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Short communication

Design of a new formulation for sustained release of gentamicin: a Carbopol hydrogel

María-José Fonseca[a,*], Anna Cabanes[a], M. Asunción Alsina[b], Francesca Reig[a]

[a] *Department of Peptides, C.I.D., C.S.I.C, Jordi Girona Salgado 18-26, 08034 Barcelona, Spain*
[b] *Physicochemical Unity, Department of Pharmacy, Placa Pius XII s/n, 08028 Barcelona, Spain*

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Abstract

Two gentamicin-containing hydrogels of different water solubility have been prepared using Carbopol as a thickening agent. The most insoluble hydrogel (A) released its drug content extremely slowly, regardless of the absence or presence of plasma. In contrast, the rate of drug release from hydrogel B was just slightly slower than the free drug in saline, whereas in the presence of plasma components just 35% of the gentamicin contained in hydrogel B was eventually released from it. Pharmacokinetic studies showed a sustained release of gentamicin from the Carbopol hydrogel (B), with an elimination half-life in excess of 2.5 h.

Keywords: Gentamicin; Carbopol; Polymer; Delivery systems; Sustained release

The aminoglycoside gentamicin is commonly used as the sulphate salt in various dosage forms including injectable and topical preparations, and is effective against a wide variety of Gram-negative and Gram-positive organisms (Weinstein and Wagman, 1978). Some pharmacokinetic characteristics, such as almost non-existent oral absorption and rapid clearance from blood, as well as the nephrotoxicity and ototoxicity associated with this antibiotic make the design of delivery systems containing gentamicin particularly interesting. With this aim, several approaches ranging from entrapment into liposomes (Klemens et al., 1990) to association to bioerodible polymers either administered by different routes as solutions (Milani et al., 1993) or used as solid implants in different parts of the body (Laurencin et al., 1993) have been developed. On this basis, the purpose of the present study was to evaluate the suitability of a novel system, Carbopol-associated gentamicin, as a sustained release device by comparing the pharmacokinetic characteristics of such formulation with those calculated for gentamicin sulphate in saline. Carbopol was chosen for being widely used both in pharmaceutical and cosmetic preparations.

* Corresponding author at: Department of Pharmaceutics, Faculty of Pharmacy, Utrecht University, PO Box 80.082, 3508 TB Utrecht, The Netherlands. Tel: + 31-30-537306; Fax: + 31-30-517839; E-mail: fonseca@klin.far.ruu.nl

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Gentamicin free base was obtained from gentamicin sulphate (supplied by Infavet) by anionic exchange chromatography in Dowex 1 × 2; 10 ml of a gentamicin base solution (7.5%) were dispersed, with stirring, in a 100 ml aqueous solution of 1% (w/v) Carbopol 934 P. The pH was adjusted to 7 by the addition of 2 N sodium hydroxide. During the neutralization process, the mixture was separated into two portions, a solid bulk (A) and a clear solution (B). Both were vacuum dried and pulverized until a homogeneous powder was obtained. The content of gentamicin was determined by HPLC (Cabanes et al., 1991). Preparation A contained 304.7 mg of gentamicin and preparation B, 217.3 mg. Percentage in weight of Carbopol calculated by difference was 76.5% and 57.8%, respectively.

The in vitro release of gentamicin from both hydrogels (A and B) was studied by determining the diffusion rate of the drug, dispersed either in an aqueous solution or in plasma, across a dialysis membrane (molecular weight cut-off, 14 000; Medicell International). Free gentamicin and preparations A and B, all of them containing 15 mg of antibiotic, were introduced by triplicate in dialysis bags and 1 ml of PBS or plasma was added. After the bags were placed into a receptor medium (250 ml phosphate buffer, pH 7.4), the system was stirred magnetically and kept at room temperature or at 37°C, respectively. Samples (1 ml) of the receptor medium were taken at various time intervals and assayed for gentamicin concentration by HPLC (Cabanes et al., 1991). Gentamicin from hydrogel B appeared in the receptor medium somewhat slower than the free drug, whereas preparation A released its drug content extremely slowly (Fig. 1). Although the content of Carbopol in preparation A was greater than that of preparation B (76.5% vs. 57.8%), this difference seems not to be enough to explain such a different behavior both in solubility and in their release pattern. Probably these strong differences may be due to the separation of the polymer molecules into two groups depending on the chain length, content of carboxylic groups or aggregation extent. In the presence of plasma it was observed that, whereas the free drug had almost totally dialysed in less than 20 h, less than 35% of the

