In Vitro and In Vivo Long Term Release of Apomorphine From Polymer Matrices

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ABSTRACT—Since apomorphine actually reveals high efficacy in treatment of Parkinson's disease but only has a very short half life, it is of only limited clinical significance. To overcome this substantial disadvantage, drug application by long term delivery systems could be one possibility. Based on this background, ethylene vinyl acetate polymeric delivery systems were manufactured that differed in size, with either coated or uncoated surfaces, but were similar in apomorphine loading. Release from uncoated polymeric delivery systems followed first order kinetics, whereas coated polymeric delivery systems showed within the first 40 days a period of first order kinetics release, in which the release rate is approximately half that of the uncoated polymeric delivery systems, followed by a zero order kinetics release for more than 130 days with a daily release rate of 3.1 ± 0.2 mg. In vivo release was investigated by determining plasma apomorphine concentrations after implanting polymeric delivery systems into the abdominal cavities of rats. Animals with uncoated polymeric delivery systems exhibited symptoms of an apomorphine overdose within 20 days after surgery. Using coated polymeric delivery systems, a steady state plasma concentration of 15 ng/ml was observed, which was maintained over a period of 130 days after an initial period of high plasma concentrations. Based on our results, it is concluded that polymeric delivery systems might be an appropriate method for applying apomorphine for the treatment of Parkinson's disease.

Keywords: Apomorphine, Ethylene vinyl acetate polymeric delivery system, Parkinson's disease, Kinetic study

Many chronic progressive diseases require a long term drug treatment which should ideally allow steady state plasma concentrations of the administered substance to be maintained. Regarding Parkinson's disease, many systems have been tested for continuous long term therapy with levodopa. Amongst these are oral slow release preparations, i.v.-infusions (1), implantable internal or external reservoir pumps (2) and the ALZET osmotic minipumps (3). Both pump polymeric delivery systems and infusion therapy are reliable for maintaining constant plasma concentrations, but they have not succeeded in becoming part of routine clinical practice due to their lack of practicability, safety and the short duration over which constant delivery can be maintained. Furthermore, drugs have to be solubilized in the reservoir, a process which limits their chemical and microbiological stability. Oral slow release preparations, on the other hand, are comfortable and compliant for patients since they can be provided on an outpatient basis (4–6). However, variations in plasma concentrations that occur due to their intermittent application represent the biggest disadvantage of this type of therapy.

A significant problem that arises during long term levodopa therapy of Parkinson's disease is that various adaptation processes renders it necessary to administer higher doses. Such problems seen after several years of treatment include choreatic hyperkinesias, "On-Off" periods and "end of dose" phenomena. About one in five patients will develop these complications (7). The "On-Off" periods appear to be one of several results of inconsistent levodopa plasma concentrations (8, 9). Hardie et al. (2) found that constant levodopa infusions was one method effective in reducing the frequency of such periods dramatically.

Another successful approach to Parkinson's therapy has been pharmacological treatment with dopamine agonists such as bromocriptine, pergolide or lisuride. Despite high clinical effectiveness, their routine use has been limited by their severe neuropsychiatric side effects. This led to clinical trials using the non selective D₁/D₂ agonist apomorphine, which was found to be effective in the treatment of Parkinson's disease (10). At 10%, the incidence of psychiatric side effects is considered rare compared to those

of other dopamine agonists (11). The main problem with apomorphine is its rapid clearance and short plasma half-life, which is estimated to be between 8 and 47 min (12–16).

Considering both the effective clinical response and the short plasma half-life of apomorphine, the only feasible means for administering apomorphine would appear to be a continuous application system. With this in mind, as well as the other outlined problems associated with currently available long term application devices, the aim of this study was to develop a slow release ethylene-vinyl-acetate polymer system that could be employed for in vitro and in vivo studies on the long term release of apomorphine and which could also show constant agent release from polymer matrices.

MATERIALS AND METHODS

Reagents and chemicals

Ethylene vinyl acetate (EVA) was purchased from DuPont (Wilmington, DE, USA) and apomorphine from Woelm-Pharma (Eschborn, Germany). All other chemicals (HPLC or analytical grade) were obtained either from Sigma (Deisenhofen, Germany) or Merck (Darmstadt, Germany).

