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Erodible perforated coated matrix for extended release of drugs

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Summary

A new oral modified release system exibiting an in vitro constant release rate has been designed and prepared. The system consists of an erodible matrix core with a central hole and is partially covered with an impermeable polymeric film. The perforated core is made of a low viscosity hydroxypropylmethylcellulose (HPMC); metoprolol tartrate and benfluorex were used as model drugs. The inner hole surface is the only releasing surface of the system. This system can be prepared by using both conventional tabletting and film coating processes.

Introduction

The literature proposes several approaches, including the modification of system geometry, for the preparation of controlled release dosage forms that exibit constant release rate (Hsieh et al., 1983; Colombo et al., 1987, 1990; Béchard and McMullen, 1988; Gazzaniga et al., 1988). A recent report (Hansson et al., 1988) describes plain perforated coated tablets in which both the coating and the central hole were produced manually. The development of modified geometry matrix devices is often limited by the need for sophisticated and expensive techniques or by difficulties in the industrial manufacturing.

On the basis of these premises the aims of this work were (i) to prepare an extended oral release dosage form, based on a biconvex coated matrix with a circular central hole and exibiting an approximating constant release rate; (ii) to apply a preparation process which enables the large scale manufacturing of the system.

The second aim generated two further objectives: (a) the preparation of perforated cores by means of a continuous operating process, (b) the use of both a traditional method and coating equipment to obtain an impermeable film on the entire surface of the core except the inner hole region.

From a theoretical point of view, drug release from perforated coated cores should occur only through the central hole, and the release kinetics depends both on the increases in the releasing

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area and on the lengthening of the diffusional path; the appropriate balance of the two processes enables the achievement of a linear drug release profile.

Therefore, we prepared and tested a central hole releasing system that consists of an erodible compressed matrix with an ethylcellulose film covering. The matrix was principally made of a low viscosity hydroxypropylmethylcellulose (Methocel® E5) and contained either metoprolol tartrate or benfluorex, model drugs chosen on the basis of their differing solubility characteristics.

Results concerning the preparation methods, a new designed punch set, in vitro release data and some formulation factors affecting the release behaviour are reported and discussed.

Materials and Methods

The following materials were employed:

(a) Core: (drugs) metoprolol tartrate (S.I.M.S., Firenze, Italy); Mol. Wt, 684.8; m.p., 120–123°C; solubility at 25°C < 1000 mg/ml; benfluorex (S.I.M.S., Firenze, Italy); Mol. Wt, 351.38; m.p., 155–156°C; solubility at 25°C > 10 mg/ml; (filler) α-Lactose (USP grade); (polymer) hydroxypropylmethylcellulose (Methocel® E5, Colorcon, Orpington, U.K.); M_n 9300 and viscosity of its 2% aqueous solution at 20°C of 5 mPa s;

(b) Film coating: (polymer) ethylcellulose 22 cps (Ethocel®, BDH, Chemicals Ltd, Poole, U.K.); (plasticisers) castor oil (USP grade); diethyl phthalate (USP grade).

Model drug, erodible polymer and filler were mixed (Turbula apparatus, WAB, Basel, CH) for 20 min. The mixture was compressed using a direct compression technique. The single punch tabletting machine (Korsh, EKO, Berlin, Germany) was equipped with specially designed punches set to produce biconvex matrix tablets with a central hole of 4 mm in diameter. The core composition of systems is reported in Table 1.

TABLE 1

Core composition (%)

Formulae	A	B
Metoprolol tartrate	25	–
Benfluorex	–	25
Methocel® E5	50	50
α-Lactose	25	25

TABLE 2

Film coating composition (% w/v)

Formulae	I	II	III
Ethocel®	8	8	8
Diethyl phthalate	0.5	–	–
Castor oil	–	0.5	–

In chloroform/ethanol (5:1)

The compressed perforated cores (12 mm in diameter, 400 mg in weight) were coated in a rotating pan by spraying organic ethylcellulose solutions of differing composition (Table 2). Considering the influence of the process factors (flow rate, atomising pressure, spray distance, etc.) on the properties of the film applied (Arwidsson, 1991), all the experimental parameters were kept constant during spraying.

The finished systems were dried overnight at room temperature.

The release tests (six replicates) were performed in distilled water (1000 ml, 37°C), using the USP XXII basket apparatus at differing stirring rates (50, 100, 150 rpm). Metoprolol tartrate and benfluorex, the model drugs, were respectively assayed spectrophotometrically at 222 and 232 nm.

The intrinsic dissolution rate of employed drugs was determined (distilled water 1000 ml, 37°C, 100 rpm) according to Wood et al. (1965).

