Scientia Pharmazeutica (Sci. Pharm.) **68**, 213–221 (2000)

Preparation of MFP Microspheres Using Polyacrylate Resins for the Therapy of Osteoporosis

A. Janka, B. Korsatko-Wabnegg, W. Korsatko*

Karl Franzens University Graz
Institute of Pharmaceutical Technology, Schubertstraße 6, 8010 Graz, Austria

ABSTRACT

Disodium Monofluorophoshate (MFP), a highly water soluble drug, was incorporated in polyacrylate resin microspheres by using the solvent-evaporation technique. The process is based on dispersing the acetone solution of the drug and the polymer in liquid paraffin. Eudragit RS 100 / S 100 in a 3:1 ratio turned out as the best coating material.
The influence of the main manufacturing factors, namely polymer-drug ratio, addition of magnesium stearate, size of the beads, production temperature and speed of stirring, on the technological characteristics of the microspheres, like release rate of the drug, shape, drug-loading and size of the particle were investigated. The findings resulted in a formulation, which obtains the desired controlled release of the drug in a convenient oral system.

Keywords: Disodium Monofluorophosphate, Osteoporosis, Solvent-evaporation technique, Controlled release, Drink suspension

INTRODUCTION

Osteoporosis is a disease whose time has come (1) and one of the most dangers of the next century for the human race with its increasing expectation of life. Fluoride preparations therefore are most potent drugs used as effective activators of the osteoblasts increasing axial bone mass and thus decreasing the vertebral fracture rate. Disodium Monofluorophosphate (MFP), as a source of fluoride, is well tolerated gastrointestinally, has a better bioavailability then NaF and can moreover be used concomitantly with calcium-containing medications or with calcium-rich alimentation. (2, 3, 4)
The purpose of the present study was to investigate controlled release microspheres using polyacrylates as core matrix for an oral drink-formulation, which ensures a good compliance by the patients.

RESULTS AND DISCUSSION

Influence of the polymer-drug ratio

Microspheres with a polymer-drug ratio of 4:1, 3:1, 2:1, 1,5:1 and 1:1 were prepared and the theoretical drug content was compared with the real content. Table 1 shows that with increasing drug content until 30% the loading efficiency is also increasing; whereas with a drug content from 30 to 50% the incorporation efficiency is decreasing. Thus the polymer-drug ratio of 2:1 was used for the further studies.

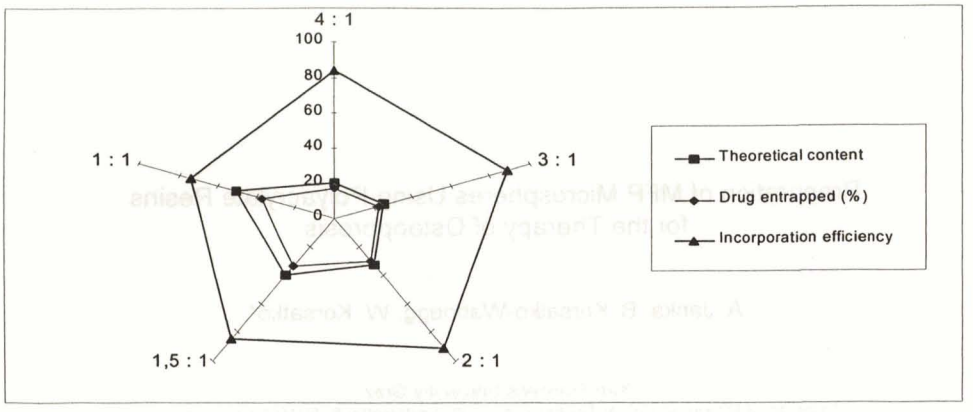


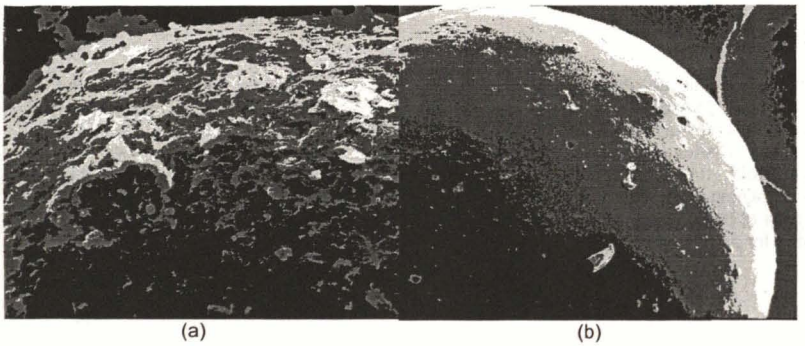
Fig. 1: Incorporation efficiency of several polymer drug ratios by a size fraction of 315-500 µm