Polymer matrix fabrication

First, crude EVA copolymer matrix was cleaned by Soxhlet extraction with acetone (56°C, 24 h). Acetone was evaporated from purified EVA polymer completely within 72 h at room temperature after which the purified polymer appeared transparent. The pure polymer was then dissolved in methylene chloride (25% weight/weight) at 37°C for 5 h before the powdered apomorphine was suspended (apomorphine/EVA-polymer, 3/1, w/w) in the solubilized polymer by thorough stirring for 5 h at 37°C. An apomorphine/EVA-polymer ratio of 3/1 was found to be optimal for our purposes. With higher ratios, fluctuations were found during the release, whereas with lower ratios, the release rate was too low to maintain a dosage of 10 mg/kg per day, which would be clinically effective in the treatment of Parkinson's disease (17). The mixture was cast into prepared disk-shaped moulds and immediately cooled down in methanol (–18°C, 30 s) and then liquid nitrogen for 15 s. It was necessary to follow this cooling sequence in order to avoid drug sedimentation as well as air inclusion in the polymer matrix. The organic solvent was evaporated over 5 days at –18°C and one day at room temperature. The polymeric delivery systems were weighed before and after evaporating. During this time, the devices lost about $48.3 \pm 0.58\%$ (mean $\pm$ S.E.M., $n=24$) of their weight. This indicated that they were free from methylene chloride since the ratio between the liquid and the solid phase was 1:1. Therefore, it was possible to calculate the exact amount

of apomorphine in each polymer. Polymeric delivery systems were then processed in one of the following manners: 1) The disc-shaped polymeric delivery systems were cut transversely into two semi-discs, which then had approximately half the volume and half the diffusion area of the original disc. 2) The polymeric delivery systems were left without further processing. 3) The raw slabs were coated with an impermeable polymer barrier so that only one side was left exposed, resulting in a 50% reduction of diffusion area while the volume remained unaltered.

Evaluation of in vitro release of apomorphine from polymer matrices

The polymeric delivery systems were shaken continuously in darkness in 200 ml saline containing 40 μ mol glutathione at room temperature. The incubation medium was changed daily for the first 50 days of incubation and every 3–4 days thereafter. Aliquots of the incubation medium were stored at –18°C until apomorphine analysis.

Kinetic studies with apomorphine

Rats (Sprague Dawley, male, about 350 g; Charles River, Kisslegg, Germany) were anesthetized with thiobutabarbital (100 mg/kg, i.p.) and artificially respired. Thereafter apomorphine (6.94 μ g/(kg·min)) was infused over a period of 5 h i.p. via a PE-50 catheter fixed. Blood samples (approximately 100 μ l) were obtained via a carotid catheter during the last 2 h of the infusion. Blood was stabilized by adding 50 μ l glutathione (200 mM) and centrifuged to provide serum, which was stored at –80°C until analysis.

Evaluation of in vivo apomorphine release from polymer matrices

Sprague Dawley rats (male, weight 300–400 g; Charles River) were housed individually at room temperature with a 12 h photoperiod. Animals received a standard diet and tap water ad libitum. For polymer implantation, the abdomen was opened under chloralhydrate anesthesia (0.4 mg/g body weight, i.p.) with a median cut along the linea alba. The polymer was then implanted into the abdominal cavity. After surgery, rats were kept in cages on wiremeshes to prevent obstipation which occurred as a result of the distinct gnawing reflex induced by apomorphine. All rats recovered from anesthesia within 2 h and the wounds healed in a couple of days without any complications. Venous blood (approximately 100 μ l) was collected from tail veins and stabilized by adding 50 μ l glutathione (200 mM). After centrifugation, plasma was immediately frozen at –18°C until analysis. Brains of rats that died in the early phase of the study were removed, snapfrozen in liquid nitrogen and stored at –80°C until analysis.