Results and Discussion

Description of the system

Fig. 1 shows the perforated biconvex erodible core, partially covered by a polymeric water impermeable film.

Preparation of perforated matrix core

Perforated biconvex matrix cores were prepared by a continuous operating process (50 ta-

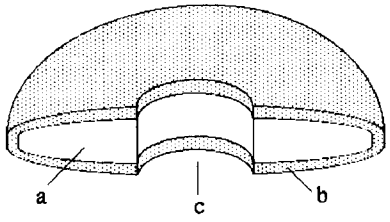

Fig. 1. Cross-section of the prepared system: (a) erodible core; (b) impermeable coating; (c) hole.

bles per min) by using a specially designed punch set. No particular problems were encountered during tabletting process with the powder mixtures used.

We obtained tablets with a 4 mm central hole, uniform weight and satisfactory technological characteristics.

The employed punches are schematically presented in Fig. 2. The lower punch is perforated and characterized by a groove that enables it to glide into the die, at the center of which is fixed a 4 mm diameter cylinder. This cylinder corresponds to a central hole on the bottom of the upper punch, above which there are two lateral holes that provide an exit for excess powder.

Film coating

Undoubtedly, there are technical obstacles to be faced when using a conventional coating method to cover perforated cores only partially. It was supposed that a reasonable solution would be to attempt to exploit the relatively unfavorable exposure of the inner surface of the hole to the sprayed film forming solution. Accordingly we examined various coating formulations with differing film forming characteristics.

Ethylcellulose was chosen as the film forming agent owing to its ability to form water-impermeable membranes (Arwidsson, 1991). The water impermeability of the film can be achieved by applying an appropriate amount of polymer.

The manufacturers recommended coating formulations, containing the plasticiser, produced a uniform, continuous film on the whole surface of the perforated matrices.

Visual examination of the coated systems indicated that, by gradually decreasing plasticiser concentration, the production of a resistant, apparently continuous layer was limited to the more exposed core surface, while an irregular and weak membrane was obtained on the inner part of the hole. These observations were confirmed by the in vitro release data.

In vitro testing

Release profiles of uncoated perforated cores containing metoprolol tartrate and benfluorex are reported in Fig. 3.

It can be observed that the differing solubility characteristics (Table 3) only slightly influence the release pattern according to a previous published paper (Zhang et al., 1990).

When the uncoated matrices are placed in dissolution medium the polymeric excipient starts swelling and a thin gel layer forms. Subsequently,

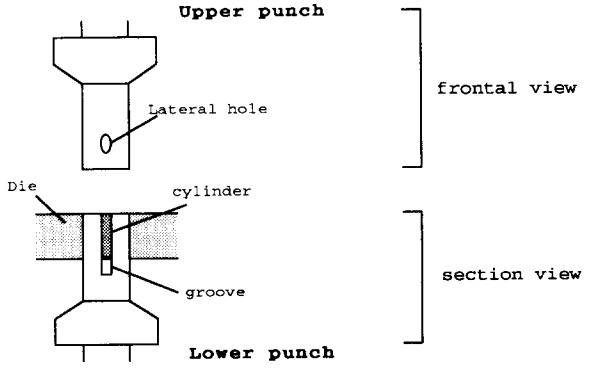

Fig. 2. Schematic representation of punches.

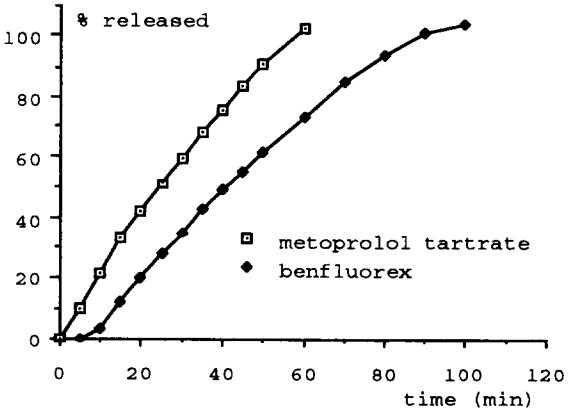

Fig. 3. Release profiles of metoprolol tartrate and benfluorex from uncoated perforated cores.

TABLE 3

Solubility characteristics of model drugs

Drug	C_s [a] (mg/ml)	I.d.r [b] (mg min^{-1} cm^{-2})
Metoprolol tartrate	> 1000	28.30
Benfluorex	< 10	0.91

[a] At 25°C.
[b] Intrinsic dissolution rate at 37°C.

the matrix dissolves and the erosion process is relatively rapid owing to the width of the surface exposed to aqueous medium.