Polymer : MFP ratio (w/w)	theoretical content (%)	drug entrapped (%)	Incorporation efficiency
4 : 1	20	16,7	83,5
3 : 1	25	22,0	88,0
2 : 1	33,3	30,1	90,4
1,5 : 1	40	33,8	84,5
1 : 1	50	36,7	73,4

Table 1: Values to Fig. 1

Influence of magnesium stearate

For the best findings the addition of 2,5%, 5%, 7,5%, 10%, 12,5% and 15% magnesium stearate was investigated. It could be shown that the increase of the magnesium stearate content until 12,5% caused favourable changes in the shape of the microspheres especially in higher concentrations. Figure 2 (b) shows the smooth surface of a MFP microsphere with 12,5% magnesium stearate compared to the surface of a MFP microsphere (a) with 5% magnesium stearate.



(a) (b)

Fig. 2: Scanning electron photographs of the surface of MFP Eudragit RS 100 / S 100 (3:1) microspheres containing (a) 5% and (b) 12,5% magnesium stearate

Influence of the stirring rate

For reaching the goal of this study, to get microspheres for a drink formulation with a size off 315 to 500 µm the influence of the stirring rate was detailly investigated. So the stirring rate was varied within a range of 250 to 400 rpm (RE 162, Janke and Kunkel, IKA-Werk, Germany). With increasing stirring speed the microsphere size decreased, like described previously (5) and due to these results a stirring rate of 400 rpm was used for the further investigations.

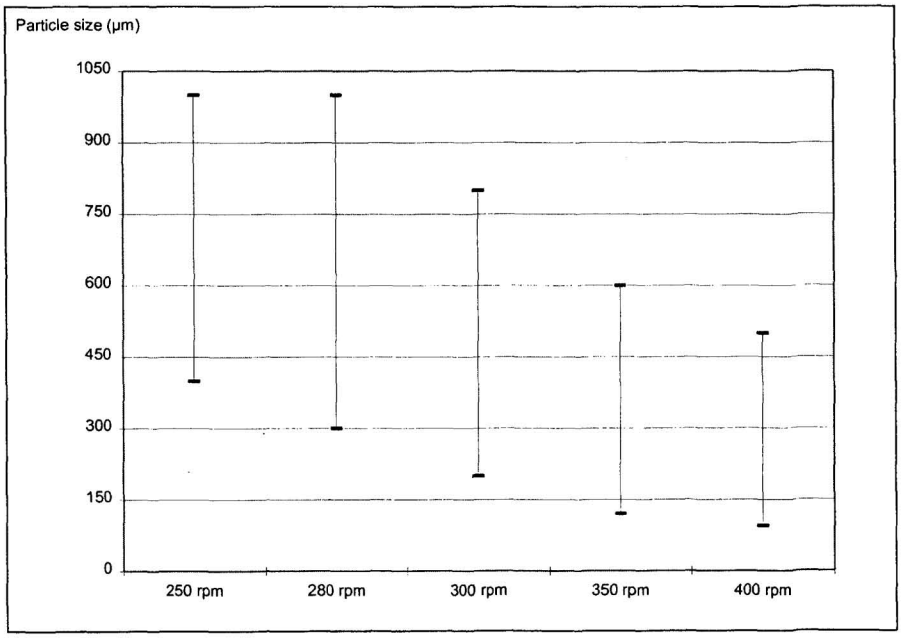


Fig. 3: Releation between stirring rate and particle size.

Influence of the product temperature

A change of product temperature between 0 and 40°C was investigated. We found out that within the range of 0 - 10°C and 18 - 30°C the quality of the microspheres became worse by changing their spherical form. Above a temperature of 30°C the evaporation of acetone occured too fast and the polymer conglomerated. So it could be demonstrated, that the optimal temperature for the production was located between 12 and 16°C, where a steady state between evaporation of the solvent and the building up of the wall matrix was provided.

