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RESEARCH PAPER

Simultaneous In Vitro Release of Levodopa and Carbidopa from Biocompatible Core-in-Cup Implants

M. P. Danckwerts[1] and J. G. van der Watt[2]

[1]*Department of Pharmacy, Medical School, University of the Witwatersrand, 7 York Road, Parktown 2193, Johannesburg, Republic of South Africa*
[2]*School of Pharmacy, Potchefstroom University for Christian Higher Education, Potchefstroom, Republic of South Africa*

ABSTRACT

Most implantable drug delivery systems do not release drug at a zero-order rate of release due to their geometry of a decreasing releasing surface. Microcapsules which can release drug at a zero-order rate are very difficult to produce and are prone to dose dumping. The purpose of this study was to test the in vitro release of levodopa and carbidopa from a new core-in-cup bioerodible implantable tablet. Core-in-cup implantable tablets with cups of Resomer® 207, and cores of Resomer RG 746 and Resomer RG 858 were tested. The core-in-cup implantable tablets were tested as to whether they released levodopa or carbidopa at a zero-order rate. Their rate and extent of erosion in normal saline were also examined. The results indicate that levodopa and carbidopa were released at a zero-order rate in vitro for up to 100 days depending on the inherent viscosity of the polymer used in the core of the implant. It was also found that the rate and extent of erosion of the cup portion of the core-in-cup implantable tablet did not adversely affect the zero-order release of the drugs.

INTRODUCTION

The inability to transfer drugs at a controlled or constant rate to various sectors in the brain is a predominant problem in the treatment of many neurological disorders. This is due to the presence of the blood–brain barrier, which obstructs the passage of many substances from blood plasma into the brain (1).

Biocompatible polymeric matrix systems have been developed to overcome this difficulty (2,3). The polymeric implants permit the sustained and localized release of neuroactive substances into the brain. More recently,

microcapsules that can be injected simultaneously have also been developed (4). These, unfortunately, are very difficult to produce on a commercial basis and are prone to dose dumping. Another problem with injectable microcapsules is that as the dosage required increases to more than 100 mg, the mass of microcapsules becomes extremely large. This is due to the fact that it is very difficult to load microcapsules with more than 20% m/m active drug and then screen the microcapsules within an acceptable particle size range.

The purpose of this study was to produce a simple implantable system that permits the localized release of levodopa and carbidopa concurrently at a controlled rate over a period of 1 to 2 months. The kinetics of drug release from the core-in-cup implantable implants were examined as to how well the rate of release fits the Korsmeyer et al. (5) relationship depicted in Eq. (1):

$$\frac{M_t}{M_\infty} = k \cdot t^n \tag{1}$$

where $M_t M_\infty$ is the fractional release of the drug, t is the release time, k is a constant incorporating structural and geometric characteristics of the release device, and n is the time exponent indicative of the mechanism of release. For example, $n = 0.5$ for square root of time kinetics and $n = 1.0$ for zero-order kinetics.

MATERIALS

Levodopa and carbidopa were supplied by Logos Pharmaceuticals, S.A., Resomer® RG 756 (inherent viscosity of approximately 0.8), Resomer® RG 858 (inherent viscosity of approximately 1.4), and Resomer® L 207 (inherent viscosity of approximately 1.6) were supplied by Boehringer Ingelheim KG, Germany. The methanol was high-performance liquid chromatography (HPLC) grade and all other ingredients were standard laboratory grade.

METHODS

Implant Production

Core-in-cup implantable tablets were produced as previously described (6). Figure 1 graphically describes such a core-in-cup tablet.

Flat, disk-shaped tablets (cores) were made consisting of 50 mg levodopa and 12.5 mg carbidopa in Resomer RG 756 [poly(D,L-lactide-*co*-glycolide, in the ratio of 75:25], or Resomer RG 858 [poly(D,L-lactide-*co*-glycolide, in the ratio of 85:15]. A total of 20 g of each combination was prepared. The levodopa, carbidopa, and Resomer were thoroughly mixed and granulated in an Erweka FGS granulator fitted with a 1-mm stainless steel screen. Methylene chloride in chloroform, 10% v/v as a fine spray, was used as granulating agent. The cores were compressed in the tableting press to a thickness of 4 mm and a diameter of 7 mm using an adjustable cup punch as described before (7).

