ELSEVIER

International Journal of Pharmaceutics 126 (1995) 79–82

international journal of pharmaceutics

Controlled release of timolol maleate from coated ophthalmic mini-tablets prepared by compression

M.F. Saettone[a,*], P. Chetoni[a], L. Mariotti Bianchi[a], B. Giannaccini[a], U. Conte[b], M.E. Sangalli[b]

[a]*Dipartimento di Scienze Farmaceutiche, Sezione Tecnologie Farmaceutiche/Biofarmacia, Università di Pisa, I-56126 Pisa, Italy*
[b]*Dipartimento di Chimica Farmaceutica, Università di Pavia, I-27100 Pavia, Italy*

Received 8 March 1995; accepted 28 April 1995

Abstract

Ophthalmic inserts (denominated mini-tablets, MT) for sustained release of timolol were prepared by a standard compression and coating technique. An adequate control of the in vitro drug release from the devices could be obtained by adjusting the type and amount of acrylic polymer coating.

Keywords: Ocular insert; Timolol maleate; Mini-tablets; Eudragit®-RS; Eudragit®-RL; Controlled release; In vitro release

A previous paper (Saettone et al., 1990) dealt with an application of the compression technique to the preparation of ophthalmic inserts containing pilocarpine. When compared with a standard solution, the inserts exhibited a sustained miotic effect in rabbit eyes, even if the drug was released in vitro with non-zero order kinetics. Subsequent work on pilocarpine inserts prepared by extrusion (Saettone et al., 1992) demonstrated that zero-order release kinetics, and improved biological effects, could be obtained by coating the devices with aqueous dispersions of acrylic polymers.

The aim of the present investigation was to apply both approaches (compression and coating) to the realisation of ophthalmic mini-tablets (MT) for sustained release of timolol (Ti). This drug is widely used as an ophthalmic solution to lower the intraocular pressure of glaucoma patients. However, a substantial portion of the solution is lost to the eye and undergoes systemic absorption via the nasal mucosa, with undesirable cardiovascular and respiratory side effects. As indicated in a recent review (Urtti and Salminen, 1993), several studies have demonstrated the possibility of increasing the ocular/systemic absorption ratio of Ti by adequately controlling the ocular release of the drug. A slow, sustained delivery might offer concrete advantages, such as improved therapeutic efficacy and reduced systemic toxicity.

* Fax: +395 021002; e-mail: mbxsaettone@mail.cnuce.cnr.it.

SSDI 0378-5173(95)04096-S

Table 1
Percent composition of the ocular mini-tablets (MT)

MT type	HPC % w/w	GPS % w/w	TiM % w/w	(A)ACR RS/RL % w/w, 80:20	(B)ACR RS/RL % w/w, 60:40
1	59.5	37.9	2.6	-	-
1C	51.0	32.5	2.3	14.2	-
2	58.0	37.0	5.0	-	-
$2C_1$	51.6	32.8	4.5	11.1	-
$2C_2$	47.7	30.3	4.2	17.8	-
$2C_3$	54.6	34.8	5.8	-	4.8

Timolol maleate, TiM (Sigma Chimica, Milano, Italy); hydroxypropylcellulose MW 300,000, HPC, (Janssen Chimica, Geel, Belgium); glyceryl palmito-stearate, GPS, (Precirol®-ATO 5 Gattefossé SA, Saint-Priest, France); acrylic copolymers, ACR-RS and ACR-RL (Eudragit®-RS and Eudragit®-RL, Rohm-Pharma, Darmstadt, Germany),and castor oil (Carlo Erba, Milano, Italy) were all used as received.

The composition of MT is indicated in Table 1. Type 1 and 2 tablets contained 0.34 and 0.68 mg TiM (equivalent to 0.25 mg and 0.55 mg Ti base) respectively; coating is indicated by the suffix C.

The tablet cores were obtained as follows: TiM was first dispersed in melted (50°C) GPS; the cooled, solidified mass was then forced through a 300 μm screen, mixed for 20 min with HPC in a Turbula® T2A apparatus (WAB, Basel, Switzerland) and tableted using a single-punch press (Kilian, Köln, Germany) equipped with concave punches (diameter, 3.5 mm).

