Drug Development and Industrial Pharmacy, 23(1), 1-8 (1997)

RESEARCH PAPER

Application of Percolation Theory to Characterize the Release Behavior of Carteolol Matrix Systems

I. Caraballo, M. A. Holgado, M. Fernández-Arévalo, M. Millán, and A. M. Rabasco

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, 41012—Seville, Spain

ABSTRACT

The paper reports a study of the capability of the percolation theory to explain the influence of several formulation factors over the release behavior of carteolol hydrochloride inert matrix systems. For this purpose, previously prepared matrix systems have been employed. The characterization of these matrices by means of "classical theories" has been reported in previous papers. Similar percolation thresholds have been found (52.7%, 56.2% v/v for the insoluble phase and 48.2% to 51.2% v/v for the soluble phase), even with changing formulation factors such as nature and percentage of polymer, type of wetting liquid and nature, and percentage of filler. This fact suggests an advantage for the application of percolation theory to the rationalization of pharmaceutical dosage forms design. From the obtained results, the characterization of a multicomponent system on the basis of percolation theory seems to be rather general. On the other hand, the relatively high percolation thresholds obtained can be attributed to the different particle sizes of the components according to correlated percolation models.

INTRODUCTION

Carteolol hydrochloride is a relatively recently developed β blocker. It has appropriate pharmacokinetic and activity profiles to make it a suitable candidate for controlled-release matrix systems (1).

Acrylic-type resins such as Eudragit® have been used as a support for inert matrix tablets (2-4). Eudragit RL and Eudragit RS are insoluble over the pH range of the digestive tract, but the former swells in aqueous medium. The technological (3) and biopharmaceutical (2,4) characterization of these systems has been carried out using classical models, including the Higuchi model, which can be referred to as "classical theories."

Percolation theory has been introduced in the pharmaceutical field by Leuenberger and his research group

(5,6). This theory brought satisfactory results in many pharmaceutical subjects (5,7,8). The field of controlled release is one of those most influenced by the application of these new theories (7,9–11).

This theory is based in the formation of clusters and in the existence of site or bond percolation phenomena. A cluster can be defined as a number of neighboring occupied sites in a lattice. An example of a two-dimension square lattice is shown in Fig. 1(a), and the resultant clusters appear in Fig. 1(b). The probability at which a cluster just percolates a system (a tablet in this case) is termed the percolation threshold. Also, it is possible to find a model for readily estimating the values of the percolation thresholds from the diffusion behavior. In this way, changes in dissolution kinetics of a matrix controlled-release system can be explained over the whole range of drug loadings (7,9).

In a previous paper (12), the percolation theory was applied, for the first time, to the study of the release behavior of multicomponent systems (carteolol hydrochloride matrix systems). For this purpose, the assumption of considering matrices as composed by two phases, a water-soluble one and a water-insoluble one, was established. This assumption allows us to obtain satisfactory results by means of the application of the principles of percolation theory to the study of the release behavior of several formulations of carteolol matrix tablets.

The main objective of this paper is to determine if the influence of several studied formulation factors on the release behavior of the prepared tablets can be explained on the basis of percolation theory. Five formulation factors have been considered in this study: nature and percentage of polymer, type of wetting liquid, and nature and percentage of filler.

The proposed percolation model provides a reasonable explanation for the influence of the studied formulation factors.

