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A study on the release mechanism of drugs from hydrophilic partially coated perforated matrices

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Abstract

Partially coated perforated systems (PCPS) based on low-viscosity hydroxypropyl methylcellulose (HPMC) as the polymeric material were formerly designed, prepared and evaluated in terms of in vitro behaviour. These systems proved to afford the pursued linear release with model drugs (metoprolol tartrate and benfluorex) of different solubility. To the aim of exploring the mechanisms concurring in the definition of zero-order kinetics, studies of drug release, polymer dissolution and medium penetration were performed on PCPS and constant release area systems (CRAS). According to the obtained results, PCPS release kinetics has to be mainly attributed to the progressive outward erosion of the core and to the related variation of the release area. The special geometry of the system, in fact, involves a gradual increase in the release surface, which allows the diffusional path lengthening to be offset. By properly selecting the shape and dimensions of the device as well as the physico-chemical characteristics of the hydrophilic polymer, the advantage of a zero-order release kinetics with programmable rate can be achieved.
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Keywords: Release mechanism; Partially coated perforated system; Zero-order kinetics; Hydrophilic polymer; Release area

1. Introduction

Many oral extended release dosage forms are based on hydrophilic polymers as the main control element of drug release rate. Among these materials, cellulose ether derivatives are quite popular and, in particular, hydroxypropyl methylcelluloses (HPMCs) represent the class of polymers most frequently used in the manufacturing of hydrophilic matrix tablets. In fact, they prove advantageous due to their physico-technological properties, versatile performances, compatibility, acceptance by regulatory authorities and availability in a broad viscosity grade variety at relatively low costs [1,2].

Depending on the physico-chemical characteristics of both the active principle and hydrophilic polymer, the release of the drug from HPMC matrices can be governed by one or more of the following processes: (i) diffusion of the aqueous fluid into the hydrophilic polymeric matrix; (ii) glassy–rubbery transition and swelling of the polymer; and (iii) drug diffusion through the gelatinous rubbery layer and/or erosion/dissolution of the hydrated polymer. As a result of these phenomena, three fronts can be observed in the matrix structure: the swelling front, that separates the rubbery region from the glassy one, the erosion front, that separates the matrix from the aqueous fluid and the diffusion front positioned between the swelling and erosion fronts, that separates the gel regions containing solid and dissolved drug, respectively. During drug release, their relative movement is important in that it contributes to determine the release kinetics. In particular, when the swelling and the erosion fronts move at the same rate, which corresponds to a constant gel thickness in the outer part of the matrix, a zero-order kinetics can be obtained for systems that expose a constant area to the aqueous fluid throughout the whole process [3–6].

In general, however, HPMC matrices prepared by tableting are cylindrical and exhibit non-linear in vitro release profiles, which are characterised by an initially

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high, afterwards approximately constant and finally exponentially decreasing drug release rate (anomalous non-fickian kinetics) [7]. Several approaches have been suggested to achieve zero-order release from matrix systems, including the modification of the device geometry [3,8–12].

In this respect, we reported the design and preparation of an oral hydrophilic dosage form able to release drugs at a constant rate [13]. The system consists of a low-viscosity HPMC-based biconvex tablet with a central hole, partially coated with a water-impermeable polymeric film. In this way, the release of drug occurs only through the uncoated surface that delimits the hole. Differently from other perforated systems described in the literature [14–21], this device can be prepared by using both conventional tableting and film coating processes, and has proved to afford linear release profiles for drugs with high as well as low solubility irrespective of the hydrodynamic conditions of the test.

In theory, the overall behaviour in terms of drug release could be ascribed to the special geometry of the partially coated biconvex perforated system and to the erosion/dissolution characteristics of the polymer matrix.

Based on the above premises, an investigation seemed worth carrying out in order to deepen the current understanding of the factors involved in the mechanism that governs drug release from such system.

Accordingly, we prepared partially coated perforated systems (PCPS) based on cores made of a drug/polymer binary mixture. In particular, in this paper, data relevant to drug release and concomitant polymer dissolution from PCPS are reported and compared with the results obtained from systems with the same quali-quantitative composition and a geometry allowing a constant release area to be maintained during the whole test.

