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Controlled release indomethacin microspheres prepared by using an emulsion solvent-diffusion technique

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Summary

The feasibility of producing controlled release indomethacin microspheres, with acrylic polymers Eudragit RS and RL, by employing two emulsion solvent-diffusion systems, is compared. Microspheres with various polymer/drug ratios and polymer combinations (Eudragit RS/RL ratios) were prepared. The physical properties, loading efficiency and dissolution behaviour depended on the emulsion solvent-diffusion technique, polymer/drug ratio and polymer combination. The drug release is described on the basis of two bi-exponential, first-order models.

Introduction

Indomethacin, like many other non-steroidal anti-inflammatory drugs, has been reported to cause gastrointestinal and central nervous system side effects (Boardman and Dudley-Hart, 1967; Merkus, 1980). These side effects may be related to the drug serum levels, due to a systemic rather than a local effect (Yokoyama et al., 1984; Hilton and Summers, 1986; Soehngen et al., 1988); therefore, their severity could be reduced if drug release were not as rapid as with conventional capsule formulations (Carless and Rowe, 1981). The present report concerns the feasibility of producing a sustained release form of indomethacin microspheres by using Eudragit RS and RL polymers and applying two modifications of the emulsion solvent-diffusion technique (Pongpaibul et al., 1984; Hoffman et al., 1987; Kawashima et al., 1989).

Eudragit RS and RL were selected, since they are synthesized from acrylic and methacrylic esters with low and high content of quaternary ammonium groups (1/10 and 1/20) and may result in microspheres with different water permeability. The underlying cause of the differences in water permeability may be changes in the pore structure of the polymers separated during the microsphere preparation, as well as variations in the hydrophilic (swelling) properties (Koenhen et al., 1977; Okor, 1982; Carli et al., 1984). Therefore, various combinations of polymers (Eudragit RS/RL) as well as different polymer/drug ratios have been employed for the purpose of investigating the effect of preparation technique on the physical properties, drug loading efficiency and in

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vitro release behaviour. Such information may be helpful in defining conditions for the design and production of controlled release microspheres having adequate oral sustained-release properties.

Experimental

Preparation of microspheres

Microspheres were prepared by employing two emulsion systems with phase distributions in the opposite order (o/w and w/o). In the o/w system the external (aqueous) phase consisted of 300 ml of 0.5% polyvinyl alcohol (PVA, mol. wt. 72000; Roth, Karlsruhe, F.R.G.) and the internal (organic) phase consisted of 75 ml of methylene chloride A.R. (Ferak, Berlin, Germany) containing increasing amounts of indomethacin and polymers. In the w/o system the external (organic) phase consisted of 270 ml paraffin oil (highly liquid; Merck, Darmstadt, F.R.G.), 30 ml silicon oil (Baysilonöl M 300; Roth) and 3 g of emulsifier (Tween 85; Roth), while the internal (aqueous) phase consisted of 200 ml anhydrous alcohol p.a. (Merck), in which increasing amounts of indomethacin and polymers were dissolved.

In both systems the emulsification was achieved by using an Ultra-turax (IKA-TP 18/10 S5, Staufen, F.R.G.). After emulsification the mixture was cooled in an ice bath and continuously stirred for 3 and 6 h, respectively, while the temperature was gradually increased to 30 °C. Stirring rates between 500 and 700 rpm were selected and the shear stress of the system was monitored with a torque indicator (IKA-RE 162, Staufen) at a level of 16.7 N cm.

The microspheres were separated from the solution by decantation and rinsed twice with 400-ml portions of water or *n*-hexane (Merck) for the o/w and w/o system, respectively. By means of an addition of 400 ml of water or *n*-hexane, the microspheres were transferred, vacuum filtered and traces of solvent removed by placing on paper and drying at room temperature. Finally, the microspheres were deaggregated by passing through a sieve of 0.5 mm aperture. Three different combinations of polymers (Eudragit RS/RL ratios: 1.0, 1.5 and 2.0) were employed.

