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On the release mechanism from coated swellable minimatrices [1]

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Summary

The approximately in vitro constant release rate shown by 'multiple unit' modified release systems that consist in coated minimatrices seems to depend on swelling properties of the cores and on permeability and/or mechanical characteristics of the applied polymeric film. The present study investigates the overall release mechanism by comparing the release kinetics of systems based on inert or swellable cores and by measuring the permeability of isolated membranes whose composition is identical to that of the applied coating. The results indicate that said coating is not capable of working as a limiting diffusional step; consequently, the release control can reasonably be ascribed to the physical restriction exerted by the film on core swelling.

Introduction

Previous papers (Colombo et al., 1985; Gazzaniga et al., 1988) and a European patent application (La Manna et al., 1987) of our group dealt with multiple unit modified release systems that contain some model drugs. The systems, composed of swellable compressed cores coated with a permeable polymeric film (coated minimatrices), exhibited an in vitro release that approximates zero-order kinetics. It has been shown that drug release modulation depended on matrix swelling force and on the mechanical properties of the film; the swelling pressure developped by the core, through interaction with the dissolution medium, led to gradual film breakage and, for as long as the film continued to adhere to a substantial part of the polymeric matrix, core swelling was limited and release profiles were affected.

The control of drug release, after film breakage, has necessarily to be ascribed mainly to the physical restriction exerted on the core by the residual adherent film coating. Prior to the rupture of the film, when the systems show constant release, possible controlling elements are the physical restriction of core swelling and/or the diffusive barrier constituted by the polymeric film.

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On the hypothesis that the polymeric membrane might work merely as a diffusion control element, a variation in drug release profile would be expected even when the film is applied to an inert (not swellable) core.

With the aim of elucidating the overall release mechanism it seemed of particular interest to explore the phase that preceds the rupture of the film; to this purpose both swellable and inert 'multiple unit' systems with identical coating were prepared and tested; in the inert system the swellable polymer of the cores was substituted with an inert one.

The release kinetics of such inert systems was examined and compared with those of the swellable system.

This work reports results relevant to systems that contain verapamil HCl or dyphylline, chosen as model drugs with differing solubilities. Furthermore, we determine permeability through membranes that have the same composition as that of the above mentioned film coating.

Materials and Methods

The following were obtained from the indicated sources: (drugs) verapamil HCl (Recordati, Milan, Italy), Mol. Wt 491.05; dec. 138–140.5°C; solubility, 70 mg/ml; dyphylline (Rhone-Poulenc, Milan, Italy), Mol. Wt 254; m.p. = 158°C; solubility, 250 mg/ml, (filler) Talc (U.S.P. grade); (polymers) hydroxypropylmethylcellulose (Methocel® K15 M, Colorcon, Orpington, U.K.), M_n 120000 and viscosity of its 2% aqueous solution at 20°C of 15 Pa s; ethylcellulose (Ethocel® 22 cps, BDH, Chemicals Ltd, Poole, U.K.), Acrylic and methacrylic ester copolymers (Eudragit® RS, Eudragit® RL, Eudragit® E (Rohm Pharma, Darmstat, Germany); (plasticizer) Castor oil (USP grade); (Colorant) FD&C lake red 3 (Capsugel, Basel, Switzerland).

The drug, polymers and filler mixtures were granulated by wetting with an isopropyl alcohol 5% solution of Eudragit® RS. The mixtures were forced through a 710 μm screen and dried at 35°C. The granules were lubricated with Magnesium stearate (0.5%) and tableted in a single punch (∅ = 3.5 mm) instrumented tableting machine (Kilian, Cologne, Germany) at a punch pressure of approx. 110 MPa.

TABLE 1

Core composition (%)

Formulae	a	b	c	d
Verapamil HCl	30	–	30	–
Dyphylline	–	30	–	30
Methocel® K15M	20	20	–	–
Ethocel®	–	–	50	50
Talc	50	50	20	20

The compressed cores were checked for diameter, height, weight and hardness. The core compositions of swellable (formula a, b) and inert (formula c, d) systems are reported in Table 1.

The cores were coated in a rotating pan with 6% w/v of isopropyl alcohol solution of a mixture composed of Eudragit® RS 58%, Eudragit® RL 15%, Eudragit® E 25% and 2% of Castor oil. 0.1% of lake red was suspended in this solution.

Samples of coated cores were withdrawn from the pan at differing times in order to obtain increasing film thickness. The finished units were dried overnight at 40°C. Film thickness was measured as reported by Gazzaniga et al. (1988). The release tests (six replicates) were performed in simulated gastric fluid (SGF) (N.F.XVI) without enzymes, using the USP XXII paddle apparatus (1000 ml, 37°C, 100 rpm); verapamil HCl and dyphylline were respectively assayed spectrophotometrically at 278 and 273 nm.

