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Uniform and improved bioavailability of newly developed rapid and sustained release suspensions of ibuprofen microspheres

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Summary

New rapid and sustained release suspensions of ibuprofen microspheres were investigated in in vitro release and in vivo drug absorption studies. The drug release rate from the suspensions was controlled by the particle size, drug-polymer ratio and internal porosity of microspheres. The rapid release suspension resulted in significantly low intersubject variation in bioavailability, demonstrating the same rate and extent of drug absorption as the conventional marketed ibuprofen granule. Out of three suspensions studied, the sustained release suspension (suspension 3) showed ideal bioavailability: an equal extent of absorption (AUC) and a 3-fold longer time of peak plasma level (T_{max}) as compared with the marketed conventional granule. More interestingly, although the drug release rates from two suspensions (suspensions 2 and 3) were identical, there were significant differences in the rate and extent of bioavailability between them. Moment analysis suggested that these differences in bioavailability could be attributed to the GI residence time of microspheres.

Introduction

An oral suspension could be one of the best dosage forms for pediatric and geriatric patients because of the ease of swallowing and the flexibility in the administration of doses. More therapeutic benefits and dispensing could be gained by incorporating functions of controlled drug release into the suspension, e.g., improvement of the rate and extent of drug absorption, higher patient compliance, reduction of side effects, and taste masking for bitter drugs (Smith et al., 1960; Moldenhauer and Nairn, 1990). Some controlled release suspensions of microencapsulated drugs were reported not to achieve adequate bioavailability, when compared to the conventional marketed tablets and granules (Raghunathan et al., 1981; Sjovall et al., 1984). This can be due to incomplete release from the microcapsules in the gastrointestinal (GI) tract, or to release at such a slow rate that the drug passes the optimal sites of absorption (Skelly et al., 1987). Obviously, these findings suggested that the bioavailability of oral controlled release dosage forms depends greatly on the rate of drug release at the absorption sites (Gibaldi et al., 1976; Lin et al., 1985).

The dissolution rate and bioavailability from suspensions were adversely affected by suspend-

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ing agents, added to the suspensions in order to increase the viscosity of their media to maintain uniform dispersibility of suspended drug particles during storage (Rahman et al., 1978; Howard et al., 1979; Abdou et al., 1989). Although highly viscous suspensions do provide much more uniform dispersibility, a marked inhibitory effect on drug absorption has sometimes been exhibited, e.g., low and variable bioavailability (Soci et al., 1980).

The present authors have developed a novel technique for preparing controlled-release ibuprofen microspheres (Kawashima, et al., 1989). In a previous paper, the newly designed ibuprofen-microsphere suspensions were prepared possessing long-term uniform dispersibility (> 6 months) without increasing viscosity (60 cp) (Kawashima, et al., 1991). The uniform dispersibility of microspheres, rheological properties (e.g., shear dependency and thixotropic characteristics) of the suspension medium, and leakage of drug from microspheres during storage were investigated. The mechanism of long-term uniform dispersibility of the coarse microspheres and the low viscosity of the suspension were elucidated quantitatively on the basis of steric hindrance and the network structure of the suspending agents.

The purpose of this study was to investigate the in vitro drug release and in vivo absorption in beagle dogs of the newly developed rapid and sustained release suspensions of the ibuprofen microspheres. The significantly low intersubject variation found in the bioavailability of the rapid release suspension was interpreted by referring to the characteristic low viscosity and multi-particulate system of this suspension. The differences in bioavailabilities among sustained release suspensions with the same drug release rate were interpreted in terms of the GI residence time of microspheres at the absorption site, by using moment analysis.

Materials and Methods

Preparation of microspheres of ibuprofen with acrylic polymer

Four controlled release ibuprofen microspheres with different release rates were prepared by the emulsion solvent diffusion method (Kawashima, et al., 1989, 1991), as described in Table 1. An ethanolic solution of Ibuprofen (Taito Koeki Co., Japan) and Eudragit RS-PM (Rohm Pharma GmbH, Germany) was poured into an aqueous solution of a sucrose ester (DK-F70, Daiichi Kogyo Seiyaku, Co., Ltd, Japan). The system was agitated at 25 ° C for 60 min, then the microspheres formed were withdrawn by filtration. The yield of this step of microsphere production was more than 89%. The internal porosities (P) of microspheres, listed in Table 1, were calculated from Eqn 1.