2. Experimental

2.1. Materials

Metoprolol tartrate (MW 684.8; m.p. 120–123 °C, solubility in water at 25 °C >1000 mg ml^{-1}, SIMS, Firenze, Italy); benfluorex (MW 351.38; m.p. 155–156 °C; solubility in water at 25 °C <10 mg ml^{-1}, SIMS, Firenze, Italy); HPMC (Methocel®E5, Colorcon, Gallarate-VA, Italy); ethylcellulose 22 cps (Ethocel®, BDH, Chemicals Ltd., Poole, UK); and cellulose acetate propionate (CAP 482-20, Eastman-Kodak, Kingsport, TN-US).

2.2. Preparation of the matrix systems

Physical mixtures (1/1, w/w) of low-viscosity HPMC (Methocel®E5) and model drug were compressed with a single-punch tableting machine (Korsh, EKO, Berlin, Germany). Perforated biconvex tablets (curvature radius 12 mm, maximum height 4.5 mm, central hole diameter 4 mm and weight 400 mg) were prepared using specially designed concave punches, as described in [13], while cylindrical tablets (diameter 9.5 mm and weight 300 mg) were obtained with flat-faced punches. The perforated tablets were coated in a conventional rotating pan, with 8% w/v ethylcellulose chloroform/ethanol (5/1) solution to give the finished PCPS. The particular composition of the coating solution, which contained no plasticizer, was selected on purpose to allow a continuous impermeable film to be formed only on the outer matrix surface and not on that delimiting the hole [13]. The cylindrical tablets were coated on all sides except for one of the bases by dipping in a CAP 10% w/v acetone solution to obtain constant release area systems (CRAS) [3].

2.3. Studies on drug release

Drug release studies (six replicates) were performed in a USP 25 basket apparatus (Dissolution System 2100B, Distek, Carthage, IL-US) using 1000 ml of distilled water at 37 ± 0.5 °C and 100 rpm. Metoprolol tartrate and benfluorex were quantified by spectrophotometer (Spectracomp 602, Advanced Products, Milano, Italy) at 222 and 232 nm, respectively.

2.4. Studies on polymer dissolution

Concomitant polymer dissolution and drug release studies (three replicates) were carried out in distilled water (1000 ml, 100 rpm, 37 ± 0.5 °C) by employing a USP 25 basket apparatus (Dissolution System 2100B, Distek, Carthage, IL-US). Model drugs were assayed as above described. The amount of dissolved polymer (Methocel®E5) was determined by a colorimetric method, as reported in [22].

2.5. Studies on solvent penetration

The advancement of the solvent penetration, i.e. the swelling front position, was measured in six replicates on CRAS by penetrometer (Mitutoyo, Kawasaki, Japan; calibration 0.01 mm and pin diameter 0.5 mm) within release tests. At fixed intervals, the systems were withdrawn from the dissolution vessels and placed under the penetrometer pin, which was carefully lowered to the contact point with the inner glassy core [3].

2.6. Calculation of the release area in PCPS

The release area was calculated in PCPS taking into consideration the geometrical shape of the core and the theoretical position of the erosion front by using the

following equation [23]:

$$A = 4\pi l(\sqrt{R^2 - l^2} - b)$$

where A is the release area, l is initially the hole radius and then the distance existing between the hole center and the erosion front, R is the core curvature radius and b is equal to R minus half the central height of the core h ($b = R - h/2$).

2.7. Analysis of drug release and solvent penetration data

The release data obtained from PCPS underwent linear fitting, whereas those relevant to CRAS were analysed according to the following exponential equation:

$$M = Kt^n$$

where M is the released amount of drug at time t, K the kinetics constant and n the diffusional exponent that depends on the release mechanism. It ranges from 0.5 (fickian release) to 1 (zero-order kinetics). Values of $0.5 < n < 1$ indicate an anomalous non-fickian release [24].

The same exponential mathematical model was applied to study the kinetics of solvent penetration in the polymeric matrix.

3. Results and discussion

The previously designed PCPS [13] were based on a core constituted by drug (metoprolol tartrate or benfluorex, 25% w/w), filler (α-lactose, 25% w/w) and polymer (Methocel®E5, 50% w/w). The core was coated with an ethylcellulose organic solution without plasticizer to obtain a water-impermeable film on the whole core surface except for the inner hole region, which hence turns out the only matrix surface in contact with aqueous fluid. These systems exhibited in vitro release profiles with rate approximately constant and much lower than that shown by the corresponding uncoated cores. Moreover, irrespective of the very high difference in solubility between the two employed model drugs, the release profiles were comparable [13].