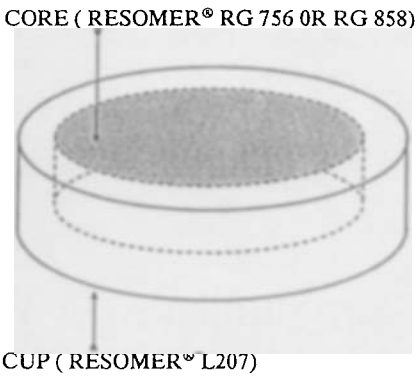

Figure 1. Schematic diagram of the core-in-cup implantable tablet.

The cups were compressed directly using the granular Resomer L 207 as supplied. Cores without cups were also tested in this study. The final core-in-cup tablets were compressed to an approximate hardness of 40 N/m^2.

In Vitro Release Studies

To determine the rate of release of the levodopa and carbidopa from the core-in-cup and core-only polymer implants, quadruplicates of each implant tablet were placed in 10-cm^3 sealed polytops containing 7 ml of 0.9% w/v saline solution with 0.2% w/v EDTA 0.2% w/v sodium metabisulfite as antioxidant. Nitrogen gas was immediately bubbled through the solutions and the polytops were firmly sealed. The solutions were then incubated at 37.5°C in a hot air oven. At various time intervals 1 ml of solution was withdrawn from each sample, 1 ml 0.1% w/v caffeine (internal standard) in 0.5% w/v EDTA aqueous solution was added, and the in vitro release of levodopa and carbidopa was monitored via HPLC analysis. Each time a sample was with-

drawn, the implants were placed in fresh release medium that was previously heated to 37.5°C, and again nitrogen gas was bubbled through the solution. The compounds were separated on a 15-cm Beckman ultrasphere ODS 5-μm column connected to a Beckman System Gold HPLC consisting of a 126 programmable solvent module and 168 diode array detector module. Analytical wavelength was set at 280 nm. The mobile phase was perfused through the column at 2 ml/min and consisted of 90% v/v citrate buffer (pH = 1.5) with 0.5% w/v EDTA added and 10% v/v methanol. Chromatograms for levodopa, carbidopa, and caffeine (internal standard) were completed within 17 min. Quantification of levodopa and carbidopa levels was based on comparison to standard solution curves.

Erosion Rate Studies

In order to determine the rate of erosion of the core-in-cup tablets, separate batches of tablets containing the exact same composition as those studied in the release rate study were weighed at 14-day intervals. At each interval, the tablets were removed from the saline solution, blotted dry with blotting paper, and dried overnight at 37°C before being weighed. After weighing they were then replaced in the saline solution for a further 14 days. To assess the erosion of the cup portion of the core-in-cup tablet, the thickness of the tablet from the middle of the exposed core to the bottom of the cup portion of the tablet was measured as a ratio of the thickness of the cup. The core-in-cup tablets were also visibly inspected to see if the erosion was even over the exposed surface of the tablet. All measurements were made to the nearest tenth of a millimeter.

RESULTS

In Vitro Release

Figures 2 and 3 show the cumulative in vitro release of levodopa (Fig. 2) and carbidopa (Fig. 3) from the various core-in-cup and core-only implantable tablets. Table 1 shows the release exponents (n) of the release rates as calculated by the Korsmeyer et al. model for levodopa and carbidopa from each formulation.