TABLE 1

Formulations and characteristics of ibuprofen-acrylic polymer microspheres

	Drug-polymer ratio	Concentration of EtOH solution (%)	Porosity (%)	Particle size (μm)
Microsphere 1	5:1	30	43.5	50–150
Microsphere 2	3:1	40	44.1	500–850
Microsphere 3	3:1	50	26.5	350–500
Microsphere 4	3:1	55	23.3	175–350

Microspheres 1–4 were dispersed in suspensions 1–4, respectively.

$$P = 1 - D_p/D_t \quad (1)$$

where D_p is the particle density and D_t denotes the true density measured using the helium-air pycnometer (model 1302, Micromeritics Instrument Co., U.S.A.). The particle density (D_p) of the microspheres was evaluated according to Eqn 2. An image analyzer (IBAS, Karl-Zeiss, Germany) was used to determine the volume (V) of n particles with weight, W. d is the Heywood diameter.

$$D_p = W/V = W/(\Sigma \pi d^3/6) \quad (2)$$

Preparation of suspensions

Microspheres (equivalent to 200 or 75 mg of ibuprofen/dose) were suspended in the pH 2.0 aqueous solutions of sodium carboxymethylcellulose (CMC-Na) (0.5 w/v%) (average degree of

polymerization and esterification of CMC-Na = 600 and 0.69, respectively. Daiichi Kogyo Seiyaku Co., Ltd, Japan) and D-sorbitol (28.0 w/v%) (Wako Pure Chemicals Co., Ltd, Japan). The composition of the present suspending medium was determined on the basis of the physicochemical studies described in the previous report (Kawashima et al., 1991). The total volume of a suspension was 10.0 ml when the pH of suspension was adjusted to 2.0 with 0.1 M HCl solution. The pH (= 2.0) of medium is acceptable for practical use when referring to the pH range, e.g., 2.0–3.0 of beverages containing vitamin C, such as lemon juice or vitamin drinks. After the suspension was formulated, it was gently shaken at appropriate intervals during storage for 1 week.

In vitro release study

The in vitro release of ibuprofen from all dosage forms was determined in a JPXI apparatus (paddle method) at 37 °C at a stirring rate of 100 rpm using a flow cell system (Toyamakagaku, Japan). The dissolution media (900 ml) were 0.2 M phosphate buffer of pH 6.8 and 0.1 M hydrochloric solution of pH 1.2, which were specified in the JPXI. The ibuprofen released was assayed spectrophotometrically at 220 nm.

In vivo absorption study

Studies of ibuprofen absorption were conducted in six male beagle dogs (2 years old, weight 14–16 kg) in a crossover manner under fasting conditions. Dogs received each ibuprofen dosage form orally with 30 ml water for a tablet and granule (Brufen® tablet and Brufen® granule, Kaken Pharmaceutical Co., Tokyo), or 20 ml for four controlled release suspensions (one rapid and three sustained release suspensions). The ibuprofen dose of a commercial tablet and granule, and suspension 1 was 200 mg in an in vivo drug absorption study of the rapid release dosage forms. The commercial granule or suspensions 2–4 with 75 mg ibuprofen was administered in the study for the controlled release dosage forms. The washout period between administrations was 7 days. Blood samples were taken at specified time intervals over an 8 h or 10 h period. The ibuprofen concentrations in plasma were analyzed spectrophotometrically at 220 nm using HPLC (Kawashima, 1989). As an internal standard, butyl *p*-hydroxybenzoate was employed.

Data analysis

Model-independent estimates of the area under the plasma ibuprofen concentration curves from zero to a final sampling time (AUC) were calculated on the basis of the trapezoidal rule. ANOVA (Stat system, Personal Media Corp., Japan) was used to evaluate statistically significant differences in plasma ibuprofen levels at each sampling time. The peak plasma level (C_{max}), and the time of C_{max} (T_{max}), and AUC were also subjected to ANOVA. Where statistically significant differences occurred, Tukey's test was used to determine which dosage forms were different ($p < 0.05$). Intersubject variation in drug bioavailability following administration of each dosage form was expressed by the coefficient of variation (CV) (SD/mean × 100). The mean residence and mean absorption times were used to estimate the GI transition time of sustained release microspheres of ibuprofen (Jackson and Chen, 1987; Kaniwa, et al., 1988).