Evaluation of the microspheres

Physical properties

Particle size Samples of microspheres were dispersed on a slide with paraffin oil and their diameter was determined by using a projection microscope (Visopan-Reichert, Austria). 200 microspheres were sized using suitable objectives. The sizes were plotted on a logarithmic scale and the cumulative percentage undersize plotted on a probability scale. The geometric mean diameter (d_g) and the geometric standard deviation (σ_g) were noted.

Density The true density (ρ_g) of the microspheres was determined on an air comparison pycnometer (Beckman, Model 930). The loose bulk density (ρ_b) and the tap density (ρ_t) were measured in a 25 ml cylinder using a J. Engelsmann volumeter, Model JEL. ST 2 (Ludwigshafen, F.R.G.). The changes occurring in packing arrangement for microspheres subjected to the tapping procedure are expressed as the compressibility index (Carr, 1970): compressibility index $= [(\rho_t - \rho_b)/\rho_t] \times 100$. The percentage of intermicrosphere porosity was calculated as: $e = [1 - (\rho_t/\rho_g)] \times 100\%$.

Drug loading efficiency

Accurately weighed portions of microspheres (50 mg) were dissolved in methanol and assayed spectrophotometrically for indomethacin, at 318 nm, using a calibration curve based on standard solutions in methanol [$X = 60.6(Y - 0.0126)$, where X = concentration of indomethacin and Y = absorbance]. Eudragit did not interfere with the assay at this wavelength. The indomethacin content was calculated and the ratio of measured to theoretical value is expressed as percent drug loading efficiency.

In vitro drug release

Release of indomethacin from the microspheres was determined using a standard USP (Method II) dissolution apparatus (Pharmatest-type PTW/SII, Haiburg, F.R.G.). Samples of microspheres con-

taining 50 mg of indomethacin were dispersed in 900 ml of phosphate buffer solution, at pH 6.5, containing 0.02% sodium lauryl sulfate to ensure sink conditions. The solution was stirred at 100 rpm. Aliquots were withdrawn at 30, 60, 90, 120 min and then at 1 h intervals up to 6 h. Indomethacin content was determined spectrophotometrically at 318 nm after filtration. Each release determination was carried in quadruplicate.

Results and Discussion

The physical properties, namely, the geometric mean diameter (d_g), geometric standard deviation (σ_g), density (true, bulk and tap), porosity (e%) and compressibility index (%) as well as the drug loading efficiency (%), of the microspheres at fixed polymer combination (Eudragit RS/RL = 1) and increasing polymer/drug ratio, are listed in Table 1.

The increase in polymer/drug ratio resulted in an increase in microsphere size and density combined with a decrease in porosity and compressibility index for both the emulsion phase-distribution systems employed. This increase in size and density may be attributed to the higher viscosity of the internal phase, due to higher concentration of the polymer, rather than to the formation of larger droplets either during emulsification or when the solvent diffuses, since the shearing rate during stirring was kept constant. Also, as shown in Table 1, the microspheres obtained with the w/o system are generally larger in size, more dense or less porous and have lower compressibility index than those obtained with the o/w system.

Despite the larger size and lower compressibility index, which indicate better flowability, it was observed that the microspheres from the w/o system did not show better flow. On the contrary, they were more cohesive, passing with difficulty through the 0.5 mm sieve during their deaggregation and tended to cake during storage.

The drug loading efficiency (Table 1) increases with polymer content, particularly for the case of the o/w system. This finding does not agree with that of Pongpaibul et al. (1984), who showed that the drug loading was affected by neither polymer content nor polymer combination (Eudragit RS/RL ratio) but was consistently slightly lower than the theoretical loading.