The polymeric films to be used for permeability studies were prepared by spraying on a glass substrate a solution whose composition was the same as that of the system coating. The films were dried at room temperature and removed from the glass. The thickness of each dry film was measured in ten different places by a micrometer (Mitutoyo Corporation, Japan). Polymeric films having an average thickness of about 100 μm (values ranging from 95 to 105 μm) were employed for permeability experiments by using dyphylline (solubility in SGF at 37°C: 330 mg/ml) as diffusant. The permeability was determined by using a Sartorius apparatus (model SM 16750)

(Stricker, 1971) that consisted of a diffusion cell, in which the film was clamped between the two compartments (effective area of the film: 4.6 cm^2). Equal volumes (100 ml) of dyphylline solution (5 mg/ml in SGF) and SGF, both previously warmed to 37°C, were continuously recirculated to the respective compartments by means of a two channel peristaltic pump. The drug was assayed spectrophotometrically.

Permeability was determined using Fick's first law of diffusion under the assumption of steady-state diffusion. The permeability (P) was defined as:

$$P = DK/h$$

where D is the diffusion coefficient, K denotes the membrane/solution partition coefficient and h is the membrane thickness (Martin et al., 1983; Julian et al., 1988). Permeability was calculated from the slope of the linear portion of amount diffused (M) vs time plots

$$M = DAKCt/h$$

where A is the membrane surface area, C the concentration of diffusant in the donor cell and t is the time.

The release tests, in some cases, were also carried out in a flow-through apparatus (Sotax AG, Basel, Switzerland) using the same flow rate (16 ml/min) as that in the permeability experiments on the isolated films.

Release data for inert systems were fitted according to the square root equation ($t^{1/2}$ dependency) and further analysed according to the equation:

$$M_t/M_\infty = k(t - t_0)^n \qquad (1)$$

where M_t/M_∞ is the fraction of drug released, k denotes the kinetic constant, t is the release time and n represents the diffusional exponent for the drug release. We introduced a time lag parameter (t_0) to the generally used exponential equation (Sinclair and Peppas, 1984; Peppas, 1985), to take into account the possibility of delay in release, which is due to film hydration. The exponent n indicates the kinetics of the release: it ranges from 0.5 (Fickian release, as generally observed for inert monolithes) to 1 (zero order kinetics). The fitting of the data was accomplished on the early portion of the curve ($M_t/M_\infty < 0.70$: confidence limits at $P = 0.95$).

Results and Discussion

The release profiles of swellable systems that contain verapamil HCl (formula a) are reported in Fig. 1

It can be observed that whereas uncoated matrix cores show a non linear release profile, for coated matrices the release kinetic shifts towards constant release depending on increases in film thickness. This concurs with the observation of the morphology of the systems during release: the swelling of the cores, due to interaction with the dissolution medium, is limited by the film coating, thus influencing the release profiles (Gazzaniga et al., 1988).

Fig. 2 reports the release curves of system with inert matrix cores that contain verapamil HCl (formula c). During release tests, no change in the volume of the cores is observed and the film does not break. The shape of the release profiles seems to remain unchanged.

Release from the uncoated cores follows, as expected, a matrix type profile; the amount of drug release is proportional to the square root of

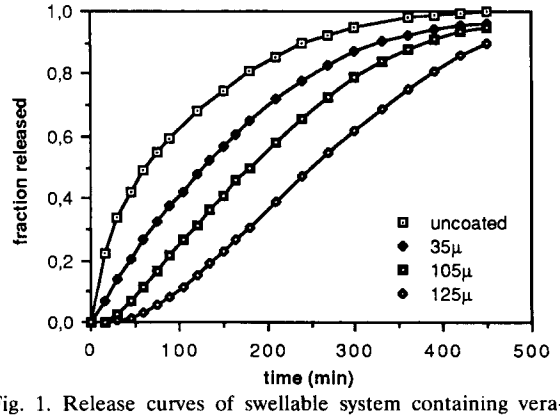

Fig. 1. Release curves of swellable system containing verapamil HCl (formula a).

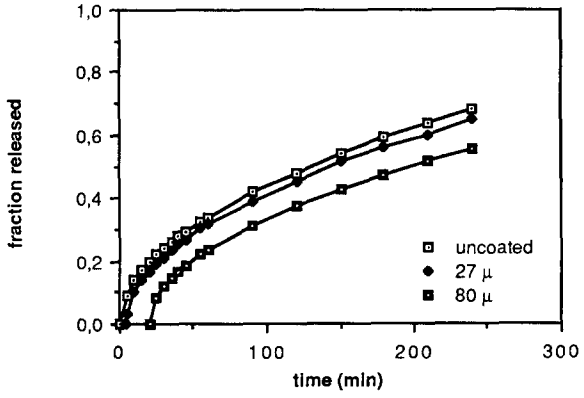

Fig. 2. Release curves of inert systems containing verapamil HCl (formula c).