Results

Controlled drug release of ibuprofen microsphere suspension in vitro

The rate of drug release from microspheres to be dispersed in suspensions was controlled by selecting the particle size, drug-polymer ratio and internal porosity of microspheres. As described in Table 1, S-1 and S-2–S-4 microspheres were employed for the rapid and sustained release suspensions, respectively.

Ibuprofen in vitro release profiles from suspension 1, granule, and tablet in a pH 6.8 phosphate buffer are shown in Fig. 1. The percent release in 20 min (D_{20}) and 40 min (D_{40}), as well as the time when release was first detected (lag time), are summarized in Table 2. Ibuprofen release from suspension 1 was smooth as well as from the granule with a brief lag time (20 s) and small standard deviations at all points. D_{20} and D_{40} of the suspension were 85.2 and 95.0%, re-

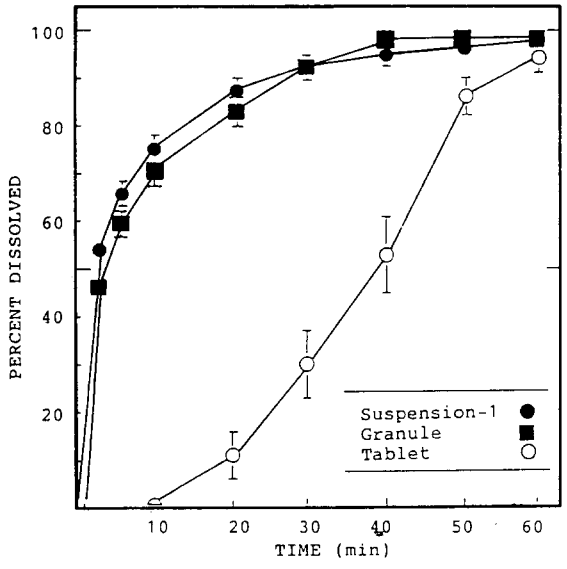

Fig. 1. In vitro dissolution profiles of ibuprofen from suspension 1, granule, and tablet.

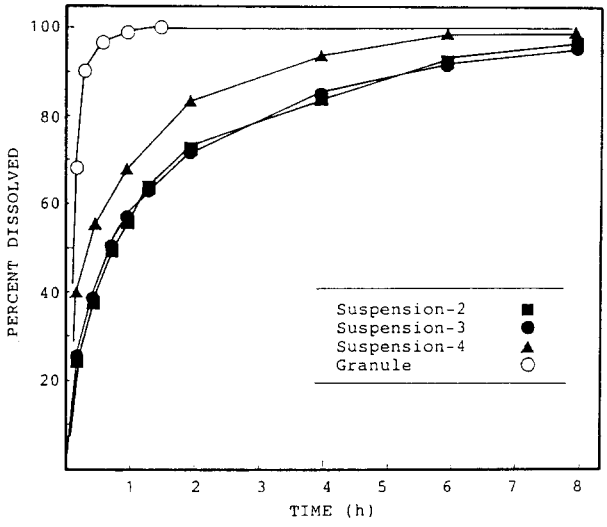

Fig. 2. In vitro dissolution profiles of ibuprofen from suspensions 2–4, and granule.

spectively. On the other hand, the tablet demonstrated a substantial difference in release characteristics. It had significantly slower release (D_{20} = 11.4%, D_{40} = 53.6%), longer lag time (> 10 min), and greater variation in drug release. For a drug to be released, the tablet must first undergo disintegration, which is reflected in the lag time. The range of lag times in tablets tested was 10–14 min. This fundamental difference in release mechanism caused the marked variation in the in vitro release profiles.

Fig. 2 depicts the drug release profiles for the three sustained release suspensions in pH 6.8 buffer. Although the sizes of microspheres dispersed in suspensions 2 and 3 were apparently different (500–850 vs 350–500 μm) (Table 1), the release profiles showed no significant difference. This result indicated that the drug release rate was controlled by the internal porosity of the microspheres (Kawashima et al., 1989). In the emulsion solvent diffusion method, the internal porosity was governed by the concentration of drug-polymer in ethanol (Table 1). The increase in drug-polymer concentration in the ethanol solution decreased the porosity of the microspheres formed. The decrease in porosity offset the increasing effect of the large specific surface area of microspheres (350–500 μm) in suspension 3. Therefore, two microspheres of different diameters could display identical release rates. Suspension 4 resulted in a faster release rate than suspensions 2 and 3. The standard deviations of all the release profiles were very small in magnitude.