The deviations of drug loading efficiency from the theoretical (100%) may be attributed to two causes. Positive deviations may be due to the separation of pure polymer during solvent diffusion and the formation of empty (neutral) microspheres, which are removed during the separation process. Negative deviations probably result from drug loss in the form of free, very small indomethacin crystals during the decantation and rinsing processes. The last explanation in connection with the general increase in drug loading efficiency as the polymer content increases, is in agreement with the observation made during particle sizing by optical microscopy that the micro-

TABLE 1

Physical properties of the microspheres with fixed polymer combination (Eudragit RS / RL = 1)

Emulsion system	Polymer/ drug ratio	Loading efficiency (%)	Size		Density (g/ml)			Porosity (e%)	Compressibility index (%)
			d_g (μm)	σ_g	True (ρ_g)	Bulk (ρ_b)	Tap (ρ_t)		
o/w	0.5	116	7	2.1	1.138	0.08	0.12	89.4	33.3
	1.0	131	11	2.2	1.182	0.14	0.20	83.1	30.0
	2.0	134	20	2.4	1.273	0.38	0.53	58.4	28.3
w/o	0.5	89	180	1.4	1.305	0.21	0.28	78.5	25.0
	1.0	98	230	1.4	1.364	0.34	0.45	67.0	24.4
	2.0	120	380	1.5	1.437	0.46	0.54	62.4	14.8

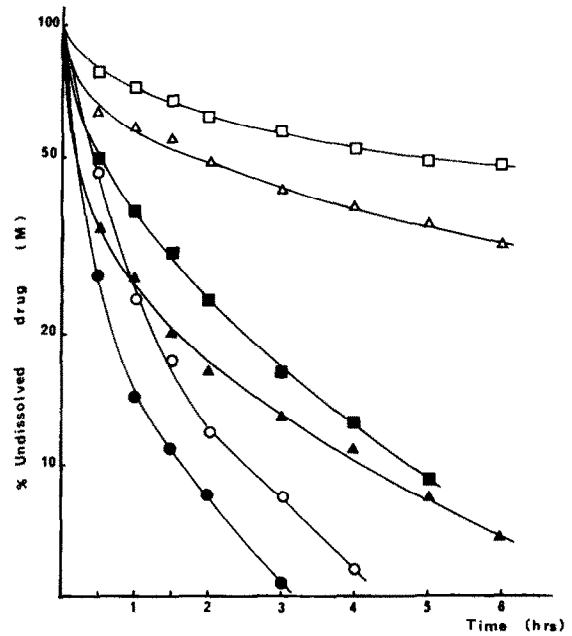

Fig. 1. Percentage of undissolved indomethacin vs time for microspheres prepared by employing two emulsion solvent-diffusion techniques and increasing polymer/drug ratios. Polymer/drug ratios: (o/w emulsion system) ●, 0.5; ▲, 1.0; ■, 2.0; (w/o emulsion system) ○, 0.5; △, 1.0; □, 2.0.

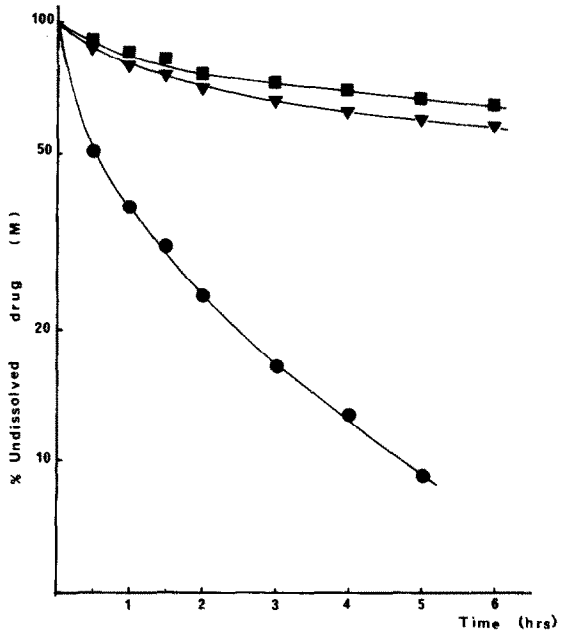

Fig. 2. Percentage of undissolved indomethacin vs time for microspheres prepared by using o/w emulsion system, fixed polymer drug ratio (2.0) and different polymer combinations (Eudragit RS/RL ratios: ●, 1.0; ▼, 1.5; ■, 2.0).

spheres with high polymer content were more or less spherical whereas those with lower polymer content contained many rod-like particles.