The resulting cores had an average weight of 13.0 mg (type 1) or 16.0 mg (type 2), a diameter of 3.5 mm and a height of 1.5 mm. None differed from the average weight by more than 5%. Their average TiM content, monitored by HPLC after quantitative extraction with methanol, was 0.34 mg (S.D. $\pm$ 0.063) and 0.68 mg (S.D. $\pm$ 0.085) for type 1 and 2 MT, respectively.

The cores (batches of 50 units) were coated in a conventional rotating pan by spraying 5% w/w solutions of acrylic copolymers (60 ml) containing 1% w/w castor oil as plasticizer. The coating solutions, both in 1:1 v/v isopropanol-acetone, had the following w/w composition: (A) 80:20 ACR-RS/ACR-RL, and (B) 60:40 ACR-RS/ACR-RL.

All MT, individually packaged in blisters, were sterilized by gamma-ray irradiation (dose = 2.5 MRad). Analytical tests demonstrated that the drug content was unaffected by the sterilization procedure.

The release tests from uncoated (1,2) and coated (1C, $2C_1$, $2C_2$ and $2C_3$) MT were carried out using a custom-made apparatus, consisting of a small, stainless steel woven wire (50 mesh) basket (diameter 18 mm, height 20 mm), rotating at 20 rpm. The dissolution medium consisted of 5.0 ml of 1.3 mM, pH 7.4 phosphate buffer, whose ionic strenght was adjusted to 0.5 M with sodium chloride; all release experiments were performed at 30°C (temperature of the eye surface). At preset time intervals, 2.0 ml samples of the receiving solution were withdrawn for analysis, and imme-

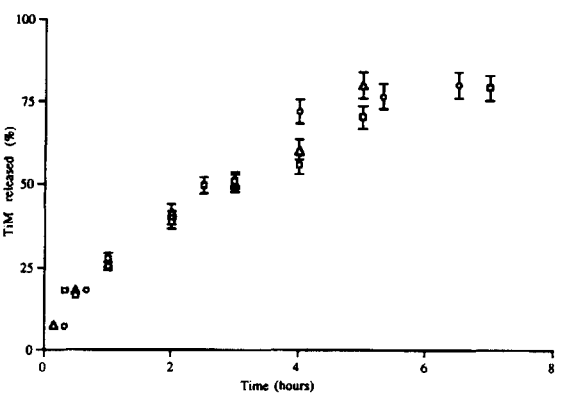

Fig. 1. Timolol maleate release from mini-tablets 1(□), 2(○) and 2C3(△). Means $\pm$ S.E. of 4 experiments are reported.

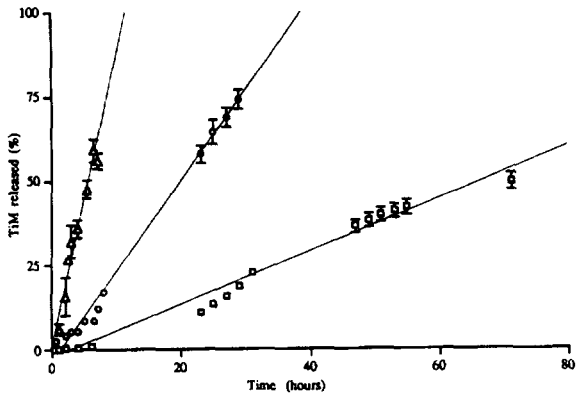

Fig. 2. Timolol maleate release from mini-tablets 2C2 (□), 1C(○) and 2C1(△). Means ± S.E. of 4 experiments are reported.

diately replaced with new buffer pre-heated at 30°C. The release tests were continued 25 hr for the uncoated MT, and up to 70 hr for the coated ones. Each test was repeated at least four times.

HPLC analyses were carried out using a LC 6A pump, 20 μl Rheodyne injector, SPD-6AV UV detector and a C-R4A integrating system (Shimadzu Corp., Kyoto, Japan). The column (Bondclone 30 × 3.9 mm, Phenomenex, Torrance-CA) was packed with m-Bondpack® C18 (pore size 10 μm) and fitted with a precolumn (Guard-Pak® Holder, Waters, Milford, MA). The mobile phase (flow rate, 1.0 ml/min) was acetonitrile/methanol/0.02M, pH 4.5 acetate buffer (10:45:45 v/v). The determination was performed at 294 nm. Under these conditions, the retention time of Ti was 4.8 ± 0.5 min; the sensitivity of the assay was better than 0.04 μg/ml. The TiM concentration in the samples was determined by comparison with a calibration curve obtained with standard solutions.