In pH 1.2 buffer, less than 5% ibuprofen was released from all suspensions, granule, and tablet over an 8 h period due to the low solubility of ibuprofen in acidic solution (ibuprofen: pK_a = 5.2). The effect of addition of 0.1% Tween 80 (nonionic surfactant) to the dissolution media (pH 1.2 and 6.8) on the drug release profiles was evaluated, however, no change was observed.

TABLE 2

Dissolution parameters for rapid release suspension 1, commercial granule, and tablet (n = 5)

Dosage form	D_{20} (%)	D_{40} (%)	Lag time
Suspension 1	82.6	96.1	< 20 s
Granule	87.3	95.0	< 5 s
Tablet	11.4	53.6	> 10 min

D_{20} denotes percent dissolved in 20 min; D_{40} the percent dissolved in 40 min. Lag time: time when drug release is detected. Dissolution medium used was 0.2 M phosphate buffer of pH 6.8.

In vivo behavior of rapid release suspension

Fig. 3 illustrates the individual plasma ibuprofen concentration-time curves of six beagle dogs following administration of three different dosage forms. Drug absorption of suspension 1 and granule in all dogs was rapid, with maximum drug concentrations occurring within 1 h of dosing. In both groups, the profiles of plasma levels appeared to exhibit considerably less variation than that of tablet. The pharmacokinetic parameters and the results of statistical evaluation are summarized in Table 3. Significant differences in plasma concentrations between suspension 1 and granule were not found during the initial 3 h, while the tablet was significantly different from suspension 1 and the granule for the first 1 h. Concerning the AUC values, there is no significant difference among suspension 1, the granule and the tablet. The intersubject variations of the three dosage forms were described by the coefficient of variance (CV) of the pharmacokinetic parameters (Table 4). The CVs of suspension 1 in C_{max} and T_{max} were slightly lower than that of the granule and the same in the AUC values, whereas the CVs of the tablet for all the parameters were about double those of the suspension. The intersubject variation of suspension 1 was found to be quite comparable to the variation of the granule, and markedly lower than that of the tablet.

The results of pharmacokinetic analysis indicated that the suspension 1 developed appeared to possess adequate bioavailability and prominent low-intersubject variation.

In vivo behavior of sustained release suspensions

Fig. 4 compares the mean plasma concentration vs time profiles for three sustained release suspensions (suspensions 2–4). The pharmacokinetic parameters and statistical analysis are summarized in Table 5, where intersubject variations in AUC are also expressed using the CVs. The decreased rate of drug release from all suspensions led to a significantly slower apparent rate of absorption, as expressed by longer T_{max} and lower C_{max} values compared with the granule. Suspensions 2 and 4 resulted in significantly low AUC values, 71.6 and 78.7 $\mu g\ ml^{-1}\ h^{-1}$, respectively, which were 60.1 and 66.6% in the relative bioavailability based on that of granule. In contrast, suspension 3 could maintain higher plasma levels than the granule from 4–8 h after adminis-

