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Study of the release mechanism of carteolol inert matrix tablets on the basis of percolation theory

I. Caraballo [a,*], M. Fernandez-Arevalo [a], M.A. Holgado [a], A.M. Rabasco [a], H. Leuenberger [b]

[a] *Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, c / Profesor García González s / n, 41012 Seville, Spain,*

[b] *School of Pharmacy, University of Basel, Totengässlein 3, 4051 Basel, Switzerland*

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Abstract

In the present paper, percolation theory has been applied to the study of the release mechanism obtained from controlled release tablets of carteolol hydrochloride. These dosage systems had already been studied on the basis of 'classical' theories. The new approach to this study has allowed us to obtain more complete information about the release behaviour of these inert matrix systems. The results obtained in this study demonstrate that percolation theory can provide useful parameters that can be considered as important tools for the proper design of these controlled release dosage forms.

Key words: Percolation theory; Percolation threshold; Controlled release; Release mechanism; Zero-order period; Inert matrix tablet; Carteolol hydrochloride

1. Introduction

Carteolol hydrochloride is a newly developed β-blocker. It has appropriate pharmacokinetic and activity profiles to make it a suitable candidate for controlled release matrix systems (Holgado et al., 1993). It is well absorbed from the gastrointestinal tract and is excreted primarily via the kidneys. Peak plasma concentrations usually occur within 1–3 h. The half-life averages 5–6 h (Luther et al., 1986a,b; Diago and Cosin, 1988).

As a support for inert matrix tablets, we have used acrylic resin types of Eudragit® (Rabasco et al., 1991; Holgado et al., 1992; Fernández-Arévalo et al., 1993). Eudragit® RL and Eudragit® RS are insoluble over the pH range of the digestive tract, but the former swells in aqueous medium.

The resultant inert matrices have been characterizated both in their technological characteristics (Holgado et al., 1992) as well as in their biopharmaceutical behaviour (Rabasco et al., 1991; Fernández-Arévalo et al., 1993). These studies have been carried out by means of 'classical theories'.

* Corresponding author. Tel: 34-5-4556724; Fax: 34-5-4233765.

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In previous papers (Rabasco et al., 1992; Caraballo et al., 1993a,b), we have applied percolation theory to the study of the release behaviour from inert matrix systems. Percolation theory, based on the formation of clusters and on the existence of site or bond percolation phenomena, was proposed by Leuenberger et al. (1987, 1990, 1992), Holman and Leuenberger (1988) and Bonny and Leuenberger (1991) to explain release processes as well as other technological properties of dosage forms.

In the present paper, percolation theory has been applied to the characterization of carteolol hydrochloride inert matrix systems to investigate their release profiles, yielding satisfactory results. Percolation theory proposes a new interpretation over the concepts of classical theories, providing a reasonable explanation for understanding the release behaviour of these matrix systems and introducing interesting concepts about this subject (percolation thresholds, infinite clusters, etc.).

On the other hand, the existence of zero-order release periods has been investigated, as well as how the addition of a soluble filler can affect the onset of this release kinetic process.

2. Materials and methods

2.1. Materials

Carteolol hydrochloride (< 75 μm) was a gift from Lab. Miquel S.A., a subsidiary of Otsuka Pharmaceutical Co. Ltd. The acrylic resins used were Eudragit® RL 100, RS 100 (both 25–200 μm) and S (Curtex, Industrias Sintéticas S.A., L'Hospitalet, Barcelona, Spain). Emcompress® (75–250 μm) (Glyco Ibérica S.A., Gavá, Barcelona, Spain) was used as a filler. Talc (Acofarma, Tarrasa, Barcelona, Spain) and magnesium stearate (Acofarma, Tarrasa, Barcelona, Spain) 9:1 mixture (< 50 μm) was used as a lubricant. All reagents conformed to the European Pharmacopoeia (2nd Edn).

Table 1
Tablet formulations (w/w) (carteolol hydrochloride 10% (w/w))

Lot	Eudragit® RL (%)	Eudragit® RS (%)	Emcompress® (%)	Lubricant (%)
1	40	–	45	5
2	60	–	25	5
3	80	–	5	5
4	–	40	45	5
5	–	60	25	5
6	–	80	5	5
7	–	40	50	–
8	–	60	30	–
9	–	80	10	–

Table 2
Tablet formulations (v/v)

Lot	Eudragit® RL (%)	Eudragit® RS (%)	Carteolol (%)	Emcompress® (%)	Lubricant (%)	ϵ_0
1	49.8	–	10.2	20.2	2.4	17.4
2	65.3	–	8.9	9.8	2.1	13.9
3	78.3	–	8.0	1.8	1.9	9.9
4	–	49.6	10.2	20.1	2.4	17.9
5	–	67.8	9.3	10.2	2.2	10.6
6	–	79.7	8.2	1.8	1.9	8.4
7	–	48.8	10.0	22.0	–	19.2
8	–	65.6	9.0	11.8	–	13.7
9	–	78.1	8.0	3.5	–	10.4

2.2. Dose determination

Nelson's method (Aiache et al., 1982) was used to measure the amount of carteolol hydrochloride contained in the matrix tablets, which had been previously determined as 30.0 mg (Holgado et al., 1992).

