Preparation of Prolonged-Release Spherical Micro-Matrix of Ibuprofen with Acrylic Polymer by the Emulsion-Solvent Diffusion Method for Improving Bioavailability

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Prolonged-release spherical micro-matrices of ibuprofen with acrylic polymer (Eudragit® RS) were prepared using a novel emulsion-solvent diffusion method. It was found by examining cross sections of the spherical matrix before and after dissolution tests with a scanning electron microscope and a porosimeter that the resultant micro-matrix had a sponge-like internal structure. The spherical matrices were successfully recovered with a relatively high concentration of the drug in ethanol (0.4—0.6 g/ml) and over a wide range of temperatures (5—35 °C). The size of the spherical matrix could be easily controlled by varying the agitation speed of the system and the concentration of emulsifier added to the aqueous medium. The drug release rate from the spherical matrix decreased with increasing concentration of polymer formulated due to the reduced diffusion path and increased tortuosity in the matrix. Spherical matrices with ibuprofen: Eudragit® RS = 3 : 1 improved the bioavailability of the drug and prolonged the drug action in beagle dogs.

Keywords spherical micro-matrix; emulsion-solvent diffusion method; ibuprofen; Eudragit®; drug delivery device; bioavailability

The present authors previously devised a novel method for the preparation of a controlled-release spherical matrix (*i.e.* the emulsion-solvent diffusion method).[1-3] In this process, ethanol diffused out of dispersed ethanol droplets containing drug and polymer into the environmental aqueous medium. The advantages of this technique included the avoidance of harmful organic solvents and additives such as polyisobutylene used in the process of microencapsulation in the phase separation and emulsion-solvent evaporation methods. Further, the new this process did not require elevation of the temperature of the system as in the phase separation method. The resultant matrix spheres were directly compressible without damaging their structure, due to their characteristic sponge-like texture, unlike microcapsules.[4]

Acrylic resins have been widely employed in coating and tableting, due to their inertness and solubility in alcohol. Microcapsules with pH-independent polymer (Eudragit® RS) are one of the possible candidates for preparing controlled- or slow-release drug formulations.[5,6] In the present study, novel prolonged-release dosage forms with Eudragit® RS to improve bioavailability were developed using the emulsion-solvent diffusion method. As a model drug, ibuprofen was selected, because reduction of the side effects, *e.g.* ulceration, and prolongation of the action of this compound have been desired to improve the therapeutic index.[7] The main purpose of the study was to identify the factors controlling the size of the microspheres and drug release rate. The mechanism of drug release from the matrix was also investigated, and a formulation for attaining improved bioavailability was determined.

Experimental

Preparation of Spherical Matrices of Ibuprofen Ibuprofen (2.5 g) and Eudragit® RS (0.5 to 1.25 g) were dissolved in 5 ml of ethanol. The resultant ethanolic solution was poured into a 0.025% (w/v) aqueous solution (200 ml) of sucrose fatty acid ester (DK-F70, Daiichi Kogyo Seiyaku, Co., Kyoto) thermally controlled at 25 °C with agitation (300 rpm) using a propeller-type stirrer (diameter, 37 mm) in a cylindrical vessel (500 ml) with three baffles. The ethanolic solution was instantly dispersed into fine gel-like droplets. Counter diffusions of ethanol and water out of and into the droplets occurred, respectively, resulting in solidified droplets having the matrix structure of the polymer with the drugs dispersed in it. It was assumed that the size of the spherical matrix could be determined by the size of the droplets formed at the initial stage, possibly by controlling the agitation speed, the concentration of emulsifier and the temperature of the system. The agitation speed and the concentration of emulsifier could affect the dispersion of the ethanol solution. The diffusions of ethanol and water could be influenced by the temperature of the system. The experimental parameters were varied as follows.

1) Concentration of drug in ethanol: 2.5 g dissolved in 3, 4, 5, 6, 7, 8, 9 and 10 ml of ethanol (*i.e.*, 0.25, 0.28, 0.31, 0.36, 0.42, 0.5, 0.63 and 0.83 g/ml).

2) Agitation speed: 100, 200, 300, 400, 500, 600, 700, 800, 900 and 1000 rpm.

3) Concentration of emulsifier: 0.025, 0.050 and 0.100% (w/v).

4) Temperature of system: 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 °C.