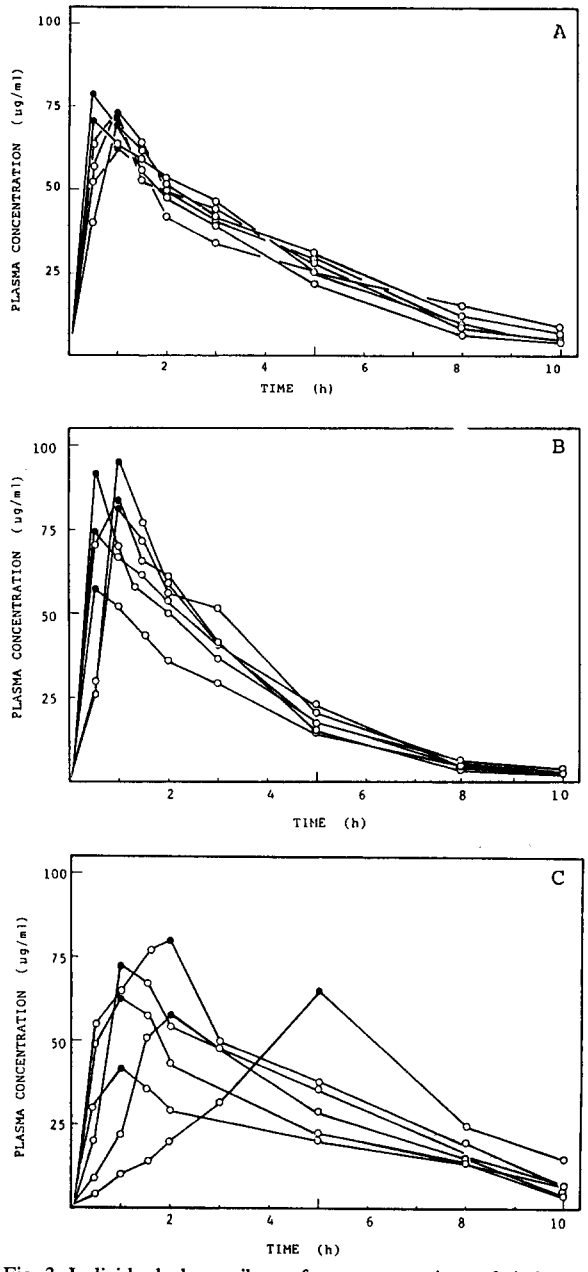

Fig. 3. Individual plasma ibuprofen concentrations of six beagle dogs following oral administration of suspension 1 (A), granule (B), and tablet (C). (●) C_{max} and T_{max} of individual profiles. Dose: equivalent to 200 mg of ibuprofen.

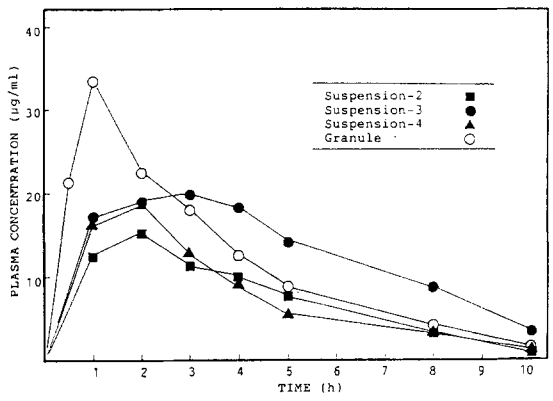

Fig. 4. Mean plasma ibuprofen concentration of six beagle dogs following oral administration of suspensions 2–4, and granule. Dose: equivalent to 75 mg of ibuprofen.

tration and displayed the highest AUC, 123.5 μg ml^{-1} h^{-1} (AUC relative to the marketed granule = 103.7%). It was found that suspension 3 could prolong ibuprofen plasma levels without reducing the extent of bioavailability. The sustained release suspension with the highest AUC (suspension 3) yielded rather large intersubject variation in AUC (19.8%). Nevertheless, a CV of 19.8% was not a significantly high value, in comparison with the CV of the marketed tablet in the AUC values, 19.6% (Table 4).

It was interesting to note that suspension 3 resulted in a 1.7-fold greater AUC than suspension 2 in the in vivo absorption study, although they showed an identical in vitro drug release rate.

TABLE 3

Pharmacokinetic data after administration of suspension 1 (S-1), granule (G), and tablet (T)

Parameter	Dosage forms			Statistical evaluation Tukey's test [a]		
	S-1	G	T	S-1 vs G	S-1 vs T	G vs T
Plasma level (μg/ml) at						
0.5 h	59.8	64.1	28.0	N.S.	$p < 0.05$	$p < 0.05$
1.0 h	68.1	75.3	44.3	N.S.	$p < 0.05$	$p < 0.05$
1.5 h	57.9	63.8	50.8	N.S.	N.S.	N.S.
2.0 h	50.7	53.2	47.6	N.S.	N.S.	N.S.
3.0 h	42.6	41.1	44.6	N.S.	N.S.	N.S.
5.0 h	27.7	18.1	36.6	$p < 0.05$	$p < 0.05$	$p < 0.05$
8.0 h	11.5	6.9	18.0	$p < 0.05$	$p < 0.05$	$p < 0.05$
10.0 h	5.8	2.8	8.2	N.S.	N.S.	$p < 0.05$
C max (μg/ml)	69.7	86.1	63.6	$p < 0.05$	N.S.	$p < 0.05$
T_{max} (h)	0.83	0.75	2.00	N.S.	N.S.	N.S.
AUC to 10 h (μg ml^{-1} h^{-1})	298.7	268.8	302.4	N.S.	N.S.	N.S.