Analysis of apomorphine

Aqueous *in vitro* samples were injected directly into the HPLC-system after dilution with incubation solution. For determination of plasma samples, 50 μ l boldine (2 μ g/ml) was added to 500 μ l plasma. Samples were then alkalinated using 150 μ l TRIS-buffer (0.2 M, pH 9.0). Apomorphine was extracted by adding 5 ml chloroform, shaking (20 min) and centrifugation (6 min, 4,500 $\times$ g). The aqueous layer was discarded and apomorphine was back-extracted from the chloroform into 300 μ l 0.2 M acetic acid (shaking and centrifugation as above). A 100 μ l sample of the aqueous layer was injected into the HPLC-system. Rat brains, which had been frozen at -80°C , were coarsely cut, suspended in buffer (50 mM monosodium phosphate, 0.1% Triton X100, 50 mM glutathione, pH 7.4, containing boldine (100 ng/ml) at 1/4, w/v, and homogenized with a tissue homogenizer (teflon/glas: 1000 rpm, 8–10 strokes, 1 min, 4°C). After centrifugation of the homogenate (10 min, 4,500 $\times$ g) apomorphine was extracted and re-extracted in the same manner as described above. Apomorphine was quantified by RP-HPLC with UV detection at $\lambda = 279$ nm. Separation was achieved with a Nova-Pak[®] C18 reversed phase column (3.9 $\times$ 15 mm, 4 μ m; Water GmbH, Eschborn, Germany). The mobile phase was a mixture of 50 mM monosodium phosphate containing 5% (v/v) acetonitrile and tetrabutyl-ammonium-hydrogensulfate (4.4 $\times 10^{-3}$ M) and adjusted to pH 3.5. The flow rate was set at 1 ml/min. Apomorphine and boldine were eluted from column with retention times of 5.9 and 7.7 min, respectively. The peaks were clearly baseline separated and distant from two other unknown peaks in plasma and tissues (retention time: 3.5 and 4.2 min, respectively), which were suspected to be degradation products of apomorphine. The concentrations of apomorphine were calculated with reference to the peak height of external standards by the method of internal standardization. The linearity of recovery was determined for a range of 10 ng/ml to 250 ng/ml plasma and for a range of 50 ng/g to 1000 ng/g brain wet

weight: The correlation coefficients were 0.991 and 0.997, and the recoveries 71% and 86%, respectively. The detection limit was 5 ng/ml plasma and 20 ng/g brain wet weight.

RESULTS

Polymer fabrication

For studying the long term release of apomorphine a number of polymeric delivery systems were manufactured and divided into 3 subclasses which differed in size, surface and weight, but not in apomorphine content. An overview of their geometric characteristics is given in Table 1. The polymeric delivery systems of group 1 and 3 showed the same exposed area from which the apomorphine effused, but they differed in their surface areas of release. The polymeric delivery systems of group 1 were uncoated, thus allowing release from all surfaces, whereas the polymeric delivery systems of group 3 were coated with an impermeable polymer coat so that release could only occur from the top surface.

In vitro release of apomorphine from polymeric delivery systems

Polymeric delivery systems with an uncoated surface released apomorphine according to monoexponential kinetics irrespective of their size until the polymeric delivery systems were depleted (Fig. 1). Variations in the absolute amounts released from the polymeric delivery systems were high. The total average amounts released were 499 mg (range: 397–644 mg, about 60% of loading dose) for the uncoated half discs (group 1) and 1360 mg (range: 1005–1702 mg, about 73% of the loading dose) for the uncoated whole discs (group 2). The released amounts of apomorphine from group 1 polymeric delivery systems were approximately 37% of those from group 2 polymeric delivery systems, indicating a correlation between the release rate and size of diffusion area. Half time constants of apomor-

Table 1. Geometric characteristics of various devices

Group	1	2	3
Geometric form	half disc no coat	disc no coat	disc bottom and side walls coated, top open
Diffusion area (cm ²)	5.43	10.86	5.43
Diameter (mm)	26.3	26.3	26.3
Weight (g)	1.2 $\pm$ 0.04	2.5 $\pm$ 0.37	2.0 $\pm$ 0.04
height (mm)	3.3–4.1	3.3–4.1	3.3–4.1
Loading (% w/w, drug/EVA)	75	75	75

Apomorphine was suspended in EVA (ethylene vinyl acetate) copolymer matrix, which had been cleaned by Soxhlet extraction and dissolved in methylene chloride. After casting the mixture into disk shaped moulds and cooling down immediately, the organic solvent was evaporated. Some raw slabs were coated with an impermeable polymer barrier so that only one side left exposed.