2.3. Preparation of tablets

The method for preparing the tablets has been described previously (Holgado et al., 1992), the mixing time of the tablet mixtures being 15 min. Eudragit® S 12.5% and acetone were used as wetting liquids. Tables 1 and 2 list the tested formulations. All the tablets were prepared with a carteolol content of 10% (w/w).

2.4. In vitro dissolution testing

Dissolution of all formulations was determined using the USP XXII basket apparatus (Turu Grau, model D-6, Barcelona, Spain) at 37 ± 0.5°C

at a speed of 50 rpm and a pH gradient method, as reported elsewhere (Rabasco et al., 1991). 3 ml samples were withdrawn at various time intervals and analyzed, without dilution, using a UV spectrophotometer (Hitachi, model U-2000, Tokyo, Japan) at 250 nm.

3. Results and discussion

The interpretation of release data from these matrix tablets using classical theories has been reported in previous papers (Rabasco et al., 1990, 1991). Therefore, in the present paper, percolation theory will be used to explain the same data in order to compare the ability of both theories.

3.1. Interpretation on the basis of percolation theory

As indicated above, all the tablets were prepared with a drug content of 10% (w/w). Nevertheless, very important changes in the release profiles were obtained by modifying the percentage of insoluble acrylic resin by means of the addition of a soluble filler (Emcompress®) or insoluble lubricant (talc-magnesium stearate) in different ratios.

In relation to the release behaviour and taking into account the differences in solubility of the several components of the tablets, these formulations can be considered as binary mixtures of a soluble phase (carteolol hydrochloride and Emcompress®) and an insoluble phase (Eudragit® and the lubricant mixture). Emcompress® possesses a pH-dependent solubility, showing poor solubility at the end of the assay. Nevertheless, considering the whole release assay, the solubility of Emcompress® is sufficient to result in complete drug release from matrices containing a 10% (w/w) drug load (see lot 7). This simplification allows application of the principles of the percolation theory to the study of the tablet release profiles. Thus, in a case of a binary mixture, A/B, a lower and an upper percolation threshold are expected, i.e., a lower threshold, where A starts to percolate together with the already percolating component B and an upper threshold, where component B ceases to percolate. The percolation thresholds depend on the packing of the particles. The range where both components A and B percolate is generally between 40 and 60% (v/v). Moreover, it should be borne in mind that the pore system is usually a third percolating phase.

3.1.1. Percolation of the insoluble phase

Fig. 1–3 show the release profiles corresponding to the several formulations. From these curves, a clear and important change is evident in the

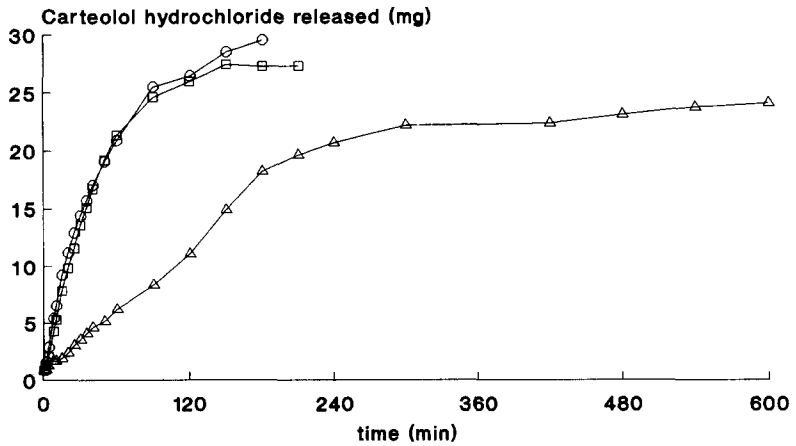

Fig. 1. Release profiles of formulations containing Eudragit® RL and lubricant. (△) Lot 1 (RL 40%), (□) lot 2 (RL 60%), (○) lot 3 (RL 80%).