Regarding indomethacin release from microspheres, the percentage of undissolved drug (M) is plotted vs time (t) in Figs 1 and 2. The effects of polymer/drug ratio on drug release are shown in Fig. 1, while those of polymer combination (Eudragit RS/RL ratio) are depicted in Fig. 2. In order to quantify these effects the goodness of fit of the release data was tested with the main models which have been proposed to describe drug release kinetics from microcapsules and matrixes:

$$\text{(zero order)} \quad 100 - M = k_0 t \tag{1}$$

$$\text{(first order)} \quad \ln M = k_1 t \tag{2}$$

$$\text{(cube root)} \quad \sqrt[3]{100} - \sqrt[3]{M} = k_2 t \tag{3}$$

$$\text{(square root)} \quad 100 - M = k_3 \sqrt{t} \tag{4}$$

TABLE 2

Fit of dissolution results to different kinetic models, for microspheres with fixed polymer combination (Eudragit RS / RL = 1)

Emulsion system	Polymer/drug ratio	First-order			Cube-root		Square-root		
		k_1 (h^{-1})	r	Lag time (h)	k_2 (h^{-1})	r	k_3 (h^{-1})	r	Lag time (h)
o/w	0.5	0.87	0.920	−0.7	0.75	0.943	39.45	0.866	−0.7
	1.0	0.38	0.866	−2.3	0.38	0.796	36.30	0.864	−0.9
	2.0	0.37	0.967	−0.9	0.36	0.916	34.68	0.938	−1.3
w/o	0.5	0.66	0.936	−0.7	0.61	0.953	37.13	0.914	−0.6
	1.0	0.15	0.921	−2.1	0.19	0.895	24.85	0.955	−1.3
	2.0	0.11	0.937	−1.6	0.14	0.923	20.67	0.984	−0.6

The values of the release rate constants, the corresponding correlation coefficients (r) and the theoretical time when $M = 100\%$ (lag time) are listed in Table 2.

The release rate constants decrease with increase in polymer content (polymer/drug ratio) and are always greater for microspheres prepared with the o/w system. The zero-order model was inapplicable, since the correlation coefficients were less than 0.8 for all microspheres investigated. The square-root and first-order models provide a better fit to the release data of the microspheres with polymer/drug ratio above 0.5. For microspheres with lower polymer content (polymer/drug ratio = 0.5), the cube-root kinetics result in a better description of the dissolution results. The last finding is in agreement with the microscopic observation that the same microsphere samples contained many rod-like particles, since the cube-root model relates to the release process controlled by the dissolution of drug particles (Bamba et al., 1979).

The absence of zero-order release kinetics suggests that the release rate changes with time. Furthermore, the partial fit to the first-order and square-root models constitutes evidence that indomethacin release from the microspheres may be due to the simultaneous operation of more than one release mechanism.

The carrier of the indomethacin in the microsphere (matrix) consists of two polymers with different pore formation and swelling properties,

