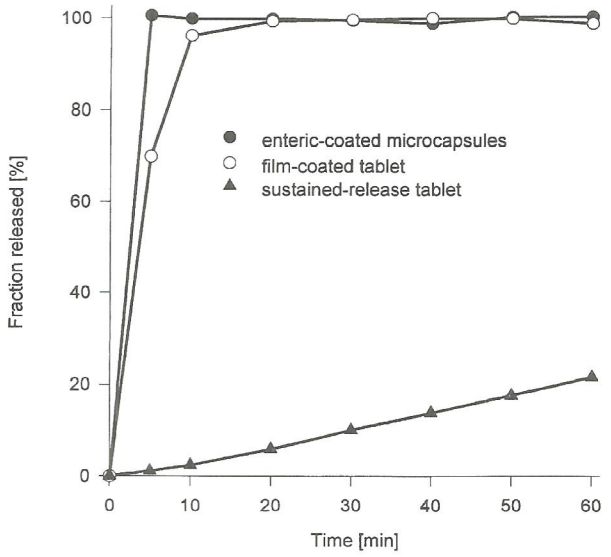

Fig. 1: In vitro dissolution profiles for ibuprofen from the test and the reference formulations (paddle, pH 7.2, 150 rpm, 900 ml, n = 6).

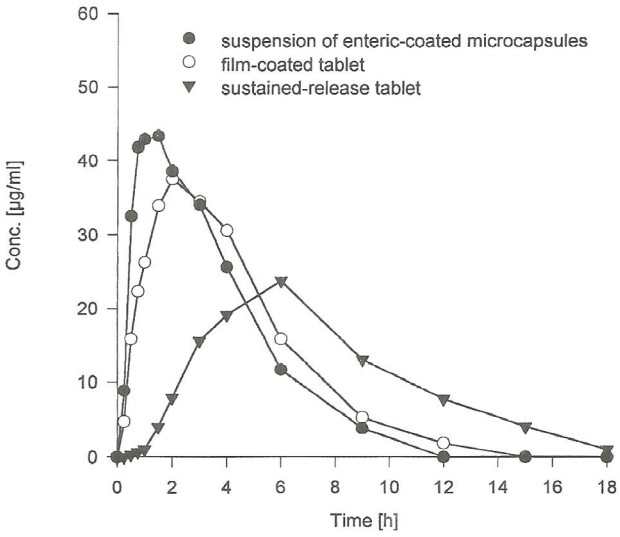

Fig. 2: Mean ibuprofen concentrations in plasma following the administration of the test and the reference formulations (mean values from 9 volunteers).

Mean plasma ibuprofen concentrations for the three modes of administration are shown in Fig. 2 and the pharmacokinetic parameters are listed in Tables 1–3. Fig. 3, 4 and 5 show the individual plasma drug concentrations for the three formulations. Following administration of the suspension of enteric-coated microcapsules, mean peak plasma drug concentrations of 54.3 µg/ml (range: 43.5 to 71.2 µg/ml) were reached within 1.9 h (range: 0.8 to 4.0 h) and concentrations declined subsequently with a half-life of 1.9 h (range: 1.7 to 2.0 h). For the film-coated tablet, a mean peak concentration of 45.2 µg/ml (range: 33.6 to 67.0 µg/ml) was observed within 2.6 h (range: 1.0 to 4.0 h). For this formulation, a half-life of elimination of 2.1 h was calculated (range: 1.8 to 3.3 h). After administration of the sustained-release tablet, a mean plasma ibuprofen peak concentration of 25.7 µg/ml (range: 16.0 to 35.9 µg/ml) and a value for t_{max} of 5.6 h (range: 4.0 to 6.0 h) were measured.

Table 1: Pharmacokinetic parameters calculated for the suspension of enteric-coated microcapsules.

Volunteer	Suspension of enteric-coated microcapsules						
	C_{max} (µg/ml)	t_{max} (h)	t_{lag} (h)	$t_{1/2}$ (h)	AUCz (µg/ml · h)	AUC (µg/ml · h)	MRT (h)
1	60.52	1.50	0.00	2.03	227.32	240.82	3.53
2	71.18	0.75	0.00	1.92	203.88	213.41	2.98
3	67.60	1.50	0.00	1.92	254.25	268.43	3.41
4	43.51	3.00	0.00	1.92	201.39	214.57	3.95
5	53.35	1.00	0.00	2.02	168.27	177.66	3.18
6	49.25	4.00	0.25	1.74	186.82	203.82	4.89
7	43.63	1.50	0.00	1.71	127.63	144.83	3.15
8	52.75	0.75	0.00	1.83	170.00	176.91	3.05
9	46.75	3.00	0.00	1.74	202.48	212.44	3.68
Mean	54.28	1.89	0.03	1.87	193.56	205.82	3.53
SD	10.10	1.16	0.08	0.12	36.50	36.53	0.60
CV	18.6	61.4	300.0	6.5	18.9	17.8	17.0

Table 2: Pharmacokinetic parameters calculated for the film-coated tablet.