To the aim of studying the mechanism governing the release kinetics from the described device, the perforated tablet core was prepared starting from a simpler formulation, in which α-lactose ($Cs = 200$ mg ml^{-1}), employed in the previous work as a soluble filler for the core, was substituted by a corresponding amount of model drug to give rise to 1/1, w/w drug/polymer binary mixture.

The release curves of metoprolol tartrate and benfluorex from binary PCPS are reported in Fig. 1. As observed for the ternary systems, the release profiles are linear ($r^2 > 0.99$ for both drugs). Moreover, the markedly different solubility characteristics of metoprolol tartrate and benfluorex, which are pointed out by the respective intrinsic dissolution rate values of 28.30 and 0.91 mg min^{-1} cm^{-2} [13], apparently affects the PCPS release performances only slightly. These results might suggest that the erosion/dissolution process of the matrix polymer plays an important role on drug release mechanism [25]. Such hypothesis seems to be confirmed by the practically superimposable profiles of drug release and polymer dissolution which were concomitantly determined for binary systems containing either model drugs (Figs. 2 and 3).

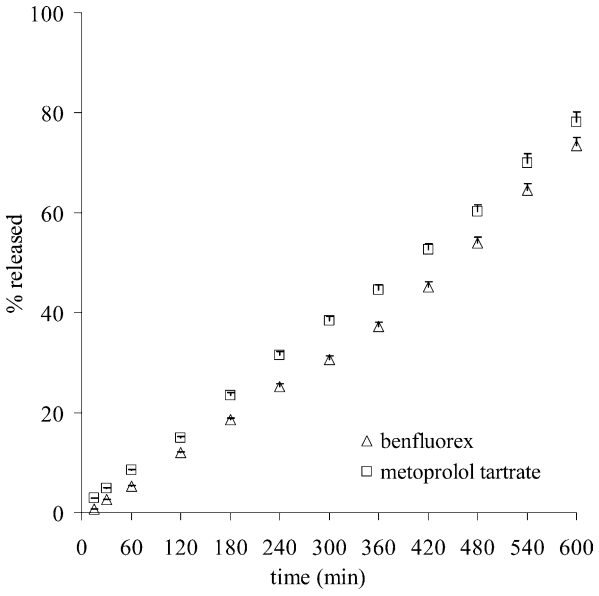

Fig. 1. Metoprolol tartrate and benfluorex release profiles from PCPS (SD is indicated by upward bars).

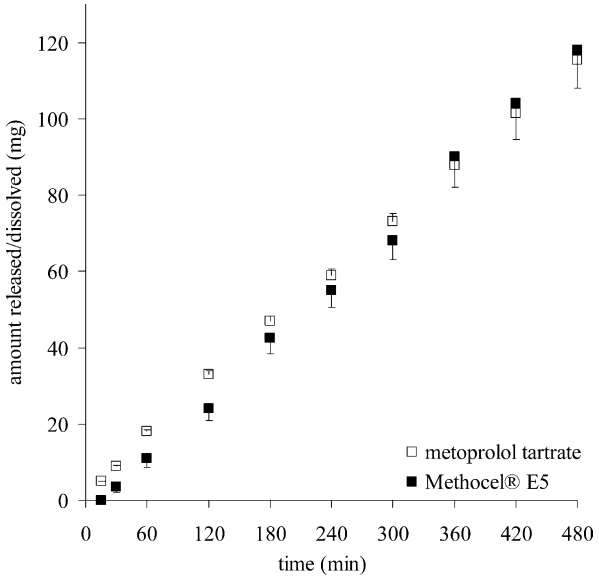

Fig. 2. Metoprolol tartrate and Methocel®E5 release/dissolution profiles from PCPS (SD is indicated by upward and downward bars for drug and polymer, respectively).