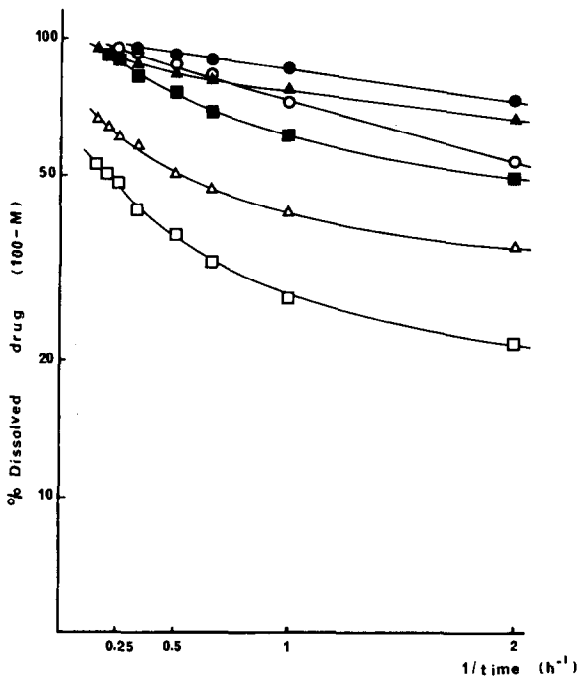

Fig. 3. Percentage of dissolved indomethacin vs reciprocal time for microspheres prepared by employing two emulsion solvent-diffusion techniques and increasing polymer/drug ratios (symbols as in Fig. 1).

due to different cation content (Koenhen et al., 1977; Okor, 1982). Therefore, the permeability of microspheres and indomethacin transfer may be affected by both pore structure and swelling ability. The dissolution liquid penetrates into the microspheres through the pores, dissolving the drug

TABLE 3

Parameters for the release of indomethacin on the basis of the equation $M = A \exp(-k_a t) + B \exp(-k_b t)$

Emulsion system	Polymer/drug ratio	Eudragit RS/RL ratio	k_a (h^{-1})	k_b (h^{-1})	A	B	Correlation coefficient		Lag time (h)	$A+B$
							Initial phase	Terminal phase		
o/w	0.50	1.0	4.46	0.46	83.6	21.9	0.996	0.998	0.01	105.5
	1.00	1.0	3.75	0.24	75.5	28.2	0.987	0.992	0.01	103.7
	2.00	1.0	1.91	0.31	48.3	44.0	0.985	0.999	−0.09	92.3
	2.00	1.5	0.94	0.04	30.3	73.5	0.944	0.996	0.11	103.8
	2.00	2.0	0.73	0.04	13.4	82.9	0.942	0.999	−0.33	96.3
w/o	0.50	1.0	2.16	0.37	77.8	25.6	0.996	0.975	0.02	103.4
	1.00	1.0	1.54	0.08	36.7	54.7	0.975	0.998	−0.13	91.4
	2.00	1.0	0.87	0.04	34.0	61.3	0.976	0.947	−0.15	97.3

which then diffuses out into the bulk solution. Also, the penetrating liquid hydrates the polymers which swell and affect the diffusion and transfer of the drug. The development of pores during microsphere preparation (emulsion solvent-diffusion and setting of the polymer) should be responsible for the initial fast release of drug. During this initial phase, the simultaneous swelling of polymer and the increase in distance that the drug must travel from within the microsphere to reach the bulk solution will decrease the release rate with time. When swelling of the microspheres has been completed, the drug release should be slower and dependent on the permeability of the swollen polymer only.

In order to elucidate the possible operation of two release mechanisms, more stringent evaluation of the dissolution data is applied. The dissolution results are expressed on the basis of two bi-exponential first-order models corresponding to the following equations:

$$M = A\ \exp(-k_a t) + B\ \exp(-k_b t) \qquad (5)$$

$$100 - M = m_1 \exp(-\alpha/t) + m_2 \exp(-\beta/t) \qquad (6)$$

Eqn 5 is analogous to that generally used to describe pharmacokinetics after rapid intravenous injection of drug, and has been used for the interpretation of indomethacin release from tablets by Laakso et al. (1984); k_a and k_b are the release rate constants corresponding to the two release mechanisms, the rapid initial and slower terminal phases, respectively. Eqn 6 takes into account two independent probabilistic mechanisms and is analogous to that proposed for the analysis of powder compression by Cooper and Eaton (1962); m_1 and m_2 indicate the percent release that would be achieved at infinite time by each particular mechanism. The total $(m_1 + m_2)$ equals 100 when re-