The results in Table 1 clearly indicate that the core-in-cup formulations release levodopa and carbidopa at a near zero-order rate as compared to the core-only formulations ($n = \pm 1.0$). The core-only formulations released levodopa and carbidopa at a rate that was most consistent with the square root of time model ($n = \pm 0.5$). When considering the effect of the different Resomer polymers on the release rate of levodopa and carbidopa from the core-in-cup implants, there was a difference between the RG 756 and RG 858 polymers used as cores in the formulations. The RG 858 polymer released levodopa and carbidopa at a slightly slower rate than the RG 756. Therefore, it is possible for one to manipulate the viscosity of the polymer used as well as possibly the hardness of compression, thus controlling the rate of delivery of the drug from the core-in-cup implants. The calculated release of levodopa and

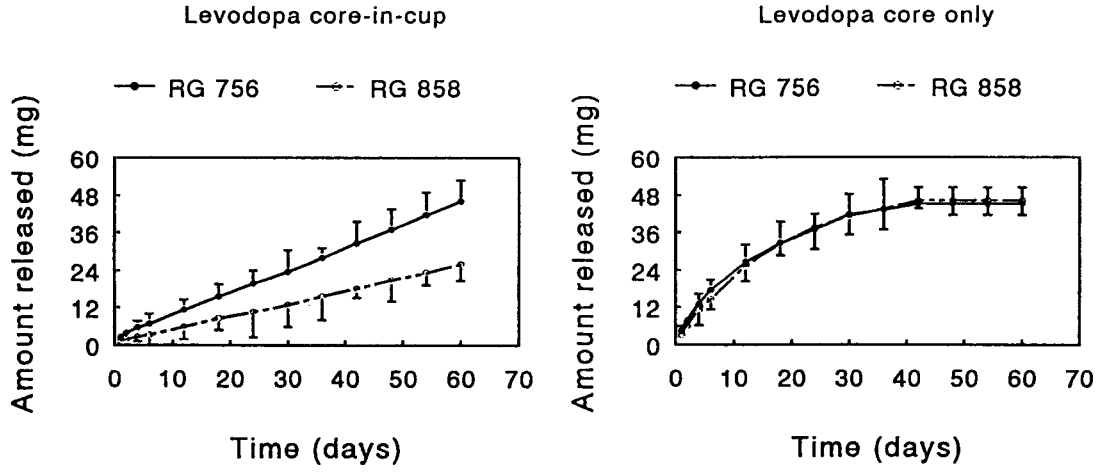

Figure 2. Release of levodopa from the core-in-cup and core-only implants.

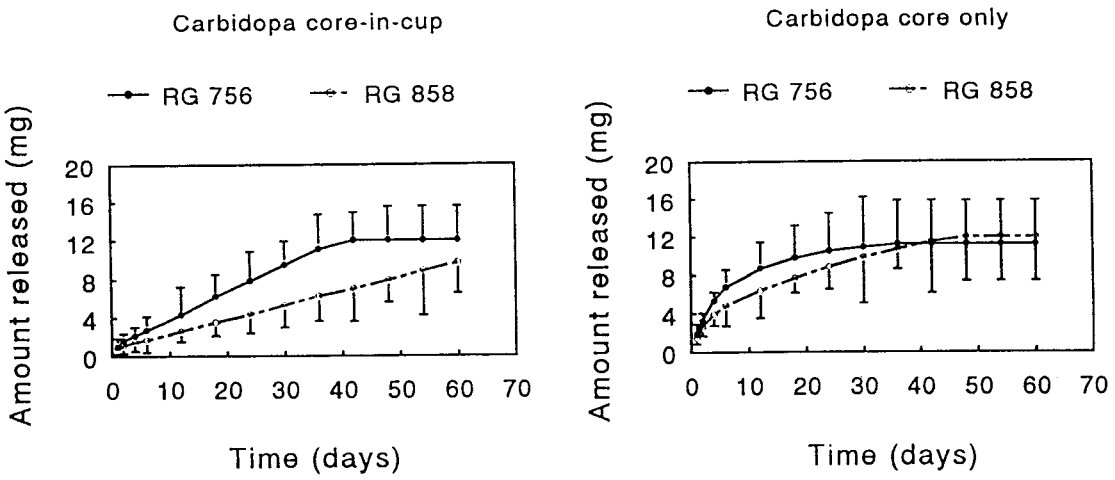

Figure 3. Release of carbidopa from the core-in-cup and core-only implants.

carbidopa from the Resomer RG 858 is approximately 100 days (this is calculated from the zero-order rate of release data obtained from the results once the initial burst rate has been subtracted).