After agitation for 30 min, the spherical matrices were decantated to separate the unagglomerated fine powders, filtered and dried in an oven (FR-4B, Izumi Manufacturing Co., Tokyo) or with a fluidized bed drier (TR-2, Glatt, Germany) at 40 °C. The intact spherical matrix before drying contained 15—20% (w/w) of water. Microcapsules with Eudragit® RS tend to become swollen during the preparation process due to the presence of quaternary ammonium groups in that polymer.[8] In the present process, such swelling was not observed. The moisture content of the spherical matrix could be decreased to below 0.2% by drying for 3 or 1 h using an oven or fluidized bed drier, respectively. The ethanol retained in the spherical matrix was reduced from 650 to 60 ppm by drying with the

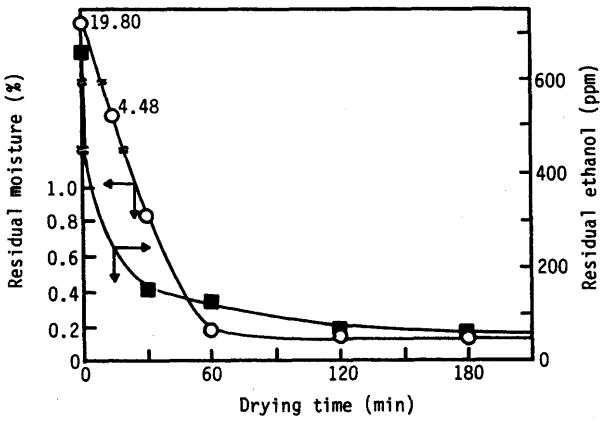

Fig. 1. Process of Removing Water (○) and Ethanol (■) from Spherical Matrices (Ibu : RS = 3 : 1) in a Fluidized Bed at 40 °C, 760 mmHg

fluidized bed drier at 40 °C (60 ppm is an acceptable value from the standpoint of toxicity). The process of exclusion of moisture and alcohol from the matrices is illustrated in Fig. 1. The water and ethanol in the spherical matrix were detected with a Karl-Fischer titrator (model MKA-3, Kyoto Electronics, Kyoto, Japan) and a gas chromatograph (model 263-50, Hitachi, Tokyo). The dried spherical matrices were sieved to determine their average size using standard sieves. The average diameter was estimated as the geometric mean diameter. The recovery was determined from the ratio of the amount of products to that of loaded powders.

Drug Release Test of Spherical Matrices Spherical matrices fractionated to 297—1000 μm containing 500 mg of drug were tested using the dissolution test apparatus specified in USP XXI (NTR-VS3, Toyama Sangyo Co., Osaka, Japan). The sample was placed in the rotating basket (mesh size, 80 mesh), rotated at 100 rpm in the disintegration test solution No. 2 specified in JP XI (900 ml) containing Polysorbate 80 (0.02% (w/v)) to improve the dispersion of the matrix particles. Two milliliters of the dissolution medium was sampled, and fresh dissolution medium was simultaneously replaced in the apparatus to keep the volume constant. The withdrawn sample was filtered with a membrane filter (TM-30, Toyo Roshi Co., Tokyo; pore size = 0.3 μm). The filtrate was assayed spectrophotometrically at 220 nm to determine the dissolved drug concentration using a spectrophotometer (Model, 100-60, Hitachi Manufacturing Co., Tokyo). After the drug release test, the spherical matrices were recovered to investigate their surface topography and internal texture with a scanning electron microscope (JSM-T330A, Nihon Denshi, Co., Tokyo) after coating with gold. The pore size distribution in the spherical matrices was measured by the mercury displacement method at various pressures employing a porosimeter (Poresizer 9305, Shimadzu Co., Japan).

Absorption Test of Spherical Matrix with Beagle Dogs Prepared spherical matrices (297 to 1000 μm) and Brufen® granules (Kaken Pharmaceutical Co., Tokyo) as a reference containing 100 mg of active ingredient wrapped in a soluble film, were administered orally with 10 ml of water to beagle dogs weighing 8.3 to 10.7 kg. At suitable intervals, 3 ml of blood was collected from the ossicular vein. The dogs were fasted for 24 h before dosing and until the last blood sample had been taken. The concentration of ibuprofen in the plasma separated by centrifugation was determined spectrophotometrically at 220 nm using a high-pressure liquid chromatograph (pump, Twincle; detector, UVIDEC-100-V; Japan Spectroscopic Co., Tokyo). As the internal standard, butyl *p*-hydroxybenzoate was employed.