Sieve analysis

Particle size distribution was determined as discribed previously. The results (Figure 4) showed a great conformity between the main manufacturing factors, which generated a good yield above 94,7%.

The partition of the microspheres came to 4% of a particle size from 200 to 315 µm, 30% from 315 to 500 µm, 45% from 500 to 800 µm and 21% from 800 to 1000 µm.

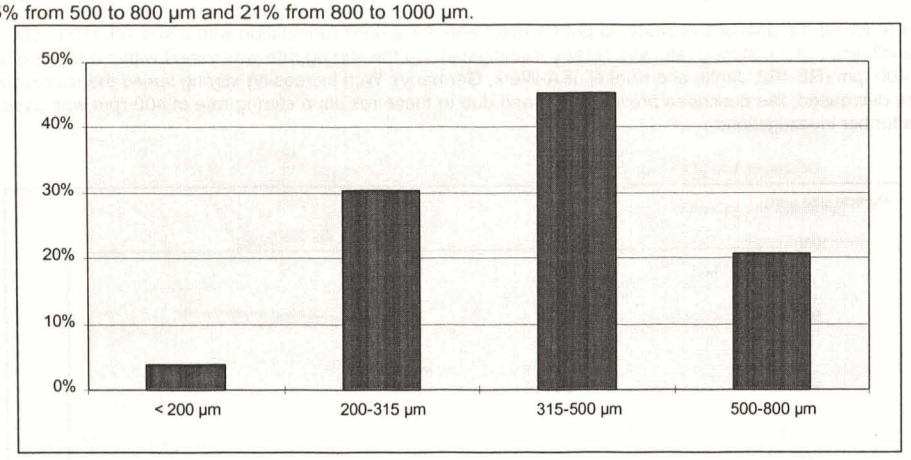


Fig. 4: Microsphere size distribution at 400 rpm

Scanning electron microscopy results

The surface characteristics were examined by means of a scanning electron microscope type 100 A from Leitz. Therefore all "theoretical" determinations described before, like the best polymer-drug ratio, the right share of magnesium stearate etc. were "visually" verified, which can clearly be seen in Figure 5. The microspheres show a regular, spherical shape without aggregation and a very smooth surface.

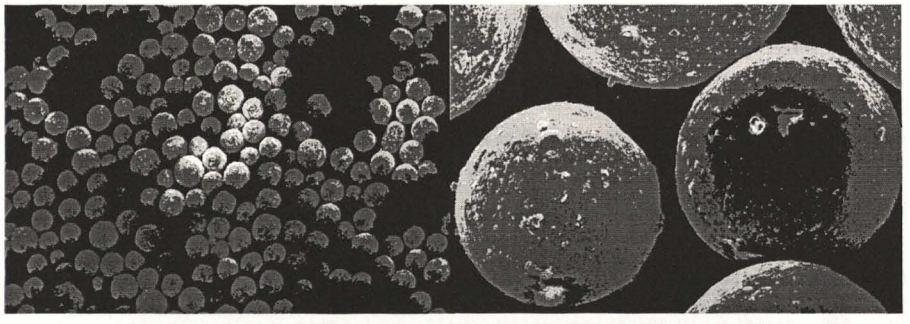


Fig. 5: SEM photographs of MFP Eudragit RS 100 / S 100 (3:1) microspheres, 20 and 100 fold

Release studies

Microspheres of different particle size were investigated for their release rate and the data were analysed according to different laws that can govern the release mechanism. Figures 6 (a), (b), (c) and (d) show dissolution curves of MFP microspheres with a particle diameter of 315 - 500 µm, 500 - 800 µm, 800 - 1000

µm and 1000 -2000 µm which are inversely related to the particle size. The drug release from microspheres with a particle diameter of 315 - 500 µm can be discribed by square root equations, microspheres with a particle diameter of 500 - 800 µm, 800 - 1000 µm and 1000 -2000 µm follow mainly zero-order (Figure 7). Table 2 shows the analysis of the data for the in vitro release of MFP from microspheres.