At first, the coating was performed on cores containing metoprolol tartrate. As mentioned above the commonly employed coating formulations (plasticiser at about the 15–20% of film former polymer) led to a uniform continuous covering of the entire surface of the perforated cores. In other words, these formulations, in terms of film quality, were not able to differentiate the region inside the hole. An impermeable film on the whole surface of the cores, including the inner hole surface, was obtained and, as a consequence, no drug release occurred from the finished systems.

We therefore tested various coating formulations with differing film forming characteristics.

When we used coating solutions that contain lower plasticiser concentrations, irregular and weak films formed on the inner hole surface, thus enabling permeation by dissolution medium, while on the surface of the erodible matrix impermeable polymeric layer deposited. The hole surface becomes the only releasing surface of the system; the aqueous fluid interacts with the polymer excipient and a progressive radial erosion of the core occurs. At the end of the release test the exhausted system, consisting of a water insoluble polymer shell, can be recovered.

Fig. 4 depicts typical release profiles of systems coated with ethylcellulose solutions containing a relatively low plasticiser concentration (about 6% of plasticiser, diethyl phthalate or castor oil, based on the polymer weight).

Following a reduction in release core surface, i.e., the surface portion achieved by the dissolution medium, a significant decrease in release rate occurred. However, in all cases sigmoidal release profiles were obtained.

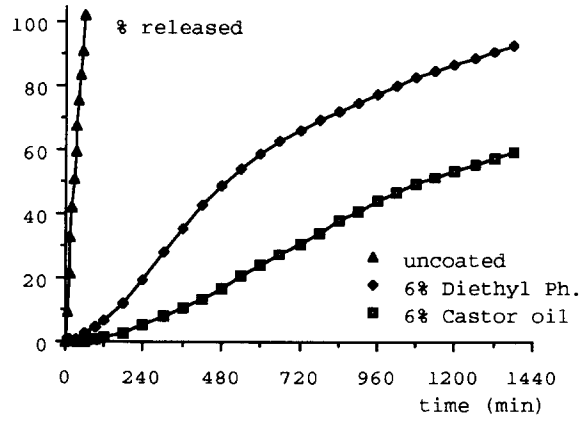

Fig. 4. Release profiles of metoprolol tartrate from uncoated cores and from systems coated with ethylcellulose film solutions containing diethyl phthalate (formula I) or castor oil (formula II).

The release curve of systems coated with an ethylcellulose solution without plasticiser is plotted in Fig. 5. A linear release profile of up to 80% was obtained. As far as the plasticiser-containing formulations are concerned, it seems probable that the film deposited on the inner surface of the hole, despite its discontinous appearance, was nevertheless capable of working, at least in the initial phase, as a 'diffusional limiting step', thus affecting drug release rate, as illustrated in Fig. 4. Analogous results in term of linearity of release, were found with systems that

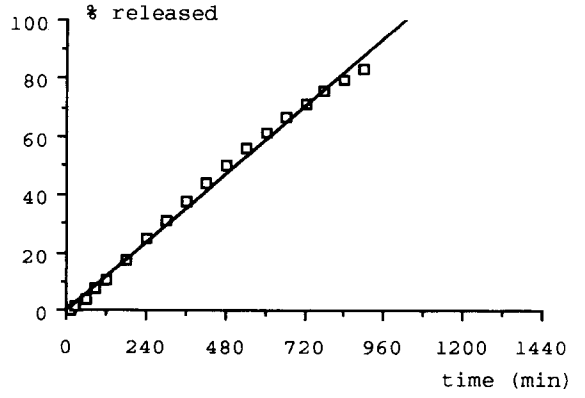

Fig. 5. Release profiles of metoprolol tartrate from systems coated with ethylcellulose film solution without plasticiser (formula III).

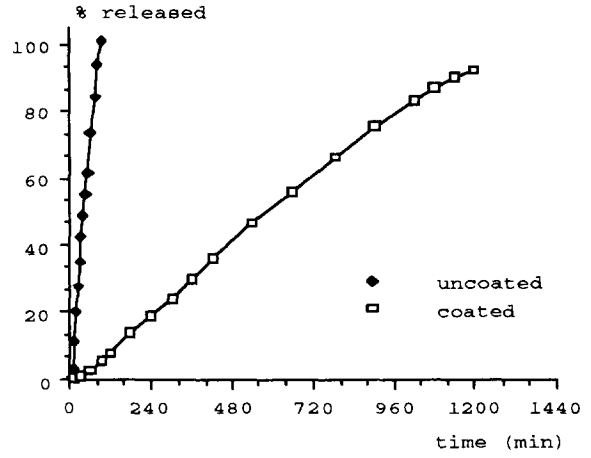

Fig. 6. Release profiles of benfluorex from uncoated cores and systems coated with ethylcellulose film solution without plasticiser (formula III).

contain a less soluble drug such as benfluorex (Fig. 6).