Volunteer	Film-coated tablet						
	C_{max} (µg/ml)	t_{max} (h)	t_{lag} (h)	$t_{1/2}$ (h)	AUCz (µg/ml · h)	AUC (µg/ml · h)	MRT (h)
1	40.80	4.00	0.25	1.97	243.43	252.35	4.83
2	66.96	1.00	0.00	1.99	219.05	231.90	3.29
3	52.25	3.00	0.00	2.04	265.03	273.27	4.34
4	39.90	4.00	0.25	1.90	186.79	204.91	4.96
5	33.65	1.50	0.00	2.05	159.34	170.56	3.79
6	37.85	4.00	0.25	2.08	194.74	203.10	5.11
7	42.15	1.50	0.00	1.84	152.48	160.14	3.54
8	44.13	2.00	0.25	3.28	196.12	231.98	6.16
9	49.37	2.00	0.00	1.79	185.96	194.77	3.49
Mean	45.23	2.56	0.11	2.10	200.32	213.66	4.39
SD	9.91	1.21	0.13	0.45	36.75	37.06	0.96
CV	21.9	47.4	118.6	21.5	18.3	17.3	21.8

Table 3: Pharmacokinetic parameters calculated for the sustained-release tablet.

Volunteer	Sustained-release tablet						
	C_{max} (µg/ml)	t_{max} (h)	t_{lag} (h)	$t_{1/2}$ (h)	AUCz (µg/ml · h)	AUC (µg/ml · h)	MRT (h)
1	25.34	6.00	1.00	2.76	206.33	219.09	7.53
2	31.24	6.00	0.25	2.96	198.86	214.48	7.89
3	35.93	4.00	0.50	8.15	253.60	323.79	12.38
4	28.96	6.00	1.50	3.62	194.90	215.00	8.17
5	15.96	6.00	1.00	3.93	146.69	170.12	9.18
6	26.62	6.00	1.50	2.89	170.32	186.25	8.74
7	20.60	6.00	1.00	2.93	139.98	161.09	7.39
8	20.12	6.00	1.00	3.13	134.47	147.15	7.34
9	26.57	4.00	1.00	3.74	206.53	220.45	8.76
Mean	25.70	5.56	0.97	3.79	183.52	206.38	8.60
SD	6.12	0.88	0.40	1.69	38.99	51.92	1.56
CV	23.8	15.9	41.6	44.5	21.2	25.2	18.2

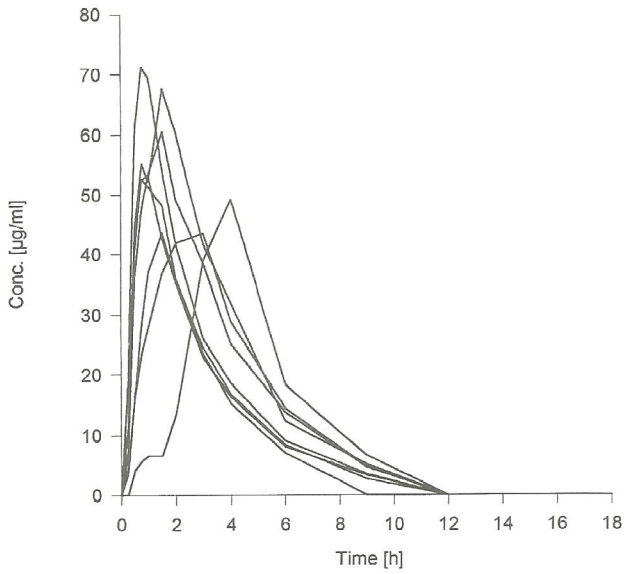

Fig. 3: Individual ibuprofen concentrations in the plasma of 9 volunteers following the administration of the suspension containing enteric-coated microcapsules.