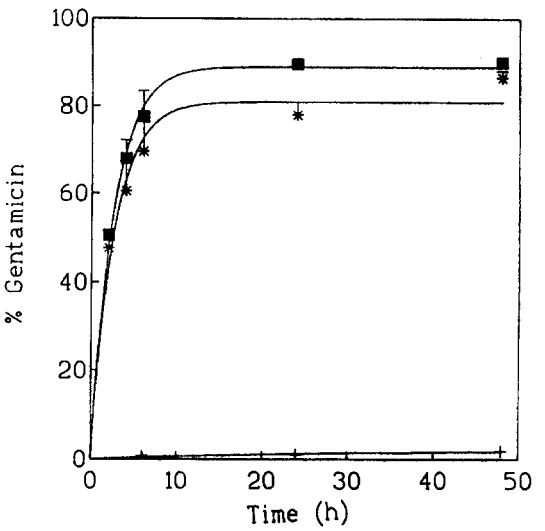

Fig. 1. Percentage of gentamicin dialysed as a function of time from two Carbopol-based hydrogels: A (+) and B (*); and from a drug solution in saline (■). In all cases the initial total amount of gentamicin was 15 mg.

drug contained in preparation B was in the receptor medium even after 160 h (Fig. 2). This fact suggests that in contact with plasma the complex gentamicin-carbopol gives rise to some structures larger in size (possibly in association with plasma proteins) that prevent the passage of the drug

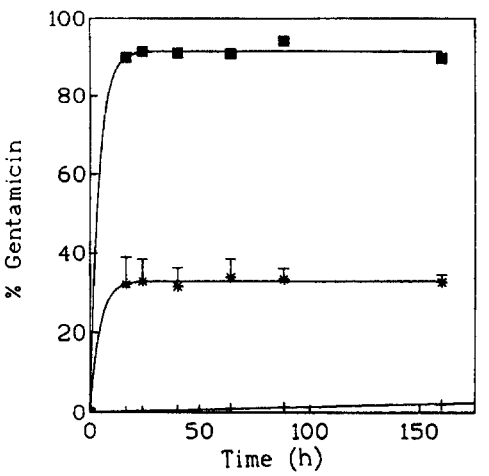

Fig. 2. Percentage of gentamicin dialysed as a function of time, and in the presence of plasma, from two Carbopol-based hydrogels: A (+) and B (*); and from a drug solution in saline (■). In all cases the initial total amount of gentamicin was 15 mg.

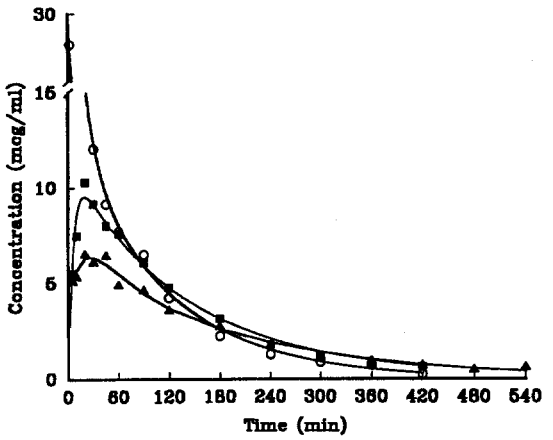

Fig. 3. Mean plasma concentrations obtained after i.v. (○) and i.m. (■) administration of a single dose of 4.5 mg/kg of free gentamicin sulphate and after administering i.m. a single dose of 3 mg/kg of gentamicin base contained in a Carbopol hydrogel (B) (▲).

across the dialysing membrane. The release of gentamicin from preparation A was, as in the previously described experiments, very slow.