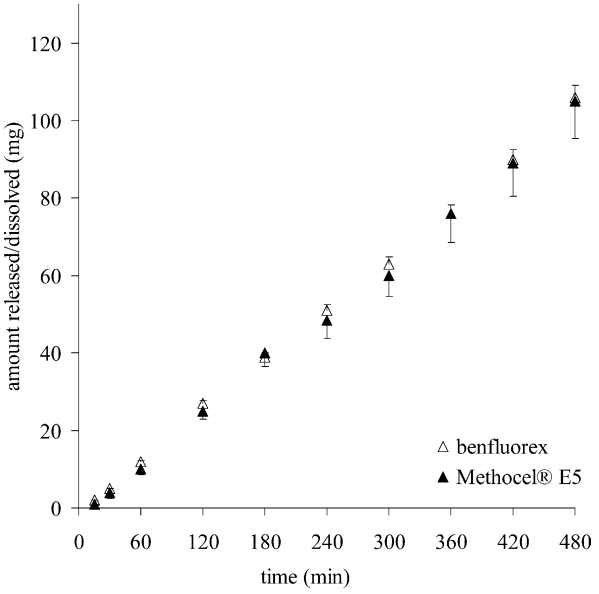

Fig. 3. Benfluorex and Methocel®E5 release/dissolution profiles from PCPS (SD is indicated by upward and downward bars for drug and polymer, respectively).

During the in vitro release test, due to the system design, the aqueous fluid can penetrate only through the uncoated central hole region. The interaction between the aqueous fluid and the hydrophilic polymer results in the glassy–rubbery transition and related swelling of the latter. When the water concentration in the swollen polymer structure exceeds a critical value, the disentangled macromolecular chains start to dissolve. A progressive radial erosion moving outwards in the core (erosion front) can be observed through the transparent coating. At the end of the release test, an empty shell constituted by the insoluble polymeric coating is recovered.

By way of example, photographs relevant to benfluorex-containing PCPS before, during and after the release test are reported in Figs. 4 and 5.

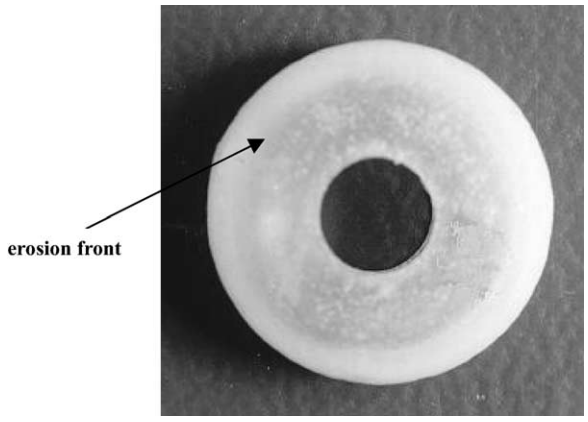

Fig. 4. Photograph of one benfluorex-containing PCPS after 480 min from the beginning of the release test.

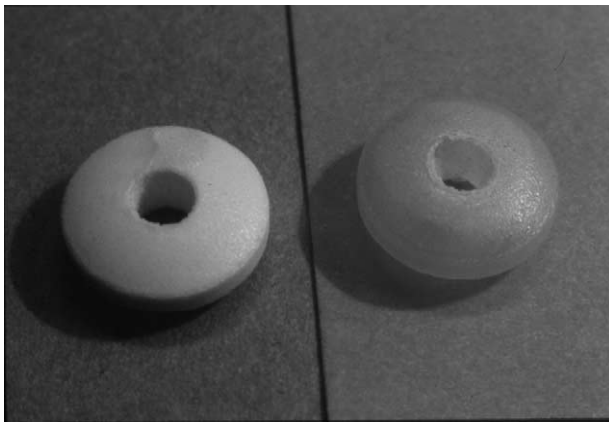

Fig. 5. Photograph of one benfluorex-containing PCPS before (left) and at the end (right) of the release test.

According to the hypothesis that the polymer erosion process might represent a major controlling element of drug release from the investigated PCPS, it seemed interesting to evaluate which influence may be exerted on the release kinetics by the progressive increase in the release area connected to the system peculiar design. To enhance the understanding of the overall release mechanism, we, therefore, investigated flat-faced systems having the same composition as the perforated cores, in which the area exposed to the release medium was kept constant through the application of an impermeable partial coating. The release curves of metoprolol tartrate and benfluorex from CRAS, reported in Fig. 6, show patterns which can be ascribed to an anomalous non-fickian behaviour, as indicated by the values of n exponent ($n = 0.86$ and 0.88 for metoprolol tartrate and benfluorex, respectively, $r^2 > 0.99$ for both drugs) resulting from data fitting through the exponential equation proposed by Korsmeyer and Peppas [7,24]. The finding of a non-fickian release profile suggests that the swelling and erosion fronts under the adopted hydrodynamic conditions are not likely to come to any synchronisation, which would be necessary to achieve zero-order release rate from hydrophilic systems with a constant release [3,5]. Also the solvent penetration, reported in Fig. 7, shows a non-fickian behaviour, as pointed out by the fitted curves relevant to the movement of the swelling front ($n = 0.63$ and 0.56, $r^2 = 0.99$ and 0.98 for metoprolol tartrate and benfluorex, respectively). The solubility of the drugs seems to affect the solvent penetration rate more than the release rate. The anomalous non-fickian patterns observed for release rate and solvent penetration lead to the assumption that a gel layer is formed, which may concur to the overall control of drug release. On the other hand, for both metoprolol tartrate- and benfluorex-containing systems, drug release and polymer dissolution profiles are practically superimposed (Figs. 8 and 9). This confirms that, although a remarkable erosion phenomenon has