There is, however, a limit to the viscosity of the Resomer used for the compressed core, due to the fact that Resomer polymers above an inherent viscosity of 7 are not compressible, as most of the combinations are in their rubbery state. Levodopa and carbidopa were released at very similar rates from all the formulations tested, thereby making it possible to combine levodopa and carbidopa in a sustained-release implant.

Table 1

Release Exponents and Correlation Coefficients of Fitted Models of Levodopa and Carbidopa from the Different Formulations

Formulation	Release Exponent $n \pm SD$ ($n = 4$)
Levodopa	
Resomer RG 756/Resomer L 207	0.9832 ± 0.0160
Resomer RG 756	0.5324 ± 0.0588
Resomer RG 858/Resomer L 207	1.0203 ± 0.0142
Resomer RG 858	0.7241 ± 0.0252
Carbidopa	
Resomer RG 756/Resomer L 207	0.9843 ± 0.0431
Resomer RG 756	0.5374 ± 0.0459
Resomer RG 858/Resomer L 207	1.0052 ± 0.0286
Resomer RG 858	0.8598 ± 0.0372

Erosion Rate

Table 2 shows the results of the erosion rate testing of the core-in-cup formulations. The cores of the core-in-cup tablets eroded in a log-linear fashion from both the polymers used in the core. The cup portion of the core-in-cup tablets eroded at a much slower rate than the core portion of the implant. Erosion of the cores as determined from the cup thickness ratio was complete within 22 weeks for the Resomer RG 756 and within 30 weeks for the Resomer RG 858. The weight loss of the core-in-cup implants shows that the core portion of the implants erodes before the cup portion, which was still partly intact after 34 weeks in the saline solution. The fact that the core eroded at a quicker rate than the cup of the tablet allowed the implant to release the levodopa and carbidopa at a near zero-order rate of release. Because the levodopa and carbidopa were released within 100 days, the drugs must be released from the implants via diffusion through the polymer and erosion of the polymer. The results of this study indicate that it is possible to produce an implant that has the ability to simultaneously release levodopa and carbidopa in vitro

Table 2

Erosion of Different Core-in-Cup Implant Formulations

Time (weeks)	Resomer RG 756 (n = 4) Weight (mg) ± *SD*	Resomer RG 756 (n = 4) Ratio ± *SD*	Resomer RG 858 (n = 4) Weight (mg) ± *SD*	Resomer RG 858 (n = 4) Ratio ± *SD*
0	451 ± 7.53	1.00 ± 0.00	453 ± 8.62	1.00 ± 0.00
2	442 ± 4.24	0.97 ± 0.07	450 ± 5.43	0.99 ± 0.14
4	430 ± 5.71	0.79 ± 0.09	450 ± 9.13	0.95 ± 0.02
6	428 ± 4.78	0.77 ± 0.05	445 ± 8.14	0.90 ± 0.05
8	415 ± 3.72	0.71 ± 0.04	430 ± 3.80	0.88 ± 0.04
10	412 ± 7.57	0.63 ± 0.12	425 ± 8.45	0.87 ± 0.04
12	385 ± 6.38	0.52 ± 0.08	416 ± 9.35	0.74 ± 0.15
14	365 ± 4.59	0.37 ± 0.06	405 ± 4.29	0.65 ± 0.06
16	331 ± 6.29	0.21 ± 0.13	390 ± 6.98	0.53 ± 0.08
18	320 ± 9.62	—	379 ± 8.43	0.48 ± 0.05
20	300 ± 5.84	—	353 ± 4.26	0.42 ± 0.12
22	280 ± 6.54	—	328 ± 5.58	0.36 ± 0.15
24	247 ± 9.48	—	308 ± 4.11	0.27 ± 0.08
26	241 ± 8.18	—	282 ± 7.41	—
28	227 ± 8.15	—	259 ± 8.56	—
30	206 ± 6.75	—	223 ± 4.32	—
32	187 ± 5.85	—	208 ± 6.16	—
34	167 ± 6.26	—	184 ± 6.40	—

at a zero-order rate for up to 3 months at a time. Further in vivo investigation could produce a possible drug delivery system for effective treatment of difficult cases of parkinsonism.

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