Results and Discussion

Parameters Affecting the Recovery and Average Size of the Spherical Matrix The average diameters and recoveries of spherical matrices (below 2000 μm) are plotted as a function of concentration of ibuprofen in ethanol in Fig. 2, in which the geometric standard deviation of the diamter is represented by bars. With increasing concentration of ibuprofen, the recoveries of spherical matrices increased rapidly. The recovery reached a maximum (*i.e.*, 92% at 0.4 to 0.6 g/ml) and then decreased slightly. At a concentration of 0.83 g/ml, the loss of spherical matrices due to adhesion to the propeller and the vessel wall became relatively larger than the recovered amount, since the volume of ethanol solution was small (3 ml). The curve for the average diameter of the matrices *versus* concentration of ibuprofen exhibited a minimum at 0.42 g/ml. At higher concentrations of ibuprofen, the ethanol solution became viscous, resulting in larger droplets of ethanolic solution in the medium. With lower drug concentrations, the ethanolic solutions were well dispersed into numerous fine droplets, which easily coalesced into larger viscous droplets during diffusion of ethanol out of the droplets, producing larger spherical matrices. At lower concentrations of ibuprofen, the reduced rate of coprecipitation of the drug with polymer also yielded unagglomerated fine powders which were not spherical.

The dispersion of the ethanolic solutions of the drug and polymer into droplets in the medium depended on the agitation speed of the system and the concentration of surfactant in the medium. The diffusion of ethanol out of the droplets resulted in a solidified spherical matrix of the

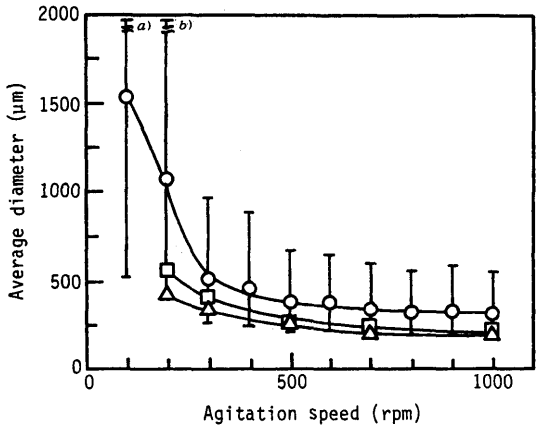

Fig. 3. Average Diameters of Spherical Matrices (Ibu : RS = 3 : 1) as a Function of Agitation Speed and Concentration of Surfactant in the Dispersing Medium

Concentration of DK-F70: ○, 0.025% w/v; □, 0.05% w/v; △, 0.1% w/v. 84.1% under size: *a*) 4539 μm; *b*) 2662 μm.

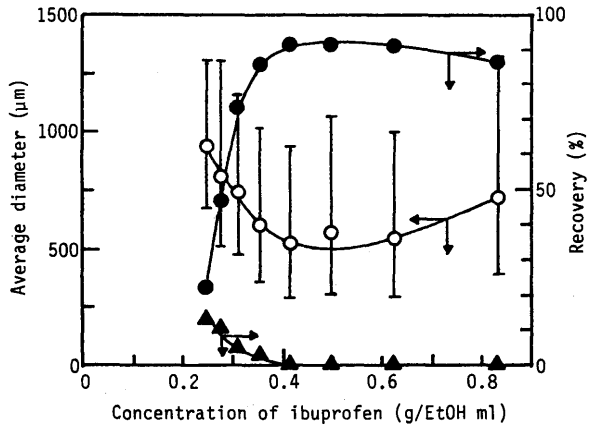

Fig. 2. Average Diameters (○) and Recoveries of Spherical Matrices (●) and Fine Powders (▲) as a Function of Concentration of Ibuprofen in Ethanol (Ibu : RS = 3 : 1)

Bars: geometric standard deviation.