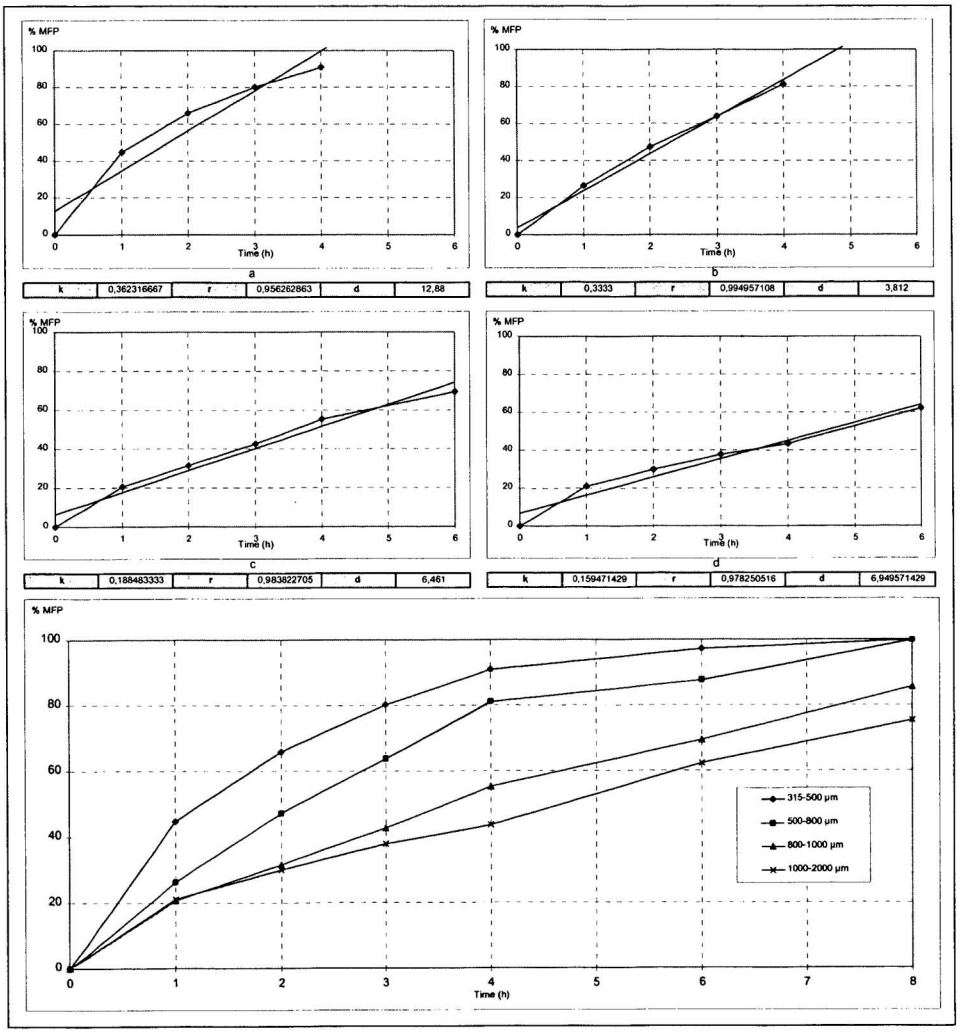


Fig. 6: In vitro release from Eudragit RS100 / S100 (3:1) microspheres with a MFP-content of a) 21,7%, b) 29,6%, c) 24,2%, d) 39 % and a particle size of a) 315-500 µm, b) 500-800 µm, c) 800-1000 µm, d) 1000-2000 µm in 750ml 0,1 N HCl + 250ml Na_3PO_4 buffer after 2 hours, 37°C;

Time (h)	1	2	3	4	6	8		
%	44,75	65,85	80,24	90,95	97,24	100		a
s(+/-) mg	6,86	54,36	6,24	11,24	6,24	13,59		315-500 µm
%	26,5	47,35	63,9	81,29	87,83	100		b
s(+/-) mg	16,56	33,72	35,95	40,53	17,36	15,59		500-800 µm
%	20,68	31,58	42,71	55,32	69,42	85,63	100	c
s(+/-) mg	1,17	3,91	5,6	1,19	1,12	0,82	2,47	800-1000 µm
%	21,09	29,97	37,85	43,58	62,3	75,35	100	d
s(+/-) mg	36,79	3,11	16,59	14,94	28,98	7,16	18,01	1000-2000 µm