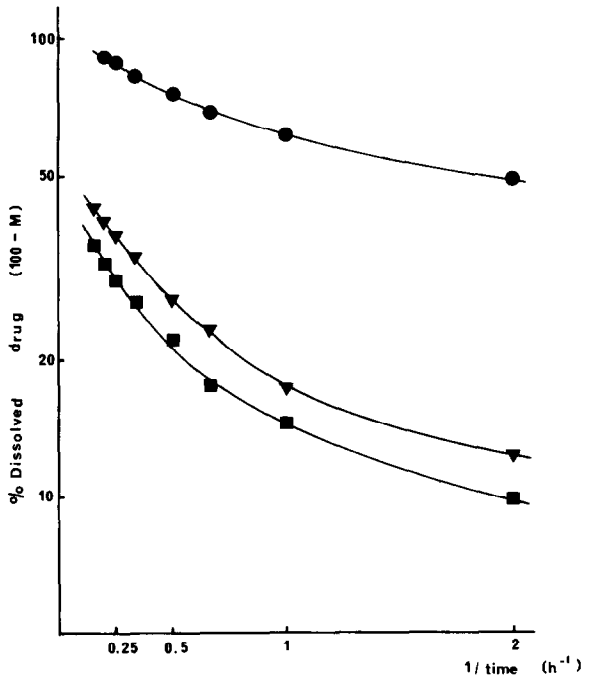

Fig. 4. Percentage of dissolved indomethacin vs reciprocal time for microspheres prepared by using o/w emulsion system, fixed polymer/drug ratio (2.0) and different polymer combinations (symbols as in Fig. 2).

TABLE 4

Parameters for the release of indomethacin on the basis of the equation $M = 100 - m_1 \exp(-\alpha/t) + m_2 \exp(-\beta/t)$

Emulsion system	Polymer/drug ratio	Eudragit RS/RL ratio	α (h)	β (h)	m_1	m_2	Correlation coefficient		$m_1 + m_2$
							Initial phase	Terminal phase	
o/w	0.50	1.0	0.16	0.99	85.5	15.8	0.998	0.995	101.3
	1.00	1.0	0.14	3.24	87.3	12.1	0.993	0.963	99.4
	2.00	1.0	0.24	3.55	80.1	28.8	0.996	0.999	108.9
	2.00	1.5	0.43	7.57	28.3	67.3	0.978	0.968	96.6
	2.00	2.0	0.39	8.55	21.7	73.9	0.999	0.990	95.6
w/o	0.50	1.0	0.32	0.65	4.4	97.5	0.989	0.998	101.9
	1.00	1.0	0.21	5.54	52.7	44.0	0.989	0.995	96.7
	2.00	1.0	0.28	7.29	37.5	62.2	0.972	0.979	99.7

lease can be completely described in terms of the two separate mechanisms. The parameters α and β, having the dimensions of time, indicate the magnitude of time when the particular mechanisms are taking place with the greater probability.

Plots of the percentage of dissolved drug ($100 - M$) vs $1/t$ are shown in Figs 3 and 4 and the values of the release parameters A, B, k_a, k_b, m_1, m_2, α and β, as well as the corresponding correlation coefficients and lag times, are listed in Tables 3 and 4.

The correlation coefficients in Tables 3 and 4 are high, the sums of $A + B$ and $m_1 + m_2$ are close to 100 and the lag times realistic (0.01–0.33 h). The plots for the microspheres with low polymer/drug ratio (0.5) tend to become rectilinear, while all the other plots in Figs 3 and 4 exhibit curvature. This tendency of the plots to become rectilinear may indicate the operation of only one release mechanism, while an alternative explanation for the linearity could be that both mechanisms operate simultaneously and cannot therefore be distinguished by Eqn 6 ($\alpha = 0.16$ and 0.32; $\beta = 0.99$ and 0.65 h).