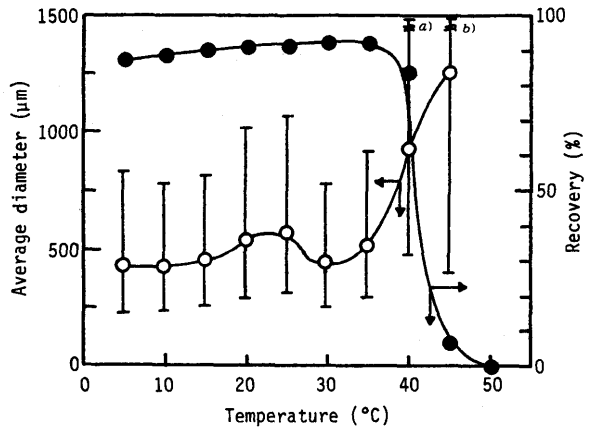

Fig. 4. Average Diameter (○) and Recovery (●) of Spherical Matrices (Ibu : RS = 3 : 1) as a Function of Temperature of the System

84.1% under size: *a*) 2422 μm; *b*) 4050 μm.

drug with the polymer. The size of the ethanolic droplets thus strictly determined that of the spherical matrix, which decreased with increasing agitation speed or concentration of surfactant (Fig. 3).

The temperature of the system determined the recovery and size of the spherical matrix, since the solubilities of the drug and polymer and the diffusion rate of solvent depended on temperature. The recovery of spherical matrix decreased sharply on raising the temperature of the system above 40 °C, as shown in Fig. 4. At a temperature of >35 °C, the recovered products consisted of aggregates swollen with water and having an irregular shape, which apparently increased the average diameter of the matrices. Swelling of Eudragit® RS has also been observed by Goto *et al.*[8] in a preparation of microcapsules obtained by the emulsion-solvent evaporation method. At a temperature of <35 °C, the variations in recovery, average size and shape (spheres) of the matrices with temperature became small. This represented an advantage of the present method compared with the solvent evaporation method.

Drug Release Behavior of the Spherical Matrices The rate of drug release from the spherical matrix clearly depended on the polymer concentration in the preparation system (Fig. 5). On increasing the polymer concentration, the drug release rate decreased. The rate of drug release was determined by the diffusion rate of dissolved drug in the matrix, as described by the Higuchi model (Fig. 6). Before the drug release test, little variation in surface morphology or internal structure of the spherical matrices with concentration of polymer was found, as demonstrated by the scanning electron microphotographs in Fig. 7A. After the drug release test, the shape of the spherical matrix recovered from the dissolution system was found to be unchanged without disintegration, but macro-pores and

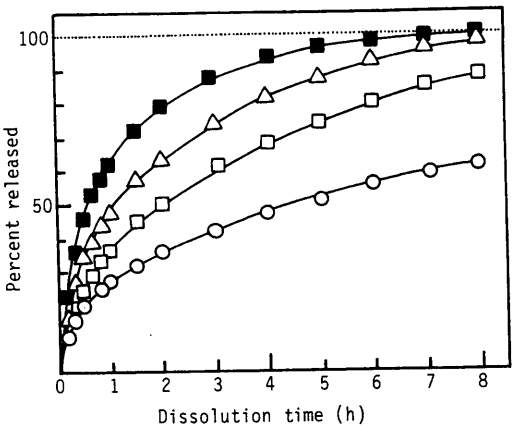

Fig. 5. Dissolution Profiles of Ibuprofen from Spherical Matrices (297—1000 μm) Prepared with Various Ratios of Ibuprofen to Eudragit® RS

Ibu:RS=2:1 (○), 3:1 (□), 4:1 (△), 5:1 (■). Dissolution medium: JP XI No. 2+Polysorbate 80 (0.02%).

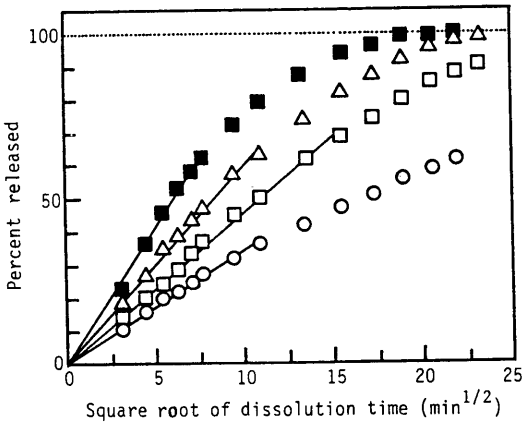

Fig. 6. Dissolution Profiles of Ibuprofen from Spherical Matrices (297—1000 μm) Prepared with Various Ratios of Ibuprofen to Eudragit® RS as Described by the Higuchi Matrix Model

Key as in Fig. 5.