Tab. 2: Values to Fig. 6

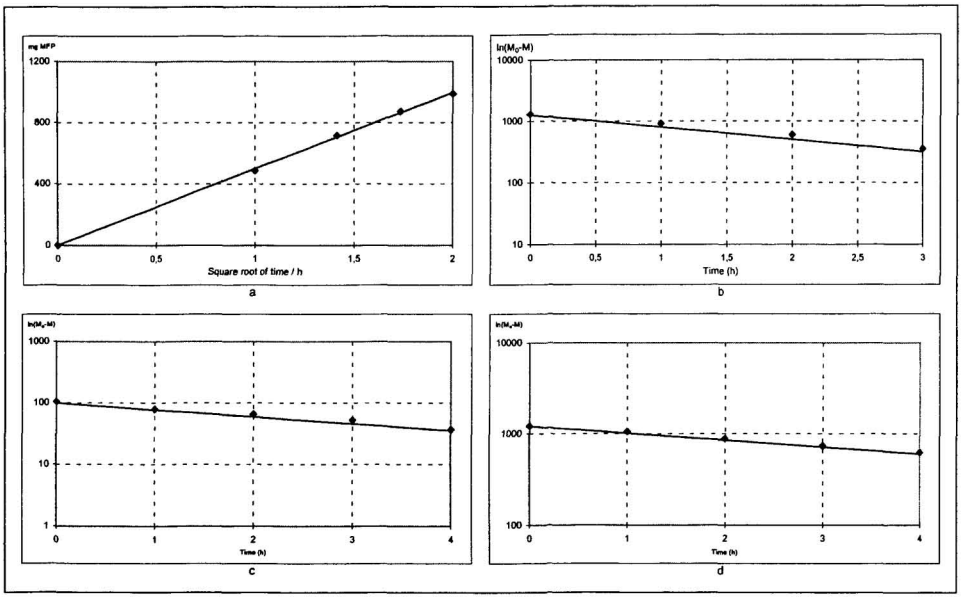


Fig. 7: Plots of MFP released from Eudragit RS100 / S100 (3:1) microspheres with a MFP-content of a) 21,7%, b) 29,6%, c) 24,2%, d) 39 % and a particle size of a) 315-500 µm, b) 500-800 µm, c) 800-1000 µm, d) 1000-2000 µm

CONCLUSIONS

Disodium monofluorophosphate, a highly water soluble and sensitive drug, could only be embedded by a special use of the solvent evaporation method, only by using Eudragit RS 100 / S 100 in a ratio of 3:1. The procedure gave satisfactory results considering size distribution, shapes of microspheres and release rates, which were manageable through the main manufacturing factors.
Finally a convenient oral system for the therapy of osteoporosis was developed in form of a drink suspension containing MFP microspheres, citric acid, calcium carbonate, anhydrous tricalcium citrate, sodium alginate and taste aroma.

EXPERIMENTAL PART

Materials

Eudragit RS 100, S 100 granules were obtained from Roehm Pharma, GmbH, Darmstadt, Germany; Alkaline phosphatase from bovine intestinal mucosa from Boehringer Mannheim, Germany; Disodium monofluorophosphate from Asta Medica, Austria; Other reagents were all of an analytical grade.

Methods

Preparation of the microspheres

Microspheres were prepared using a modification of the solvent evaparation method (6). 12,8 g Eudragit RS 100/S 100 (3:1) was completly dissolved in 160 ml acetone, then 1,6 g magnesium stearate and 6,4 g MFP were added. The dispersion was stirred at 5°C over 30 minutes at 400 rpm and 320 ml of cold liquid paraffin were poured slowly to the mixture. The speed was increased in order to obtain the desired particle size and during the next 12 hours the microspheres were formed after full evaporation of the acetone. They were seperated from the paraffin oil by filtration under vacuum and were washed several times with n-heptane.
Then the obtained microspheres were dried under vacuum at room temperature for 24 hours up to a constant weight.