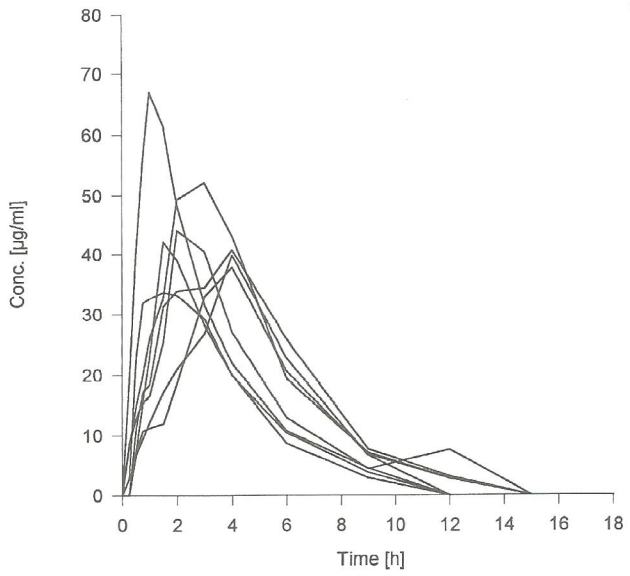

Fig. 4: Individual ibuprofen concentrations in the plasma of 9 volunteers following the administration of the film-coated tablet.

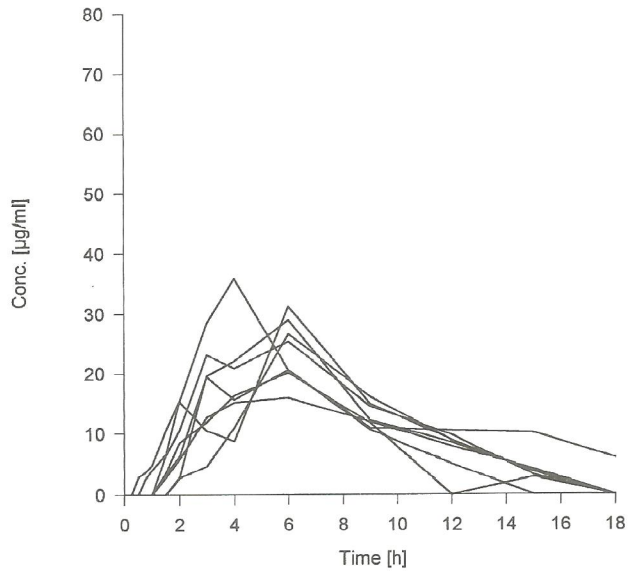

Fig. 5: Individual ibuprofen concentrations in the plasma of 9 volunteers following the administration of the sustained-release tablet.

Table 4: Geometric means and 90 % confidence intervals following ln-transformation of the data.

	Suspension of enteric-coated microcapsules vs. film-coated tablet			Suspension of enteric-coated microcapsules vs. sustained-release tablet		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
C_{max}	1.07	1.21	1.36	1.89	2.14	2.42
AUC	0.88	0.96	1.05	0.92	1.01	1.10

Thereafter, plasma ibuprofen concentrations decreased with an apparent half-life of elimination of 3.8 h (range: 2.8 to 8.2 h).

Table 4 shows the 90 % confidence intervals calculated for the AUC and C_{max}. For the AUC, the point estimates were 0.96 (compared to the film-coated tablet) and 1.01 (compared to the sustained-release tablet) with the corresponding confidence interval ranges from 0.88 to 1.05 and 0.92 to 1.10, respectively. Being within the recommended bioequivalence range of 0.8 to 1.25, equivalence for the test formulation can be concluded for the extent of absorption. In contrast to the AUC, the calculated confidence intervals for C_{max} are not within the recommended range mentioned above. Since the confidence interval for the film-coated tablet ranges from 1.07 to 1.36, equivalence can only be assumed for this parameter if the interval range is widened from 0.7 to 1.43. For the sustained-release tablet, a point estimate µT/µR of 2.14 was calculated, suggesting bioinequivalence for this parameter.

The mean cumulative fraction of ibuprofen absorbed from the different formulations is shown in Fig. 6. Mean absorption profiles for the enteric-coated microcapsules and the film-coated tablet show a first-order absorption kinetic. Within the first 2 h, absorption of ibuprofen from the suspended enteric-coated microcapsules clearly occurred faster than from the film-coated tablet. Comparing the rapid-release formulations, significant higher amounts of the drug were absorbed from the enteric-coated microcapsules than from the film-coated tablet within 0.5 to 1 h post administration ($p < 0.01$). For the sustained-release tablet, the mean absorption was nearly linear from 2 h to 6 h after the administration.