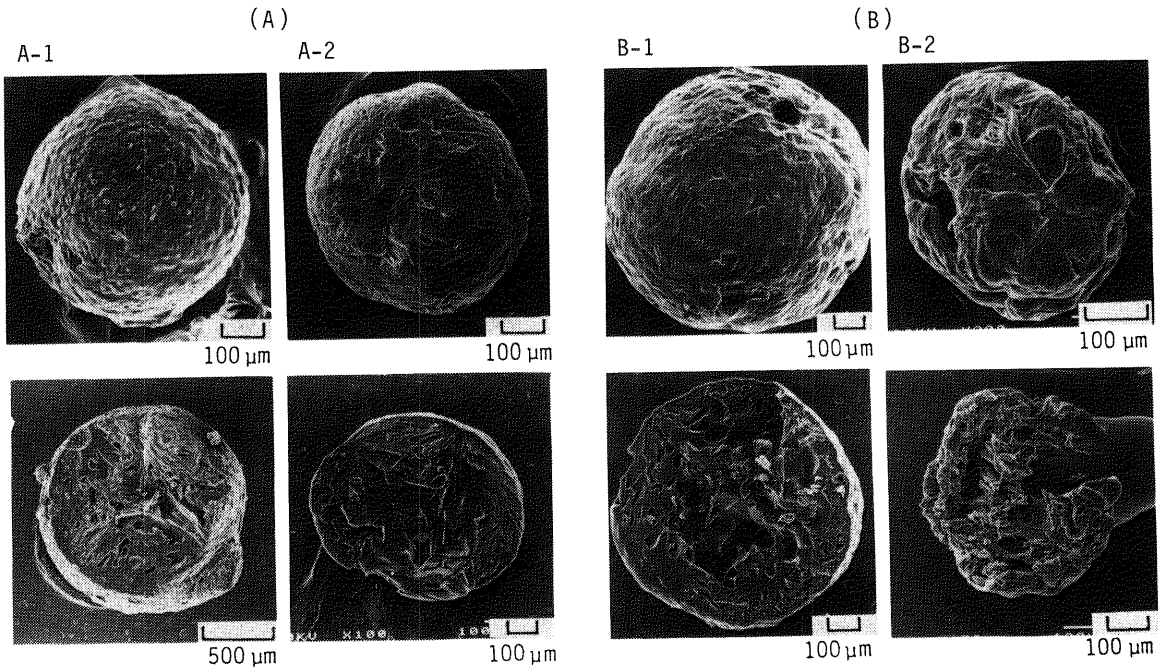

Fig. 7. Scanning Electron Microphotographs of Spherical Matrices before (A) and after (B) the Dissolution Test

Ibu:RS=2:1 (A-1, B-1), 5:1 (A-2, B-2). Above, surface; below, cross sections.

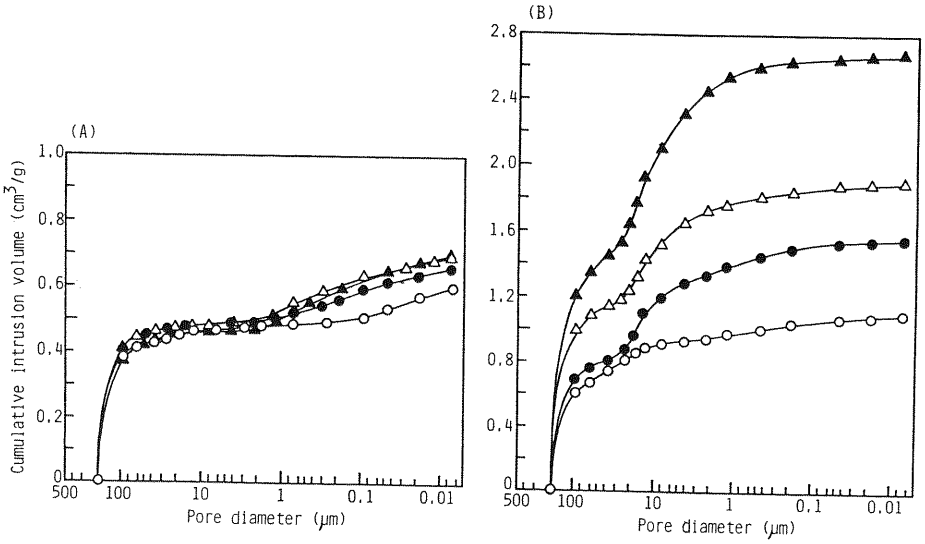

Fig. 8. Cumulative Pore Size Distribution of Spherical Matrices before (A) and after (B) the Dissolution Test

Ibu : RS = 2 : 1 (○), 3 : 1 (●), 4 : 1 (△), 5 : 1 (▲). The samples were fractionated from 500 to 710 μm.