The in vitro release profiles of TiM from the uncoated MT 1 and 2, and from the $2C_3$ samples (coated with the more permeable polymer mixture B) are illustrated in Fig. 1. The release profiles of the other MT, coated with the less permeable mixture A, are reported in Fig. 2.

The release data were analyzed according to the semi-empirical equation: $M_t/M_\infty = Kt^n$ where M_t and M_∞ denote the amount of drug released at time t and at infinite time, respectively; K is the kinetic constant, t is the release time and n is the diffusional exponent of the drug release (Korsmeyer and Peppas, 1983; Peppas, 1985). In particular, the exponent n is indicative of the release kinetics: a value of 0.5 corresponds to conventional Fickian kinetics, while $n = 1$ is indicative of zero-order kinetics. A value of n between 0.5 and 1 indicates anomalous drug release kinetics.

The parameters for in vitro release of TiM from the test dosage forms, reported in Table 2, were determined from log (M_t/M_∞) vs log (t) plots. In the case of MT 1, 2 and 2B, data fitting was performed on the early portion of the curve ($M_t/M_\infty < 0.7$).

As shown in Table 2, whereas the uncoated MT showed diffusive (MT1, $n = 0.53$) or anomalous (MT2, $n = 0.77$) release kinetics, those coated with the less permeable polymeric coating (A) approximated zero-order kinetics ($1.12 > n > 0.96$), with decreasing rates (R30% = 0.07, 0.02 and 0.0081 for $2C_1$, 1C and $2C_2$, respectively) with increasing amount of coating (11.1, 14.2 and

Table 2
"In vitro" release parameters of TiM from the mini-tablets

MT type	n (± 95% C.L.)	K, (s^{-n})	$t^a_{30\%}$ (hr)	$R^b_{30\%}$ (hr^{-1})
1	0.53 ± 0.073	0.28	1.14	0.14
1C	0.96 ± 0.199	0.023	14.6	0.02
2	0.77 ± 0.086	0.22	1.5	0.15
$2C_1$	0.99 ± 0.250	0.075	4.04	0.07
$2C_2$	1.12 ± 0.202	0.002	46.7	0.0081
$2C_3$	0.653 ± 0.059	0.26	1.24	0.16

[a]Time required for release of 30% TiM.
[b]Instantaneous release rate at time of 30% release.

17.8%). Coating with a low amount of the more permeable polymer mixture (B), as in $2C_3$, led to anomalous, non-Fickian, release kinetics (n = 0.65). Evidently, in this case the thickness and permeability of the polymer film were not sufficient to control release. The release behaviour of MT 1 and 2 was presumably due to the presence of 58-59% HPC, whose swelling in the dissolution medium led to fast (R 30%: 0.14 and 0.15 respectively) release of TiM with a predominant diffusional mechanism.

In vivo data for the constant-rate releasing MT will be the object of a separate communication.

Acknowledgements

A grant from M.U.R.S.T. is acknowledged.

References

Korsmeyer, P.W. and Peppas, N.A., Macromolecular and modeling aspects of swelling-controlled systems. in Mansdorf, S.Z. and Roseman, T.J., (Eds), *Controlled Release Delivery Systems*, Dekker, New York, 1983, pp. 77-90.

Saettone, M.F., Chetoni, P., Torracca, M.T., Giannaccini, B., Naber, L., Conte, U., Sangalli, M.E. and Gazzaniga, A., Application of the compression technique to the manufacture of pilocarpine ophthalmic inserts. *Acta Pharm. Technol.*, 36 (1990) 15-19.

Saettone, M.F., Torracca, M.T., Pagano, A., Giannaccini, B., Rodriguez, L. and Cini, M., Controlled release of pilocarpine from coated polymeric ophthalmic inserts prepared by extrusion. *Int. J. Pharm.*, 86 (1992) 159-166.

Peppas, N.A., Analysis of Fickian and non-Fickian drug release from polymers, *Pharm. Acta Helv.* 60 (1985) 110-111.

Urtti, A., and Salminen, L., Minimizing systemic absorption of topically administered ophthalmic drugs. *Surv. Ophthalmol.*, 37 (1993) 435-456.