[a] Statistical evaluation: after ANOVA, Tukey's tests were carried out at $p < 0.05$.

TABLE 4

Intersubject variability of C_{max}, T_{max} and AUC following administration of suspension (S-1), granule (G), and tablet (T)

Parameter	Lowest and highest value of each parameter						Intersubject variation (CV)		
	S-1		G		T		S-1	G	T
	Lowest	Highest	Lowest	Highest	Lowest	Highest			
C_{max} (μg/ml)	61.3	76.8	74.3	95.8	42.7	80.7	7.4	9.1	20.3
T_{max} (h)	0.5	1.0	0.5	1.0	1.0	5.0	31.0	36.5	77.5
AUC (μg ml^{-1} h^{-1})	255.9	333.6	218.5	295.3	210.2	389.8	10.9	9.8	19.6

Discussion

Uniformity of bioavailability of rapid release suspension 1

Analysis of variance indicated no statistically significant difference ($p > 0.05$) in the extent of drug absorption between the newly developed rapid release suspension of ibuprofen microspheres (suspension 1) and the conventional marketed granule. Evaluation of the pharmacokinetic parameters demonstrated that suspension 1 could provide significantly low intersubject variations, which were lower than the granule in C_{max} and T_{max}.

The drug release rate and bioavailability can be affected by the components and viscosity of the suspension medium, resulting in erratic and incomplete drug absorption (Abdou, 1989). In a previous study of drug release from the present microsphere suspension and microspheres alone, both formulations showed the same rate of release for ibuprofen (Kawashima et al., 1991). This result indicated that the suspension medium studied did not affect the property of drug release. In this study, suspension 1 with the same release profile as that of granule resulted in the same bioavailability for the granule. These results demonstrated that the present suspension medium had no inhibitory effect on the drug release rate or bioavailability.

The multi-particulate unit system has been claimed to be more appropriate to minimize the variation of drug absorption, since the individual particles will be widely dispersed in the GI tract after oral administration (Bundgaard et al., 1982). This claim is consistent with our results: CVs of suspension 1 and granule in C_{max}, T_{max} and AUC are about half of those of the tablet.

The suspension of microspheres can be considered a multiparticulate unit system, since the microspheres are dispersed uniformly in a certain amount of aqueous medium. This might correspond to the post-deaggregation stage of the tablet. The tablet first disintegrates, then deaggregates and finally dissolves and can be absorbed. This characteristic advantage of suspensions was attributed to the low variation in the rate and extent of drug absorption.

TABLE 5

Pharmacokinetic data after administration of suspensions 2–4 (S-2–S-4), and granule (G)

Parameter	Dosage forms				Statistical evaluation Tukey's test		
	S-2	S-3	S-4	G	S-2 vs G	S-3 vs G	S-4 vs G
Plasma level (μg/ml) at							
0.5 h	N.M.	N.M.	N.M.	21.3			
1.0 h	12.6	17.2	16.8	33.9	$p < 0.05$	$p < 0.05$	$p < 0.05$
2.0 h	14.6	19.3	18.5	22.2	$p < 0.05$	N.S.	N.S.
3.0 h	11.2	20.4	12.5	18.2	$p < 0.05$	N.S.	$p < 0.05$
4.0 h	10.1	17.9	9.4	12.8	N.S.	$p < 0.05$	N.S.
5.0 h	7.1	13.3	5.7	8.6	N.S.	$p < 0.05$	N.S.
8.0 h	3.4	7.0	3.8	4.1	N.S.	$p < 0.05$	N.S.
10.0 h	0.6	3.5	1.0	1.6	N.S.	N.S.	N.S.
C_{max} (μg/ml)	16.2	24.3	20.6	37.2	$p < 0.05$	$p < 0.05$	$p < 0.05$
T_{max} (h)	1.83	3.17	2.00	0.83	$p < 0.05$	$p < 0.05$	$p < 0.05$
AUC to 10 h (μg ml^{-1} h^{-1})	71.6	123.5	78.7	118.1	$p < 0.05$	N.S.	$p < 0.05$
CV of AUC	17.0	19.8	16.3	10.2			
Relative AUC (%)	60.1	103.7	66.6				

N.M., blood sample was not taken at this point; N.S., difference in data was not significant.