Fig. 1. Cumulative in vitro release of apomorphine (mean, $n=3$) from uncoated (group 1: half disc, ∇ ; group 2: disc, $\square$) and coated (group 3: disc, $\circ$) ethylene vinyl acetate polymeric delivery systems loaded with apomorphine (apomorphine/EVA, 3/1, w/w). Polymeric delivery systems were shaken in saline within 167 days. Incubation medium was changed regularly and apomorphine was determined by HPLC and UV-detection. The release of apomorphine from group 1 (∇) and 2 ($\square$) polymeric delivery systems followed first order kinetics until the polymeric delivery systems were depleted. The cumulative in vitro release of apomorphine (mean, $n=3$) from coated polymeric delivery systems (group 3, $\circ$) followed zero order kinetics after an initial burst phase of about 20 days. The study was terminated after 167 days. At that time release rates still amounted to about 3.1 mg apomorphine daily.

phine release calculated by non-linear curve fitting were 12.1 days for the uncoated discs ($R=0.99$) and 16.2 days for the uncoated half shape discs ($R=0.99$).

Coated polymeric delivery systems initially showed a rapid release over the first 40 days, which corresponded to a rate of 26.1 ± 4.8 mg per day and followed first order kinetics. Later on apomorphine was released by zero-order kinetics until the study was terminated at 167 days (Fig. 1). The release rates during this constant phase of apomorphine release were calculated by linear regression to be 3.1 ± 0.2 mg per day. Kinetic studies on these polymeric delivery systems were terminated before they were exhausted of drug. As such, it was not possible to describe the last phase of the curve and thereby the total yield. However, when the experiment was terminated, $73 \pm 5.9\%$ of the total apomorphine had been released. This was similar to the yields observed with the uncoated whole disc polymeric delivery systems.

Polymeric delivery systems were also examined at different phases of the study by electron microscopy. The electron micrographs shown in Fig. 2 (A and B) were taken before and at the end of the in vitro study, respectively. Before apomorphine was released, the drug crystals were embedded within the polymer matrix, whereas after release, the polymer matrix had become interlaced with pores and

channels through which the saline had penetrated and dissolved the apomorphine crystals. Only a few crystals with differing dimensions remained due to the fact that these were totally enclosed by the EVA polymer. In Fig. 2C, a coated polymer is depicted: it can be seen clearly that coating inhibits drug diffusion since no pores extend through the coat so that release is only possible from one side. After 160 days, there is a clearly visible line separating the area with pores and channels from the area where no diffusion had occurred and the apomorphine crystals had remained intact.

Pharmacokinetic studies with apomorphine

In order to simulate release of apomorphine from polymeric delivery systems and to monitor the corresponding plasma concentrations, apomorphine ($6.94 \mu\text{g}/(\text{kg} \cdot \text{min})$) was infused i.p. 3 h before and over the 2-h period of blood sample collection. As seen in Fig. 3, apomorphine concentrations reached a steady state of approximately 75 ± 45 ng/ml (mean $\pm$ S.D.). It can therefore be concluded that intraperitoneal implantation provides an appropriate means to facilitate a fast absorption of the drug after its release from the polymer matrix.

In vivo release of apomorphine

Three groups were investigated and in each group, a total of 5 rats was operated upon. Only one rat in group 1 (half disc, no coat) survived until the end of the study. The others died within the first 20 days after surgery. After an initial phase of 20 days with high plasma concentrations of apomorphine, the surviving rat reached a relatively short lasting steady state of 8 ng/ml for about 60 days. Moreover, since apomorphine plasma concentrations were stable within 60 days, it is suggested that apomorphine reached an equilibrium between the free and plasma-protein-bound part. A decline in plasma concentration was observed from day 80 until the release had ceased. In all of the deceased rats, an equilibrium between invasion and effusion was not reached at the time of death, which lead to severe fluctuations in plasma concentrations. All 5 rats in which group 2 polymeric delivery systems (disc, no coat) were implanted died within the first days after implantation. The initial plasma concentrations of these rats varied between 59 and 205 ng/ml, but steady state concentrations were not reached at the time of death. Apomorphine concentrations in the brains of 3 of those rats were 970 ng/g (mean, range 351–1408 ng/g) and therefore 6.2-fold higher compared to plasma concentrations measured in the same animals (Fig. 4). Two of the rats in which group 3 (disc, coated) polymeric delivery systems had been implanted died in the initial phase of the study, whereas the others survived through to the end. The gnawing reflex (a stereotypical reaction of rats undergoing dopaminergic stimulation) was

Fig. 2. Electron micrograph pictures of an uncoated apomorphine device before (A) and after (B) incubation and of a coated polymer during in vitro release (C). In picture A (enlargement: $\times 263$, scale: one bar indicates 0.1 mm), crystals of apomorphine that are embedded within the polymer matrix (A, see white arrow) are clearly visible. Picture B (enlargement: $\times 263$, scale: one bar indicates 0.1 mm) shows mainly pores and interconnecting channels that remained after dissolution of the apomorphine (white arrow). Only a few crystals with different sizes are left that are not accessible to the dissolving medium. In picture C (enlargement: $\times 17.2$, scale: one bar indicates 1 mm), the impermeable coat (indicated by arrow 1) is visible at the side and at the bottom. The diffusion line (see arrow 2) separates the polymer into 2 parts: on the bottom side, the drug crystals are still embedded into the polymer matrix, whereas the top side of the polymer is criss-crossed by pores and interconnecting channels.