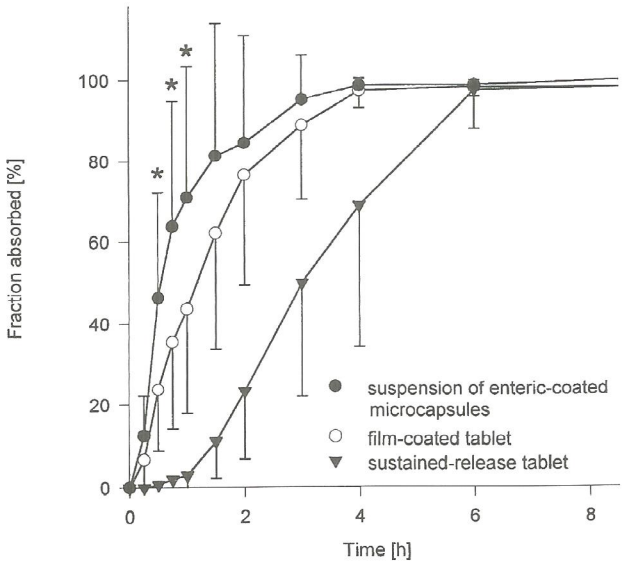

Fig. 6: Mean fraction absorbed following administration of the test and the reference formulations (mean values from 9 volunteers). For both rapid-release formulations (suspension of enteric-coated microcapsules and film-coated tablet), a statistical evaluation was performed using student's paired t-test for the period 0 to 2 h. Significant differences of the fraction absorbed are indicated by an asterisk ($p < 0.01$).

4. Discussion

The objective of the present study was to investigate the pharmacokinetics of ibuprofen in a new formulation containing ibuprofen in a suspension of enteric-coated microcapsules. As a reference, two commercially available products, a rapid-release film-coated tablet and a sustained-release tablet, were administered.

Absolute bioavailability of ibuprofen from oral formulations is approximately 100 % and, in general, is not influenced even if vast differences of the oral formulations are evident [8]. A reason for this unproblematic pharmacokinetic characteristic is the nearly complete absorption of the drug from the small and large intestine without first-pass metabolism [9, 10]. The findings of the present study confirm the equivalence in the extent of absorption of ibuprofen from rapid-release and sustained-release formulations. The concluded equivalence for the extent of absorption from the new formulation also indicates reliable release of the drug from the enteric-coated microcapsules.

Differences in the pharmacokinetics of ibuprofen from the suspended enteric-coated microcapsules and the reference formulations were detected in rate-dependent parameters. The highest peak plasma concentration with the corresponding shortest t_{max} and t_{lag} was determined for the enteric-coated microcapsules. Equivalence for C_{max} of the test formulation and the film-coated tablet can only be concluded if the confidence limits for acceptance range from 0.7 to 1.43. However, this would be an unusual approach for a drug with pharmacokinetic properties such as ibuprofen.

The higher rate of drug absorption from the microcapsules is not surprising for the comparison to the sustained-release tablet, but is so to the rapid-release film-coated tablet. Both rapid-release formulations have rate-limiting processes prior to absorption. The enteric-coated microcapsules have to pass the acidic medium of the stomach and the film-coated tablet has to disintegrate before releasing the drug for absorption. However, it is assumed that in our study processes lasted only a few minutes. In a fasted state, the suspension, containing the microcapsules, passes the stomach as a liquid independently from gastric motility [11] and the film-coated tablet disintegrates in vitro within 5 min, indicating another rate-limiting process for the slower drug absorption from the film-coated tablet. Weiß et al. [4] investigated the in vitro release rate of ibuprofen from the enteric-coated microcapsules and the uncoated ibuprofen crystals. In comparison to uncoated ibuprofen, they found a significant increase of the drug release rate from the enteric-coated microcapsules at pH 7.2, suggesting an improved wettability of hydroxypropyl methylcellulose phtalate coated ibuprofen crystals. We see also this rapid drug release from the test formulation in comparison to the rapid-release film-coated tablet. This result implies that the wettability of ibuprofen crystals of the film-coated tablet is not significantly changed by the tablet ingredients. This finding is in accordance with the results of studies comparing the pharmacokinetics of ibuprofen following administration of the whole tablets in comparison to predisintegrated tablets in different beverages [2, 3]. Depending on the beverage, the rate of absorption from the extemporaneous formulations was comparable to the whole tablet or even slower, but never faster.

The rapid absorption of the drug following administration of the suspension is also observed in the in vivo absorption profiles. Within the first hour especially, significant higher amounts of the drug are absorbed from the suspension than from the film-coated tablet. With respect to the indications of the drug, rapid onset of efficacy is advantageous. Clinical studies should be performed, to evaluate the benefit of this increase of absorption rate.

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