Finally, the ability of a Carbopol hydrogel to provide sustained release of the antibiotic gentamicin after i.m. administration in rabbits was evaluated. Mean drug concentrations in plasma as a function of time after i.m. administration of 3 mg/kg of Carbopol-associated gentamicin in a saline dispersion are depicted in Fig. 3. As reference, a single dose of 4.5 mg/kg of free gentamicin sulphate in saline (equivalent to 3 mg/kg of gentamicin base) was i.v. and i.m. injected. Both, free and Carbopol-associated gentamicin showed a biphasic elimination profile, which is consistent with that reported by other researchers (Trapote et al., 1989). Pharmacokinetic parameters obtained after i.m. administration of both formulations (Table 1) were statistically compared by use of the Mann-Whitney U-test. Differences were considered significant at $P < 0.05$. Three features are noteworthy.

(a) Maximal plasma concentration (C_{max}) obtained after i.m. administration of gentamicin in Carbopol (7.5 μg/ml) was significantly lower than that observed for the antibiotic in the free form (18.5 μg/ml), which may have a beneficial effect in terms of toxicity, since lower peak concentrations are expected to induce less toxic effects.

(b) Elimination half-life ($t_{1/2\beta}$) was increased more than 2-fold when gentamicin was administered within a Carbopol hydrogel (161.4 vs. 79.3 min). Probably the existence of a net positive charge in the antibiotic molecule and negative charges along the polymer net gives rise to small complexes of both components able to reach the circulation by themselves, thus retarding the appearance of free gentamicin. According to the results obtained in the in vitro release experiments, those microaggregates would bind to plasma proteins to a higher extent than the free drug, thus prolonging the time it circulates in blood.

Table 1
Pharmacokinetic parameters (± S.D.) obtained after i.v. and i.m. administration of a single dose of 4.5 mg/kg of free gentamicin sulphate and after administering i.m. a single dose of a Carbopol hydrogel containing 3 mg/kg of gentamicin base

Variables	i.v.	i.m.-free	i.m.-hydrogel
α (min^{-1})	0.147 ± 0.085	0.036 ± 0.031	0.015 ± 0.009
β (min^{-1})	0.010 ± 0.001	0.009 ± 0.002	0.004 ± 0.001
k_{01} (min^{-1})	—	0.103 ± 0.048	0.267 ± 0.239
$t_{0.5\alpha}$ (min)	7.1 ± 4.5	41.7 ± 29.3	56.2 ± 28.6
$t_{0.5\beta}$ (min)	71.8 ± 9.9	79.3 ± 13.3	161.4 ± 28.8
V_d (l/kg)	0.29 ± 0.02	—	—
C_{max} (μg/ml)	—	18.5 ± 5.3	7.5 ± 1.4
t_{max} (min)	—	81.7 ± 13.0	25.4 ± 24.0
AUC (μg/min per ml)	1637.1 ± 270.0	1336.8 ± 213.0	1322.1 ± 448.2
Cl (ml/min per kg)	2.9 ± 0.5	—	—
F (%)	—	81.6 ± 13.0	76.4 ± 21.67

(c) The bioavailability of gentamicin administered in a Carbopol gel was very similar to that obtained after i.m. administration of the same dose in the free form, thus indicating that all the drug eventually abandon the polymer system, in order to exert its antimicrobial activity.

The more insoluble hydrogel (preparation A) could not be dispersed in a homogeneous suspension that could give rise to therapeutic concentrations of gentamicin. Nevertheless, a formulation based on this latter preparation could be useful as a solid implant in certain parts of the body (e.g. eyes, skin, bones) when a very slow release is required.

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