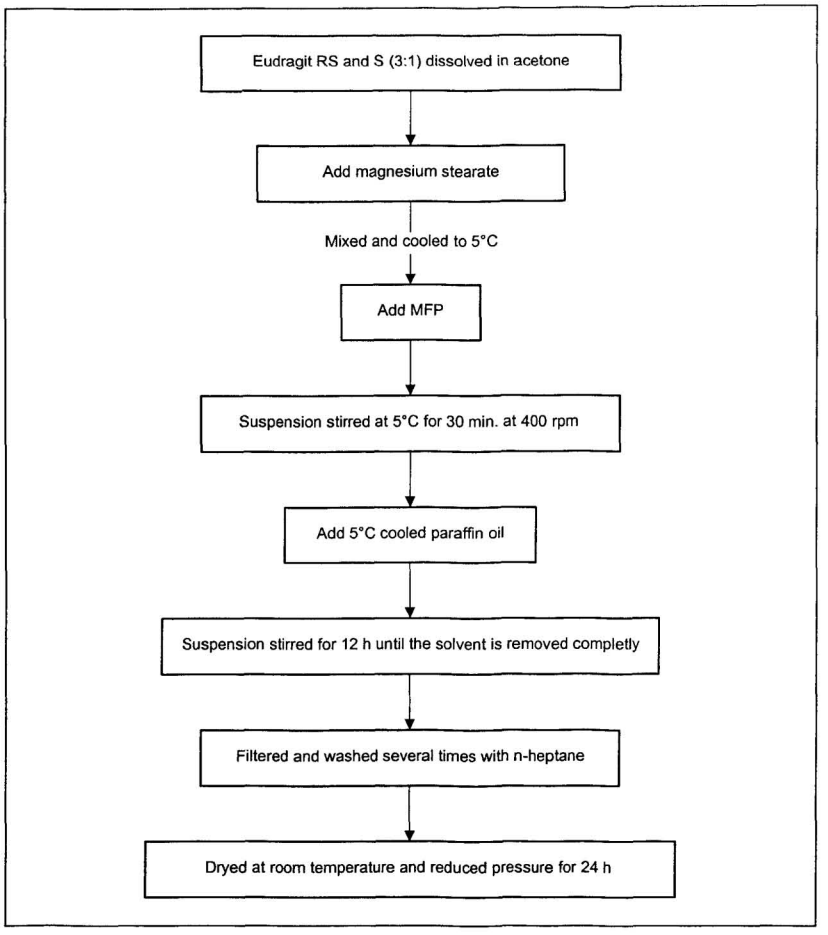


Fig. 8: Microspheres Preparation Scheme

Characterization of the microspheres

Determination of the microsphere size distribution
Microspheres size distribution was determined by passing through a set of standard sieves by Retsch, Germany with following mesh sizes: 1000, 800, 500, 315, 200 and 100 µm.

Determination of drug content in microspheres

The drug release from the microspheres was studied using the paddle method according to USP XXII. For each batch 5 g of microspheres containing approximately 1,8 g MFP were submitted to release in 750 ml

hydrochloric acid, (pH 1,5) at 37°C with 120 rpm for two hours. After this time 250 ml of a solution of Na_3PO_4 were added and the pH reached 6,8. Periodic samples (1ml) were determined for their drug contents and were immediately replaced with 1 ml of fresh dissolution medium equilibrated at 37°C. The determinations were performed with a specific fluoride ion-sensitive electrode and a reference calomel electrode (Microprocessor pMX 2000, WTW, Weilheim, Germany) by using alkaline phosphatase, glycin buffer and TISAB buffer. The total drug content was measured after dispersing the microspheres in an ultrasonics bath. The reported results were the average of 5 determinations.

Acknowledgement

The SEM-photographs were taken at the „Forschungsinstitut für Elektronenmikroskopie und Feinstrukturforschung", Technische Universität Graz.

REFERENCES

1. Riggs B.L., Melton L.J. (1988)
Osteoporosis: Etiology, Diagnosis and Managment
Raven Press, New York

2. Ericson Y. (1983)
Caries Res.17: 46.

3. Fuchs C., Heimann G., Tonn R. (1982)
Orthop. Praxis 18: 738.

4. Liote F., Bardin C., Liou A., Brouard A., Terrier J-L., Kuntz D. (1992)
Calcif. Tissue-Int. 50: 209.

5. Barkai A., Pathak Y., Benita S. (1990)
Drug Development and Industrial Pharmacy 16: 2069.

6. Pongpaibul A., Maruyama K.J. (1988)
Pharm. Pharmacol. 40: 530.

Corresponding author:

Univ. Prof. Mag. Dr. Werner Korsatko
Institut für Pharmazeutische Technologie
Schubertstraße 6
8010 Graz, Austria

Received March 10th, 2000
Accepted May 2nd, 2000