[a] Statistical evaluation: after ANOVA, Tukey's tests were carried out at $p < 0.05$; relative AUC = (AUC of a tested suspension/AUC of granule) × 100.

Improved bioavailability of sustained release suspension 3

Suspension 3 showed an equal extent of bioavailability and prolonged rate of drug absorption (AUC and T_{max}) when compared with the commercial granule. The differences shown by the formulation of this suspension from the other suspensions were the size of the dispersed microspheres and the in vitro drug release rate. The rate of release of drug was not a key factor in explaining the finding that suspension 3 demonstrated ideal bioavailability, since suspension 2 with an identical drug release rate to suspension 3 could not provide such high bioavailability. AUC and T_{max} for suspension 3 were 72.5 and 73.2% greater, respectively, than for suspension 2 (Table 5).

The mean residence time (MRT) and mean absorption time (MAT), introduced by Yamaoka et al. (1978) and Cutler (1978), were shown to be useful parameters for predicting the behavior of drug in the body after oral administration (Kaniwa et al., 1988; Aoyagi et al., 1990). The MRT value for suspension 3 is 32.4% greater than that for suspension 2 (Table 6). If the total ibuprofen clearance is constant for two treatments, then the greater MRT is due to the microspheres remaining in the GI tract longer (Mason and Winer, 1983). The MAT value of suspension 3 is about 2.5 times greater than that of suspension 2, which clearly demonstrates a longer time period for absorption of ibuprofen with suspension 3 (Tanigawara et al., 1982). These results (MRT and MAT) in the moment analysis indicated that the residence time in the GI tract of the microspheres of suspension 3 was longer than that of suspension 2. The higher AUC of suspension 3 might be brought about by the continued drug release from the microspheres retained in the GI tract.

The microspheres in suspension 3 were smaller compared to those in suspension 2, namely, 350–500 and 500–850 μm, respectively. The principles and techniques for prolongation of the GI transit time of oral dosage forms have been exploited. The present authors (Kawashima et al., 1989) have demonstrated interaction between positively charged microspheres (ibuprofen-Eudragit microspheres) and negatively charged mucosubstances on the surface of the GI tract, leading to a prolonged GI residence time. Another report also indicated that the electrostatic interaction between polymer and mucin layer could play a significant role in mucoadhesion (Leung and Robinson, 1990). The surface of ibuprofen-Eudragit microspheres is positively charged to a considerable extent (Kawashima et al., 1989). This charge increases with increasing specific surface area of the microspheres.

Lehr et al. (1989) reported that when the adherence of a dosage form to the surface of GI tract is intended, a multiple-unit system is preferred. Furthermore, smaller particles (100–500 μm) could provide the possibility of greater interaction with the various folds and crevices of the GI mucosa (Lehr et al., 1989).

The aforementioned available evidence suggests that the increase in GI residence time of the smaller microspheres (350–500 μm, suspension 3) may be brought about by electrical and physical interactions between the microspheres and the GI tract.

TABLE 6

Mean residence time (MRT) and mean absorption time (MAT) of suspensions 3 and 2

Parameter	Suspension 3		Suspension 2	
	Average (h)	±S.D.	Average (h)	±S.D.
MRT [a]	5.539	0.755	3.779	0.559
MAT [a]	2.500	0.775	0.740	0.559

[a] Significant difference between two suspensions by paired t-test at $p < 0.05$.

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References

Abdou, H.M., *Disssolution of Suspensions, Dissolution, Bioavailability & Bioequivalence,* Mack, PA, 1989, pp. 173–188.

Aoyagi, N., Kaniwa, N. and Ogata, H., Effects of food on bioavailability of two indomethacin capsules containing different size of particles. *Chem. Pharm. Bull.*, 38 (1990) 1338–1340.

Bundgaard, H., Hansen, A.B. and Kofod, H., *Optimization of Drug Delivery*, Munksgaard, Copenhagen, 1982, pp. 67–79.

Cutler, D.J., Theory of the mean absorption time, an adjunct to conventional bioavailability studies. *J. Pharm. Pharmacol.*, 30 (1978) 476–478.

Gibaldi, M., Lachman, L., Lieberman, H.A. and Kanig, J.L., *Biopharmaceutics, The Theory and Practice of Industrial Pharmacy*, Lea and Febiger, Philadelphia, 1976, p. 78.