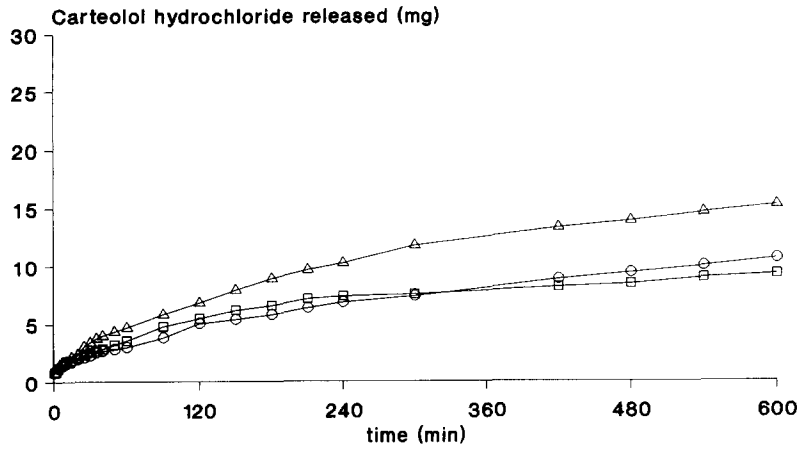

Fig. 2. Release profiles of formulations containing Eudragit® RS and lubricant. (△) Lot 4 (RS 40%), (□) lot 5 (RS 60%), (○) lot 6 (RS 80%).

release of tablets containing 40% (w/w) of polymer. This difference is due to the fact that in tablets containing 40% (w/w) of Eudragit®, the insoluble phase does not percolate the entire tablet, remaining as finite clusters. The probability at which a cluster just percolates a system (a tablet in this case) is termed the percolation threshold.

Therefore, the percolation of the insoluble phase is assumed to be between 40 and 60% (w/w) of Eudragit® for all the tablets tested.

3.1.1.1. Release behaviour above the percolation threshold. As indicated above, tablets prepared with 60 or 80% (w/w) of Eudragit® contain infinite clusters of the insoluble phase. A cluster is referred to as infinite when it extends from top to bottom and from left to right of the sample.

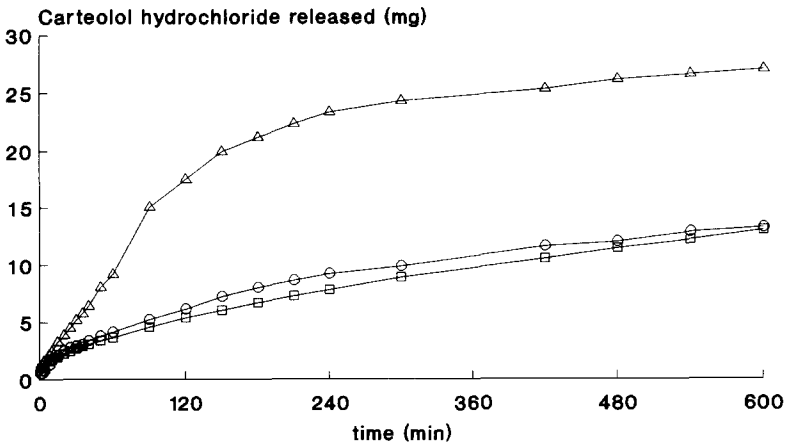

Fig. 3. Release profiles of formulations containing Eudragit® RS without lubricant. (△) Lot 7 (RS 40%), (□) lot 8 (RS 60%), (○) lot 9 (RS 80%).

Hence, the nature of the polymer will strongly determine the release behaviour of these matrix systems.

When Eudragit® RS (insoluble, hydrophobic and non-swelling polymer) was used, drug release was incomplete and took place slowly (Fig. 2 and 3, lots 5, 6, 8 and 9). Nevertheless, when Eudragit® RL (insoluble but swelling compared to Eudragit® RS) was employed, the swelling effect and its relatively hydrophilic nature allowed the very rapid penetration of water into the tablets. These characteristics determine the much more rapid release rates in comparison with all the other lots. Furthermore, with increasing tablet volume, the percolation threshold was also observed to change. At the same time, the pore volume demonstrated an increase and water began to penetrate into these new pores. Due to these circumstances, carteolol release from these tablets almost reached completion, as shown in Fig. 1 (lots 2 and 3).