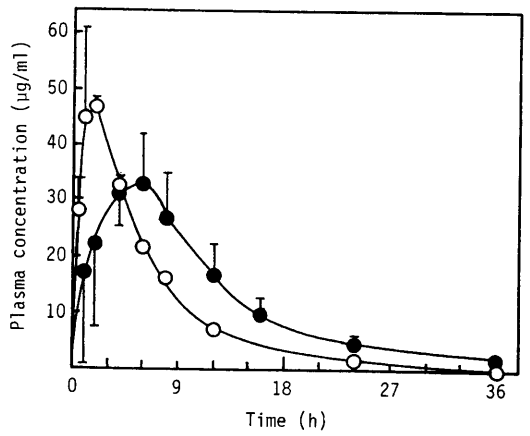

Fig. 9. Mean Plasma Concentration of Ibuprofen after Oral Administration of Spherical Matrices ($n=5$) and Brufen® Granules ($n=2$) Containing 100 mg of Ibuprofen to Dogs

●, Ibu : RS (3 : 1) spherical matrices (297—1000 μm); ○, Brufen® granules.

voids were observed in the matrix as illustrated in Fig. 7B. The pore size distributions of the spherical matrices before and after the dissolution test are shown in Fig. 8. The porosity with a pore size range of 1—100 μm, which corresponded to the crystal size of ibuprofen in the matrix, increased after the dissolution test. In particular, at a lower concentration of polymer, pore sizes of 5—25 μm in the matrix exhibited a marked increase (Fig. 8B). These results agreed well with the observations on cross sections of the spherical matrices after drug release obtained by scanning electron microphotographs (Fig. 7B). It is suggested that a reduced diffusion path and increased tortuosity may retard the drug release rate from the matrix at higher concentrations of polymer. A rigid honeycomb structure of the matrix could prevent any initial burst of drug release during the test. In fact, smooth drug release curves without bursts following the Higuchi model were found (Fig. 6).

Bioavailability of Spherical Matrix of Ibuprofen The bioavailability of the spherical matrices of ibuprofen was investigated in comparison with that of Brufen® granules. The mean plasma concentrations of ibuprofen for the spherical matrices and Brufen® granules are shown in Fig. 9, following oral administration in beagle dogs. The data can be well described in terms of a one-compartment model assuming that the drug absorption and elimination are apparent first-order processes. The pharmacokinetic parameters of the spherical matrices and the commercial granules as calculated by the method of Gibaldi and Perrier[9] are listed in Table I. The apparent absorption rate constant of the spherical matrices, which was smaller than that of the commercial granules, depressed the initial rapid increase in plasma concentration, as can be seen in Fig. 9. The reduced apparent elimination rate constant of the spherical matrices resulted in prolongation of the time to peak and increase of the area under the plasma concentration–time curve (AUC). In acidic medium (pH <3), the spherical matrix with Eudragit® RS strongly adsorbs polysaccharide derivatives such as sodium carboxymethylcellulose and sodium alginate.[10] These findings suggest that the spherical matrix should interact with mucosubstances on the surface of the stomach, leading to prolongation of its residence time in the stomach. Thus, delayed stomach transit of the spherical matrix as compared to Brufen® granules might contribute to improving the bioavailability of the spherical matrix.

Table I. Pharmacokinetic Parameters Following Oral Administration of Spherical Matrices and Brufen® Granules to Dogs

Dosage form	AUC_0^{36} [a] (μg·h/ml)	K_a [b] (/h)	K_e [c] (/h)	C_{max} [d] (μg/ml)	t_{max} [e] (h)
Spherical matrices	442[f] ±85	0.388 ±0.104	0.112 ±0.016	31.3 ±5.5	4.51 ±0.51
Brufen granules	347 ±24	1.552 ±0.206	0.196 ±0.009	46.3 ±0.8	1.54 ±0.11

a) The AUC from 0 to 36 h was calculated using the trapezoidal rule. *b*) Apparent absorption rate constant. *c*) Apparent elimination rate constant. *d*) Maximum concentration. *e*) Time at maximum concentration. *f*) Numerical values = average ± S.D.

In conclusion, it was found that spherical micro-matrices of ibuprofen with acrylic polymer prepared by the emulsion-solvent diffusion method provided a new prolonged-release dosage form with an improved bioavailability.

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