On the basis of the release parameters given in Tables 3 and 4, one can determine what kind of effects any preparation variable (emulsion solvent-diffusion technique, polymer/drug ratio and polymer combination) has separately had on the two release mechanisms, the fast initial and slower terminal phases. From the present results it may be concluded that:

(a) The release of indomethacin from the microspheres is biphasic except for those with polymer/drug ratio 0.5.

(b) The release rate constants of the fast initial as well as slow terminal phase decrease with increase in polymer content, particularly for the insoluble Eudragit RS.

(c) The times when both the particular release mechanisms are taking place with greater probability increase with polymer/drug ratio and with Eudragit RS content.

References

Bamba, M., Puisieux, F., Marty, J.P. and Carstensen, J.T., Release mechanisms in gelforming sustained release preparations. *Int. J. Pharm.*, 2 (1979) 307–315.

Boardman, P.L. and Dudley-Hart, F., Side-effects of indomethacin. *Ann. Rheum. Dis.*, 26 (1967) 127–132.

Carless, J.E. and Rowe, J.S., The use of critical flicker fusion frequency test for evaluating some central nervous effects of two indomethacin formulations. *J. Pharm. Pharmacol.*, 33 (1981) 336–337.

Carli, F., Capone, G., Colombo, I., Magarotto, L. and Motta, A., Surface and transport properties of acrylic polymers influencing drug release from porous matrices. *Int. J. Pharm.*, 21 (1984) 317–329.

Carr, R.L., Particle behaviour storage and flow. *Br. Chem. Eng.*, 15 (1970) 1541–1549.

Cooper, A.R. and Eaton, L.E., Compaction behavior of several ceramic powders. *J. Am. Ceram. Soc.*, 45 (1962) 97–101.

Hilton, J.E. and Summers, M.P., The effect of polyvinylpyrrolidones on intestinal ulceration caused by indomethacin. *Int. J. Pharm.*, 32 (1986) 13–19.

Hoffman, A., Babay, D. and Benita, S., The design of controlled release indomethacin microspheres for oral use. *Proc. Int. Symp. Control. Rel. Bioact. Mater.*, 14 (1987) 115–116.

Kawashima, Y., Niwa, T., Handa, T., Takeuchi, H., Iwamoto, T. and Itoh, Y., 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 (1989) 425–429.

Koenhen, D.M., Mulder, M.H.V. and Smolders, C.A., Phase separation phenomena during the formation of asymmetric membranes. *J. Appl. Polym. Sci.*, 21 (1977) 199–205.

Laakso, R., Kristoffersson, E. and Marlova, M., Bi-exponential first-order release kinetics of indomethacin from tablets containing polysorbate 80. *Int. J. Pharm.*, 19 (1984) 35–42.

Merkus, F.W.H.M., Drug intake and oesophageal injury. *Pharm. Int.* 1 (1980) II.

Okor, R.S., Effect of polymer cation content on certain film properties. *J. Pharm. Pharmacol.*, 34 (1982) 83–86.

Pongpaibul, Y., Price, J.C. and Whitworth, C.W., Preparation and evaluation of controlled release Indomethacin microspheres. *Drug Devel. Ind. Pharm.*, 10 (1984) 1597–1616.

Soehngen, E., Godin-Ostro, E., Fielder, F., Ginsberg, R., Slusher, M. and Weiner, A., Encapsulation of Indomethacin in liposomes provides protection against both gastric and intestinal ulceration when orally administered to rats. *Arthritis Rheum.*, 31 (1988) 414–422.

Yokoyama, Y., Nakamura, H and Shimizu, M., Gastrointestinal ulcerogenic activity of tolmetin sodium in rats in comparison with those of indomethacin and aspirin. *Chem. Pharm. Bull.*, 32 (1984) 4580–4584.