3.1.1.2. Release behaviour close to and below the lower threshold. As already mentioned, the insoluble phase in tablets containing 40% (w/w) of polymer may be close to or below the lower threshold. Hence, the nature of Eudragit® (RL, RS) has a much weaker influence on the release behaviour of such tablets during the initial phase of the dissolution process (see Fig. 4). On the other hand, concerning the robustness of the formulation, the rate of dissolution may depend strongly on the relative position of the percolation threshold. In addition, it must be emphasized that the percolation of pores plays an important role in drug release from the matrix and these pores may show a hydrophilic or more hydrophobic nature as a result of the presence of a lubricant. In the case of Eudragit® RS, itself hydrophobic, this effect can be excluded.

As a consequence, for these formulations and considering those containing Eudragit® RS (lots 4 and 7), a greater release rate than that of tablets containing Eudragit® RS infinite clusters should be expected. Nevertheless, in the case of Eudragit® RL (lot 1), a slower release rate was found in comparison with matrices containing Eudragit® RL infinite clusters. This situation is related with the slower water uptake exhibited by lot 1 (water penetrates more slowly through the soluble substances).

On comparison of lots 1 (49.8% (v/v) Eudragit® RL and 2.4% (v/v) lubricant mixture) and 4 (49.6% (v/v) Eudragit® RS and 2.4% (v/v) lubricant mixture), no significant differences in their initial release periods were found (see Fig. 4). With progression of the dissolution process, the amount of water inside the tablets becomes sufficient and, hence, the swelling effect of Eudragit® RL leads to a faster rate of release of carteolol.

The soluble fraction of lot 7 (formulated with 48.8% (v/v) of hydrophobic Eudragit® RS with-

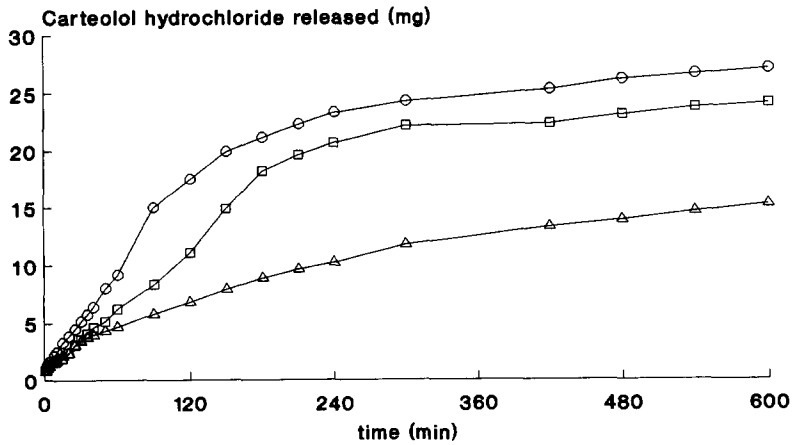

Fig. 4. Release profiles of formulations containing 40% (w/w) of acrylic resin. (□) Lot 1, (△) lot 4, (○) lot 7.

out insoluble lubricant) is greater in comparison with lot 4. This implies a different release behaviour related to the presence of a infinite soluble cluster, as discussed in the next section.

3.1.2. Percolation of the soluble phase

Percolation of the soluble phase is of considerable importance, since it determines whether drug release will reach completion or, in contrast, whether some finite clusters of carteolol will remain encapsulated by the insoluble phase. For this purpose, as considered in previous papers (Bonny and Leuenberger, 1991; Caraballo et al., 1993b), the contribution of the initial porosity has been taken into account in addition to the porosity due to the dissolution of the soluble phase, since it also participates in the release of drug.

On comparison of lots 4 and 7 (Fig. 4), it is clear that lot 4 did not allow complete drug release. This means that the soluble phase of this formulation may not percolate the tablet. Thus, the difference in dissolution rate between lot 7 (Eudragit® RS without lubricant) and lot 4 (Eudragit® RS with 5% (w/w) lubricant) may not be attributed solely to the effect of the matrix being rendered hydrophobic by the lubricant.

A mere 3% (v/v) increase in the total porosity (initial porosity and porosity due to the dissolution of the soluble substances) led to the resultant matrix yielding complete release of carteolol (lot 7 without insoluble lubricant). Therefore, it can be concluded that the percolation threshold of the soluble phase falls within the range between 55 and 60% (w/w) of total porosity, corresponding to a volume ratio of 48.2 and 51.2% (v/v).

On the other hand, lot 1 also exhibited complete carteolol release. Nevertheless, as indicated previously, this fact does not imply the existence of a soluble phase infinite cluster at the outset of the release process. Consequently, this behaviour is due to the swelling process undergone by Eudragit® RL that produces a change in the percolation thresholds, as well as an increase in the pore volume. Therefore, the completion of the release process is, in this case, effected by means of the formation of a pore infinite cluster.