Howard, S.A., Mauger, J.W., Hsieh, J.W. and Amin, K., Suspending agent effects on steroid suspension dissolution profiles. *J. Pharm. Sci.*, 68 (1979) 1475–1479.

Jackson, A.J. and Chen, M.L., Application of moment analysis in assessing rates of absorption for bioequivalency studies. *J. Pharm. Sci.*, 76 (1987) 6–9.

Kaniwa, N., Aoyagi, N., Ogata, H. and Ejima, A., Gastric emptying rates of drug preparations. I. Effects of size of dosage forms, food and species on gastric emptying rates. *J. Pharmacobio-Dyn.*, 11 (1988) 563–570.

Kawashima, Y., Niwa, T., Handa, T., Takeuchi, H., Iwamoto, T. and Itoh, K., Preparation of controlled-release microspheres of ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method. *J. Pharm. Sci.*, 78 (1989a) 68–72.

Kawashima, Y., Niwa, T., Handa, T., Takeuchi, H., Iwamoto, T. and Itoh, K., Preparation of prolonged-release spherical micro-matrix of ibuprofen with acrylic polymer by the emulsion-solvent diffusion method for improving bioavailability. *Chem. Pharm. Bull.*, 37 (1989b) 425–429.

Kawashima, Y., Iwamoto, T., Niwa, T., Takeuchi, H. and Itoh, Y., Preparation and characterization of a new controlled-release ibuprofen suspension for improving suspendability. *Int. J. Pharm.*, 75 (1991), 25–36.

Lehr, C.M., Bouwstra, J.A., Tukker, J.J. and Junginger, H.E., Design and testing of a bioadhesive drug delivery system for oral application. *STP Pharma*, 12 (1989) 857–862.

Leung, S.S. and Robinson, J.R., Polymer structure features contributing to mucoadhesion. II. *J. Controlled Release*, 12 (1990) 187–194.

Lin, Y. and Chien, Y., Formulation factors affecting oral bioavailability, *Controlled Drug Bioavailability*, Wiley, New York, 1985, pp. 39–43.

Mason, W.D. and Winer, N., Kinetics of aspirin, salicylic acid, and salicyluric acid following oral administration of aspirin as a tablet and two buffered solution. *J. Pharm. Sci.*, 70 (1981) 262–265.

Mason, W.D. and Winer, N., Influence of food on aspirin absorption from tablets and buffered solutions. *J. Pharm. Sci.*, 72 (1983) 819–821.

Moldenhauer, M.G. and Nairn, J.G., Formulation parameters affecting the preparation and properties of microencapsulated ion-exchange resins containing theophylline. *J. Pharm. Sci.*, 79 (1990) 659–666.

Raghunathan, Y., Amsel, L., Hinsvark, O. and Bryant, W., Sustained-release drug delivery system 1: Coated ion-exchange resin system for phenylpropanolamine and other drugs. *J. Pharm. Sci.*, 70 (1984) 379–384.

Rahman, A., Cradock, J.C. and Dauignon, J.P., Dissolution and absorption of the antineoplastic agent ellipticine. *J. Pharm. Sci.*, 67 (1978) 611–614.

Smith, H.A., Evanson, R.V. and Sperandio, G.J., The development of a liquid antihistaminic preparation with sustained release properties. *J. Am. Pharm. Assoc., Sci. Ed.*, 49 (1960) 94–97.

Sjovall, J., Stogvist, R., Huitfeldt, B. and Nygvist, H., Correlation between the bioavailability of microencapsulated bacampicillin hydrochloride in suspension and in-vitro microcapsule dissolution. *J. Pharm. Sci.*, 73 (1984) 141–145.

Skelly, J.P. and Barr, W.H., Regulatory assessment, *Controlled Drug Delivery*, Dekker, New York, 1987, p. 304.

Soci, M. and Parrott, E., Influence of viscosity on absorption from nitrofurantoin suspensions. *J. Pharm. Sci.*, 69 (1980) 403–406.

Tanigawara, Y., Yamaoka, K., Nakagawa, T. and Uno, T., Moment analysis for the separation of mean in vivo disintegration, dissolution, absorption, and disposition time of ampicillin products. *J. Pharm. Sci.*, 71 (1982) 1129–1133.

Yamaoka, K., Nakagawa, T. and Uno, T., Statistical moment in pharmacokinetics. *J. Pharmacokinet. Biopharm.*, 6 (1978) 547–558.