Fig. 3. Steady state plasma concentration of apomorphine of 3 rats (rat 1: ●, rat 2: ■, rat 3: ▲, mean: solid line) after an intraperitoneal apomorphine infusion ($6.94 \mu\text{g}/(\text{kg} \cdot \text{min})$) within 5 h. Blood was withdrawn from the carotid artery within the last 2 h of infusion. Apomorphine was determined in plasma samples with HPLC and UV detection after extraction/back extraction into chloroform/acetic acid.

well developed after surgery, but it decreased over time. In the 3 surviving rats, an initial phase of drug release was shown, followed by constant plasma concentrations of

Fig. 4. Comparison between apomorphine concentrations in brains and blood of rats which died in an early phase of the study. The concentration in tissue was on average 6.2-fold higher than in plasma. Apomorphine was determined in plasma and tissue by HPLC/UV after extraction into chloroform and reextraction into acetic acid.

apomorphine for at least 130 days. The mean steady state concentration was approximately 15 ng/ml (mean, $n = 3$; Fig. 5). Due to the apomorphine HPLC-assay in which apomorphine not bound to serum protein and no metabolites were determined, we did not have to consider any protein binding (about 90%, ref. 18) for any pharmacological statements. The decline of apomorphine concentration in

Fig. 5. Plasma concentrations of apomorphine after implantation of polymeric delivery systems (disc, coated) into rats (rat A: ●, rat B: ■, rat C: ▲, mean: solid line). Apomorphine was determined in plasma samples with HPLC and UV detection after extraction/back extraction into chloroform/acetic acid. After an initial burst phase, a long phase with a constant steady state plasma concentration of about 15 ng/ml was reached after 130 days, lasting until the study was terminated. The decline of plasma concentration in rat B at day 137 was due to an inflammatory encapsulation of the polymer, which was confirmed at the end of the study.

rat B was due to an inflammatory response, as confirmed by post-mortem studies.

DISCUSSION

The use of ethylene-vinyl-acetate copolymers as polymeric delivery systems for administering long term drug therapy was demonstrated first in the 70's (19) and taken up by Rhine et al. (20) and Freese et al. (21). When using this approach, the agent is embedded in the polymer matrix and solubilization proceeds at the polymer surface and continues into central polymer areas. For continuous and constant delivery of drug, a homogeneous distribution of the drug in the matrix must be achieved. The presumed release mechanism (22), as well as the homogeneous distribution were both confirmed by electron microscopy (Fig. 2). About 30% of the total apomorphine could not be recovered despite the fact that the release was observed to cease. This was due to occlusion of the drug from the solvent brought about by embedding dry crystals in the pre-existing polymer. The occluded fraction of the pharmaceutical agent increases as the relative polymer loading is reduced (20). Several other physical parameters influence release rate including diffusion area, solubility, the size of the embedded drug crystals, and drug loading (20, 23). Preliminary studies showed that a 75% drug loading was optimal.

Only coated polymeric delivery systems seem to be of

therapeutical value since they were the only devices that displayed zero order kinetics for drug release. The release of apomorphine in this phase corresponds to a daily rate of 3.1 ± 0.2 mg per day after an initial high rapid release phase. Although the total amounts of apomorphine released over the complete course of the in vitro studies on these polymeric delivery systems varied, the daily release rates in the 130 days lasting phase of zero-order kinetics were much more consistent with one another. One could propose that the surface of drug crystals accessible to medium remains constant over the whole incubation time while the diffusion distance increases, thus leading to a zero-order kinetic release. When the period of constant release had ensued, about 40 days after implantation, around half of the total embedded apomorphine had been released. The particularly high initial release rates may have been more dependent on factors such as very short diffusion distances. Rhine et al. (20) also described three release phases: 1) a burst phase of rapid release, 2) a phase of linear release, 3) a final period in which the polymer slowly depletes and the release tapers off until it ceases completely. Our results show clear evidence of the first two phases reported by Rhine et al. (20). The third phase could not be confirmed in our in vitro study, since the experiments were terminated too early.