3.1.2.1. Release behaviour above the percolation threshold.

As mentioned above, complete drug release is achieved above the soluble phase percolation threshold (see Fig. 4).

It is essential to point out that the dose of carteolol was fixed in advance at 30 mg, as reported previously (Holgado et al., 1992). Therefore, the previously indicated assumption of a single soluble phase composed of carteolol and Emcompress® acquires great importance. This hypothesis supposes the possibility of releasing the total amount of drug from an inert matrix at any dose, changing only the polymer/filler ratio.

The formulations studied were prepared with a 10% (w/w) drug load. As predicted on the basis of the aforementioned assumption, complete release of carteolol hydrochloride from formulations containing soluble substance infinite cluster was achieved (lot 7).

On the other hand, significant changes in the release behaviour become evident immediately upon attaining the percolation threshold, as reported for these systems by Leuenberger et al. (1992). Consequently, this assumption also implies the possibility of obtaining different release kinetics by producing a soluble infinite cluster without increasing the drug loading of the matrix system.

3.1.2.2. Release behaviour below the percolation threshold.

As indicated previously, formulations prepared with Eudragit® RS contain only finite clusters of soluble substance with the exception of lot 7 (section 3.1.2.1). As predicted by percolation theory, formulations which do not contain infinite soluble clusters do not result in complete drug release. This situation was found to hold true for lots 4–6, 8 and 9 (see Fig. 2 and 3).

The behaviour of lots containing Eudragit® RL has already been explained as being determined by the formation of a pore infinite cluster.

3.2. Zero-order release periods

The existence of zero-order release periods has been described in inert matrix compacts (Gurny et al., 1982; Potter et al., 1992) and inert

Table 3
Zero-order release parameters

Lot	Onset (min)	End (min)	K_r (mg/min)	n	r	F	p
4	420	600	$0.01071 \pm 2.20E-4$	4	0.99958	2359.87	< 0.001
5	300	600	$0.00589 \pm 1.55E-4$	4	0.99931	1447.87	< 0.001
6	210	600	$0.01082 \pm 2.10E-4$	7	0.99906	2666.97	< 0.001
7	420	600	$0.00740 \pm 4.05E-5$	4	0.99997	33365.02	< 0.001
8	300	600	$0.01386 \pm 2.09E-4$	5	0.99966	4408.55	< 0.001
9	20	150	$0.03629 \pm 6.86E-4$	10	0.99907	2802.05	< 0.001

matrix tablets (Caraballo et al., 1993a,b). The presence of these release periods is attributed to the saturation of drug in the water-filled pores of the matrix. Under these conditions, the rate of dissolution becomes slower than that of diffusion and, hence, determines the release kinetics of the process. Therefore, the existence of a greater drug load than that which implies a saturation concentration in the water-filled matrix pores is an obvious prerequisite for the existence of these periods.

The onset and end of the zero-order release period of these carteolol inert matrix tablets have been calculated in accordance with previous papers (Caraballo et al., 1993a,b). The data obtained are listed in Table 3.

In the former papers, it has been concluded that an increase in the drug loading of the matrices produces an advance in the onset of the zero-order release period. This phenomenon is attributed to the more rapid saturation of drug in the pores of the matrices.

As has been indicated, a fixed drug load was employed in the present study. Different amounts of soluble filler (Emcompress®) were added. In this manner, the soluble fraction of matrix tablets can be modified without changing the dose. Under our experimental conditions, a delay in the onset of the zero-order release period was found to occur on increasing the soluble phase fraction of matrices prepared with Eudragit® RS (lots 4–9, see Table 3).

The above finding is due to the increase in pore volume as a result of dissolution of the filler. This greater pore volume prevents the rapid saturation of drug. Thus, zero-order release periods appear later in those matrices containing greater fractions of soluble phase.

Matrices prepared with Eudragit® RL (lots 1–3) did not exhibit clear zero-order release periods. This finding is related to the considerably larger pore volume which is developed by these matrices (drug saturation cannot be clearly reached in these systems).

To summarise, it can be concluded that the application of percolation theory to the study of the mechanism of release from matrix systems provides more relevant information than the classical theories. The concepts of percolation thresholds and finite or infinite clusters, introduced by percolation theory, are useful tools for researchers involved in the development of controlled release formulation. Furthermore, percolation theory appears to possess great versatility. As has been demonstrated in this study, merely by assuming some simplifications, the concepts proposed for this theory are applicable to the design of an increasingly large number of pharmaceutical dosage forms.

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