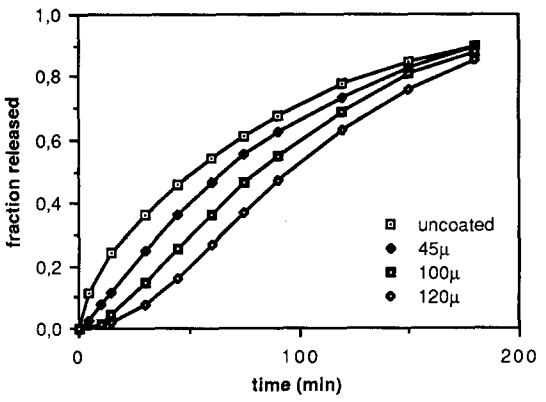

Fig. 3. Release curves of swellable systems containing dyphylline (formula b).

time ($r = 0.99$). It can be noted that the release profiles of coated inert systems show a time lag, which is related to the thickness of the film. The release needs varying periods of time to start; thereafter, both release rate and release kinetics are no longer influenced by the film.

The release data of both uncoated and coated inert systems are well described by the square root law ($r = 0.99$ in all three cases), thus indicating that the release kinetics is not influenced by the presence of the applied film. Furthermore, the delay in release that is due to the film barrier can be highlighted by treating the release data according to Eqn 1. Upon optimisation of the fitting (achieved by varying the t_0 parameter) an n value of 0.5 is obtained in all cases (Table 2). This confirms that the release kinetics for such inert systems is always merely Fickian, irrespective of the presence of the coating.

Analogous results were obtained with swellable and inert systems that contain a more soluble drug, such as dyphylline.

The relevant release profiles and parameters are respectively given in Figs 3 and 4 and in Table 3.

Further information about the role played by the polymeric coating was obtained by measuring permeability through membranes that have the same composition as that used for both swellable and inert systems. The permeability of dyphylline through the tested films was 8.76×10^{-5} cm s^{-1} (c.v. = 8.9%, 12 replicates).

As anticipated in the Introduction, the coated swellable systems, which even before film rupture show a constant release rate, could possibly work as 'classical' reservoir devices. This, however, does not seem to be the case, since the release rate, which is calculated on the basis of membrane permeability data for hypothetical reservoir system (outer membrane of 100 μm), is much higher (357 vs 35 mg/h) than that actually determined for the corresponding swellable coated systems. This, furthermore, suggests that the films here investigated control the release rate through a

TABLE 2

Release parameters according to Eqn 1

Film thickness (μ)	t_0 (min)	$n \pm 95\%$ c.l.
–	–	0.5 ± 0.01
27	4.3	0.5 ± 0.01
80	20.0	0.5 ± 0.01

TABLE 3

Release parameters according to Eqn 1

Film thickness (μ)	t_0 (min)	$n \pm 95\%$ c.l.
–	–	0.5 ± 0.02
25	3.3	0.5 ± 0.01
95	13.5	0.5 ± 0.02

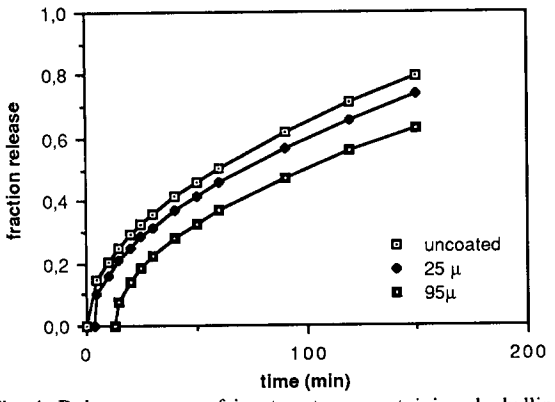

Fig. 4. Release curves of inert systems containing dyphylline (formula d).

mechanism that does not depend exclusively on their permeability.

In conclusion, the results which derive from the release data of inert systems and from permeability experiments indicate that the polymeric film is not capable of working as a diffusional barrier (i.e. as possible limiting step in drug release).

The polymeric film coating on inert cores, even in the absence of rupture, does not influence release, which still follows the square root law. When swelling is not present (inert cores), no additional control is exerted on release mechanism by the film. Therefore, drug release control in the swellable coated systems, even before film rupture, can reasonably by attributed to the physical restriction imposed by the polymeric film coating on the swelling of the cores.

Such systems, given that they are primarily based on the above said novel release control mechanism, can be defined as 'swelling restricted systems'.

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