In contrast to the coated polymeric delivery systems, uncoated polymeric devices showed first-order kinetics for apomorphine release consistent with models incorporating a decreasing diffusion area in their explanations. Since the apomorphine is dissolved from all sides, the volume of polymer occupied by the drug in the rigid matrix would shrink. Hence the release rate would be dependent both on changing diffusion areas and distances.

The principles of apomorphine release established in vitro were confirmed in vivo. Only after implantation of one-side-coated devices, a long lasting steady state plasma concentration of 15 ng/ml could be achieved (Fig. 5). Initial higher plasma concentrations (60 ng/ml) decline after about 15 days to steady state concentrations. Interindividual variations in plasma concentrations observed in both the pharmacokinetic and in vivo studies were most likely due to differences in individual resorption capacities, as suggested by Ganther et al. (24). One explanation for the large differences between the initial and steady state plasma concentrations may be the rapid and still lasting burst release according to the release phase 1 of Rhine et al. (20) for a period of about 15–20 days, although devices were washed some days before implantation. Indeed, many rats suffered symptoms of overdosage (i.e., gnawing reflex) during the first days of the study, especially in the groups receiving uncoated polymeric delivery systems. On the other hand, enzyme induction could be a second explanation for the decline in plasma concentrations which is sup-

ported by following results: stable plasma concentrations of 75 ng/ml were observed after i.p. infusions at 6.94 $\mu\text{g}/(\text{kg} \cdot \text{min})$ over 5 h (total apomorphine within infusion time amounts to 730 μg). Based on this, presumed daily doses of 3.5 mg are quite similar to the 3.1 mg release observed from one-side-coated devices over 24 h in vitro. Assuming comparable pharmacokinetics for i.p. infusion and polymer implantation, and no enzyme induction, the release of 3.1 mg per day from devices should result in plasma concentrations of approximately 66 ng/ml ($= (3.1 / 3.5) \times 75 \text{ ng/ml}$), which correspond to initial plasma concentrations observed directly after implantation (60 ng/ml). Therefore, it is suggested that high initial release reflects steady state release from devices and that lower concentrations observed after 15 days results from an enzymatic breakdown due to enzyme induction. Less frequent cataleptic reactions such as the gnawing reflex within time support this hypothesis. However, changes in behavior may also be attributed to a down regulation of central D_2 -receptors.

The about sixfold apomorphine concentrations in brains of rats dying within the first days after polymer implantation compared to their corresponding plasma concentrations confirmed the effective penetration of apomorphine into the brain (11, 16).

In the treatment of Parkinson's disease, apomorphine is not a substitute but a supplement to levodopa. This might delay the onset of the severe side effects that are a hallmark of levodopa therapy. Progression of the disease might also be delayed since dopamine turnover in the nigral neurons is thought to be one of the major etiological factors for selective cell death in the substantia nigra (25), and externally applied levodopa accelerates this process. Whether apomorphine administration through use of polymeric delivery systems is of benefit towards the therapy of Parkinsonism cannot be answered and was not in any case a goal of the study. Finding a suitable dose of apomorphine for therapeutic use is difficult since there are large differences in individual responses to apomorphine treatment (26–30). Gancher et al. (31) estimated the minimal effective plasma concentration to be 13.1 ng/ml. The plasma concentration of 15 ng/ml reported here is just above the therapeutic minimum, but the absolute release rates of about 3.1 mg per day are far below the doses required for human therapy. Applications from other studies range between 15 and 207 mg per day (17, 26, 28, 30, 32, 33). Both an increased rate and prolongation of release could be achieved by increasing diffusion area, overall size and drug loading. In this study, the size of the object that could be implanted into the rat's peritoneum was obviously limited. Furthermore, it is envisaged that implantation of polymeric delivery systems would be most effective locally near the substantia nigra where the pathophysiological deficit of dopa-

mine occurs. This would minimize the release requirements of the devices, since the distribution volume would be reduced and the released apomorphine would be relatively unavailable for undergoing systemic metabolism or inducing side effects. In summary, our data show that with the help of EVA polymeric delivery systems, a constant apomorphine delivery of 3.1 mg per day could be provided and that plasma concentrations achieved were in the range required for the treatment of Parkinson's disease.

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