An interesting feature of the perforated coated systems is their ability to face differing hydrodynamic conditions. Figs. 7 and 8 show the release profiles at different stirring rates of uncoated cores and finished systems, respectively. It can be observed that whereas the release rate of uncoated systems increases as a function of increasing stirring conditions, no significant differences on release rate were observed for coated systems.

A well known limitation of modified geometry matrices for controlled release of drugs is generally the need for effective industrial manufacturing procedures; in this respect the method of fabricating the coated perforated matrix, based on conventional tabletting and coating operations, seems acceptable in view of large scale manufacture. The coated perforated systems provide an approximating in vitro zero order release for drugs of differing solubility. The reduction of the releasing area renders the system suitable and promising for extended release of very soluble drugs such as metoprolol tartrate. Moreover, the in vitro release proved to be substantially independent of stirring conditions.

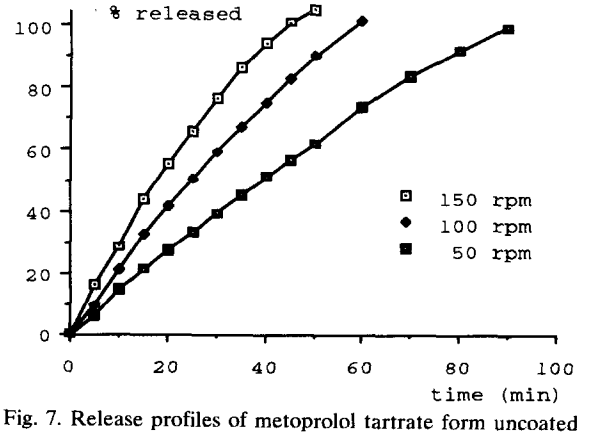

Fig. 7. Release profiles of metoprolol tartrate form uncoated perforated core at different stirring rates.

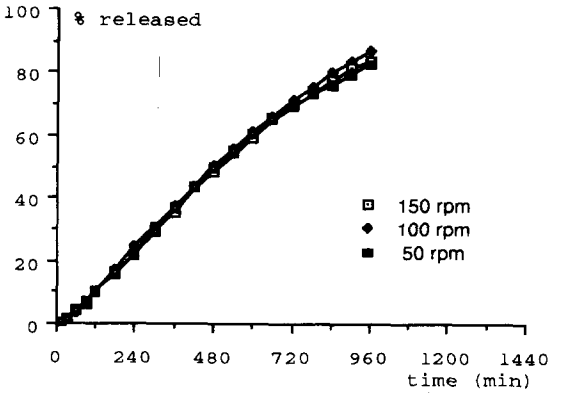

Fig. 8. Release profiles of metoprolol tartrate form coated systems (formula III) at different stirring rates.

References

Arwidsson, H., Properties of ethylcellulose films for extended release I. Influence of process factors when using organic solutions. *Acta Pharm. Nord.*, 3 (1991) 25–30.

Béchard, S. and McMullen, J.N., Solute release from a porous polymeric matrix: inwardly tapered disk with a central releasing hole. *J. Pharm. Sci.*, 77 (1988) 222–228.

Colombo, P., Gazzaniga, A., Caramella, C., Conte, U. and La Manna, A., In vitro programmable zero-order release drug delivery system. *Acta Pharm. Technol.*, 33 (1987) 15–20.

Hsieh, D.S.T., Rhine, W.D. and Langer, R., Zero-order controlled-release polymer matrices for micro- and macromolecules. *J. Pharm. Sci.*, 72 (1983) 17–22.

Colombo, P., Conte, U., Gazzaniga, A., Maggi, L., Sangalli, M.E. and Peppas, N.A., Drug release modulation by physical restrictions of matrix swelling, *Int. J. Pharm.*, 63 (1990) 43–48.

Gazzaniga, A., Conte, U., Colombo, P., Sangalli, M.E., Caramella, C. and La Manna, A., A multiple unit modified release system, *Polymer in Medicine III*, Elsevier Amsterdam, 1988, pp. 201–208.

Hansson, A.G., Giardino, A., Cardinal, J.R. and Curatolo, W., Perforated coated tablets for controlled release of Drugs at Constant Rate. *J. Pharm. Sci.*, 77 (1988) 322–324.

Wood, J.H., Syarto, J.E. and Letterman, H., Improved holder for intrinsic dissolution rate studies. *J. Pharm. Sci.*, 54 (1965) 1068.

Zhang, G.H., Vadino, W.A. and Chaudry, I., Drug release from erodible tablets, *17th International Symposium of Controlled Release Bioactive Materials*, Reno, 1990, Vol. I, pp. 333–334.