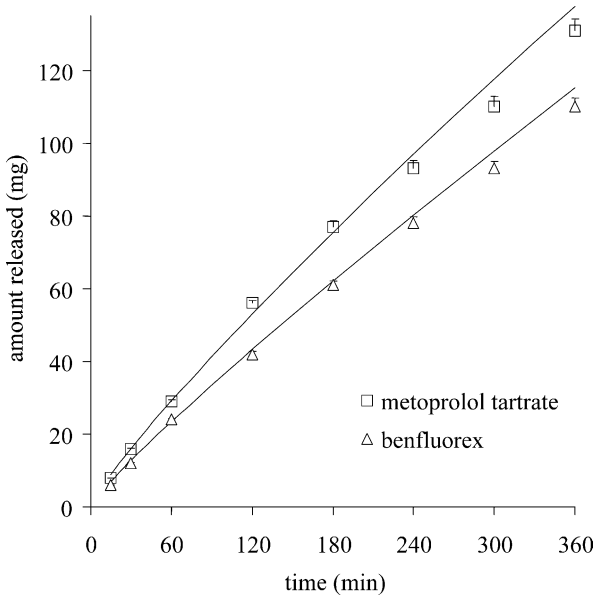

Fig. 6. Metoprolol tartrate and benfluorex release profiles from CRAS (SD is indicated by upward bars; the solid line represents the fitted curve).

turned out to take place, it is however, not able to prevent an increasingly thick gel layer to be formed, which becomes responsible for the anomalous non-fickian diffusion mechanism.

The results obtained from CRAS strengthen the appropriateness of a device envisaging a progressive release area increase as a possible way of achieving a zero-order kinetics from hydrophilic matrices based on low-viscosity swellable polymers.

Actually, the proposed PCPS properly matches this approach, as demonstrated by the release area variation calculated as a function of the theoretical distance of the erosion front from its initial position (Fig. 10). Such area increase evidently counterbalances the effect exerted on the release rate by the progressive lengthening of the path, which the drug molecules have to cross in order to be delivered into the bulk medium.

4. Conclusion

The results obtained indicate that the mechanism governing the release kinetics of the hydrophilic partially coated perforated matrices under investigation can mainly be ascribed to the progressive radial erosion of the core. As drug release proceeds, the geometry of the system leads to an increase in the release area, which proves to counteract the gradual reduction in the release rate associated with the formula composition. In fact, when was used to prepare CRAS, such formula composition was shown to fail in achieving linear release profiles, at least under the stated hydrodynamic conditions.

Through the selection of both opportune geometrical and formulation parameters, i.e. curvature radius and height of the core, diameter of the central hole as well as physico-chemical characteristics of the hydrophilic polymer, the system will allow a proper definition of drug release to be effected.

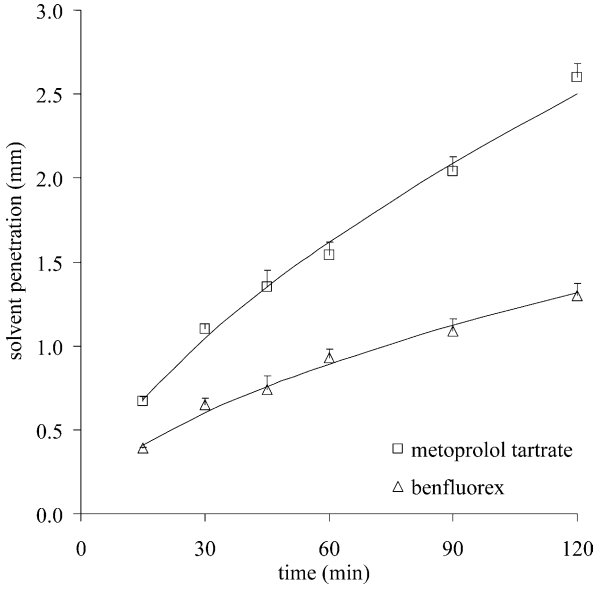

Fig. 7. Solvent penetration in CRAS-containing metoprolol tartrate or benfluorex (SD is indicated by upward bars; the solid line represents the fitted curve).

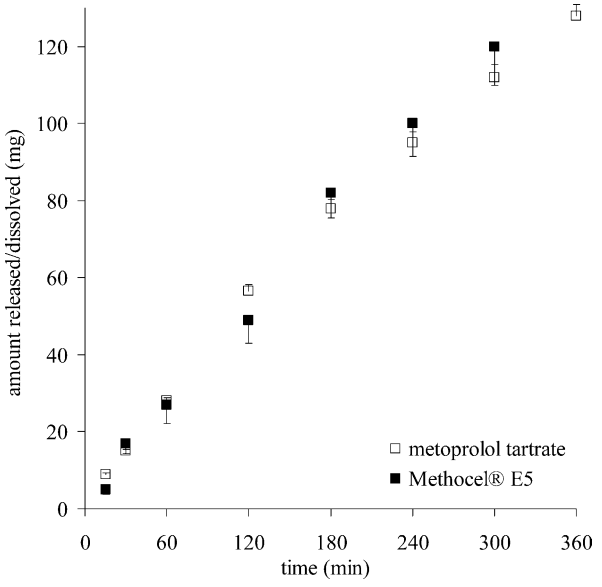

Fig. 8. Metoprolol tartrate and Methocel®E5 release/dissolution profiles from CRAS (SD is indicated by upward and downward bars for drug and polymer, respectively).

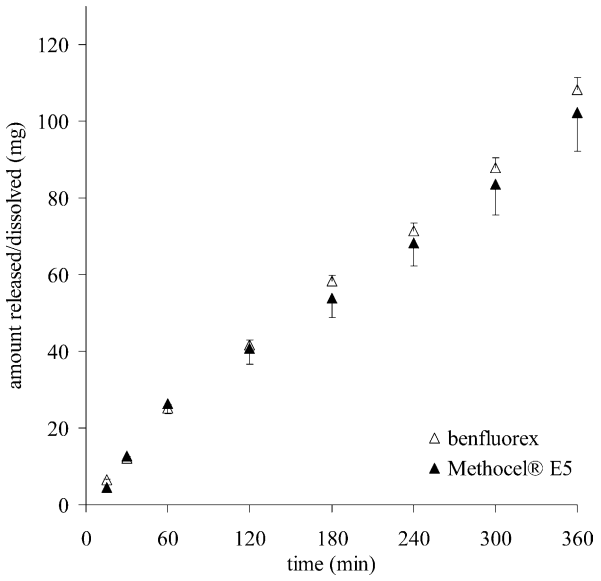

Fig. 9. Benfluorex and Methocel®E5 release/dissolution profiles from CRAS (SD is indicated by upward and downward bars for drug and polymer, respectively).

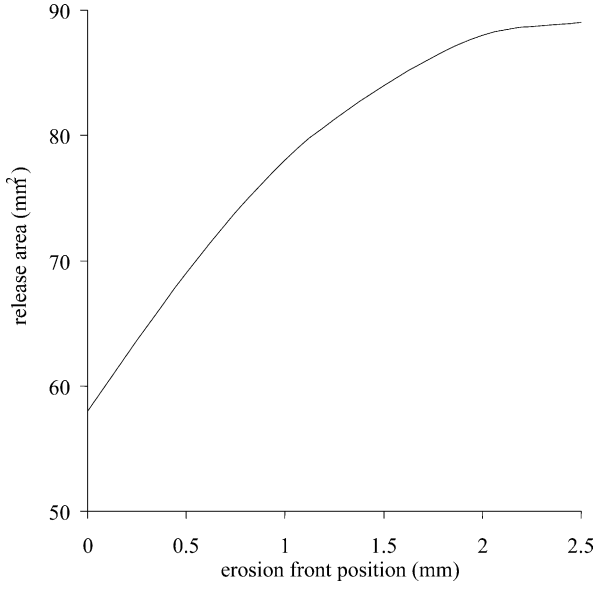

Fig. 10. Calculated release area versus theoretical position of the erosion front in PCPS.

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