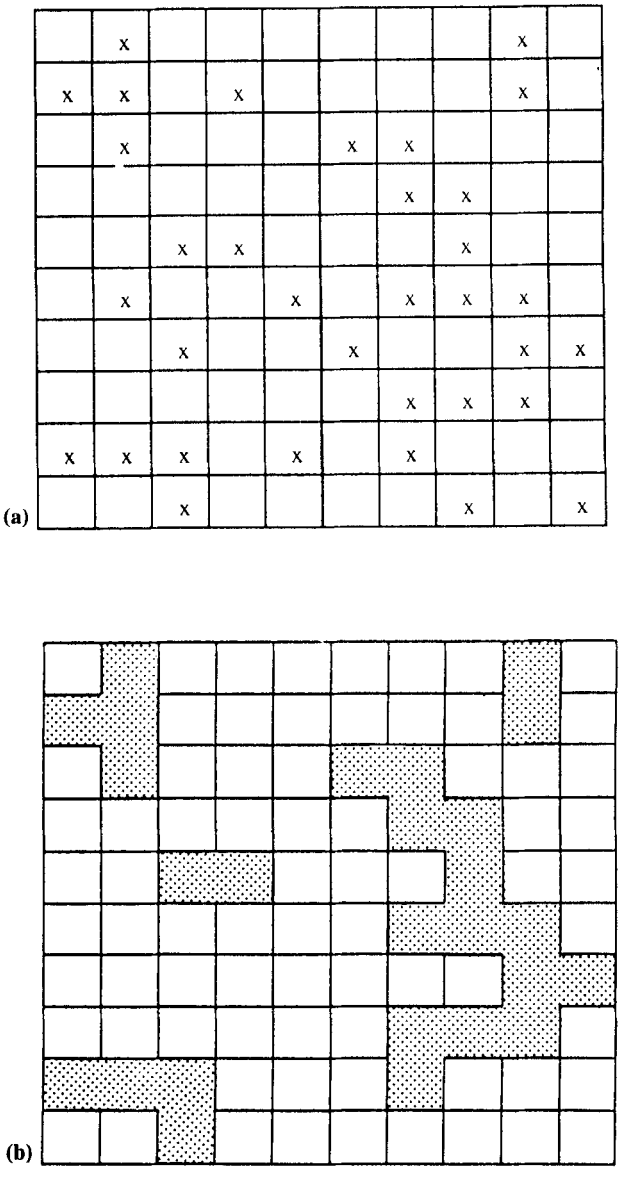

Figure 1. Example of a square lattice in two dimensions: (a) representation of the occupied sites (X); (b) the resultant clusters have been shaded (two occupied sites are considered as neighbors when they have one side in common).

MATERIALS AND METHODS

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 and RS 100 as matrix supporting materials (both 25–200 μm) and Eudragit S 12.5% and L 12.5% as wetting liquids (Curtex, Industrias Sintéticas S.A., L'Hospitalet, E-Barcelona). Emcompress® (75–250 μm; Glyco Ibérica S.A., Gavá, E-Barcelona) and mannitol (50–250 μm; Acofarma, Tarrasa, E-Barcelona) were used as fillers.

A talc (Acofarma, Tarrasa, E-Barcelona) and magnesium stearate (Acofarma, Tarrasa, E-Barcelona) 9:1 mixture (<50 μm) was used as lubricant. All reagents conformed to the European Pharmacopoeia.

Preparation of Tablets

The method used for preparing the tablets has been previously reported (3). The mixing time of the formu-

lations was 15 min. Eudragit S 12.5% or L 12.5% (10 ml) and acetone (1 ml) mixtures were used as wetting liquids. Tables 1 and 2 show the tested formulations.

In Vitro Dissolution Testing

The dissolution of all the formulations was tested using the USP XXIII basket apparatus (Turu Grau, model D-6, E-Barcelona) at 37 ± 0.5°C at a speed of 50 rpm, with a pH gradient method, as was published elsewhere (2). Samples, 3 ml, were withdrawn at various time intervals and analyzed, without dilution, using an ultraviolet (UV) spectrophotometer (Hitachi, model U-2000, J-Tokyo) at 250 nm.

RESULTS AND DISCUSSION

The interpretation of the release data from these matrix tablets by means of classical theories has been reported in previous papers (2,13). In a recent publication (12), a general percolation model has been proposed for the characterization of some of these formulations.

This model is based on the assumption of considering a binary mixture of a soluble phase (carteolol hydrochloride and filler) and an insoluble phase (Eudragit and lubricant mixture). In the case of a binary mixture A/B, a lower and an upper percolation threshold are expected: 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 threshold depends on the packing of the particles. The range where both components A and B percolate is global between 40% (v/v) and 60% (v/v). Furthermore, it is important to consider that the pore system is usually a third percolating phase. This phase plays an important role in the release process. These pores may show either a hydrophilic or a more hydrophobic nature as an effect of the presence of a lubricant. In the case of Eudragit RS, which is hydrophobic itself, this effect can be excluded.

This model was proposed in a previous study (12). In this case, only matrices prepared with Eudragit S (lots 4–6 and 10–15 in Table 1) were considered. The percolation thresholds were found to be in the range of 48.2–51.2% v/v for the soluble phase, and 52.2–65.6% v/v for the insoluble phase. In the present work these values have been confirmed by studying 8 new formulations. Furthermore, those percolation ranges have been more closely calculated.

On that score, it can be pointed out that by changing the formulation factors, different systems can be obtained; and due to the resulting modification in their technological properties, percolation thresholds can also change. Nevertheless, and considering all the tested formulations, no significant changes in percolation

Table 1

Tablet Formulations (w/w)

Lot	Eudragit RL (%)	Eudragit RS (%)	Eudragit L	Eudragit S	Carteolol (%)	Emcompress (%)	Mannitol (%)	Lubricant Mixture (%)
1	40	—	+	-	10	45	—	5
2	60	—	+	-	10	25	—	5
3	80	—	+	-	10	5	—	5
4	40	—	-	+	10	45	—	5
5	60	—	-	+	10	25	—	5
6	80	—	-	+	10	5	—	5
7	—	40	+	-	10	45	—	5
8	—	60	+	-	10	25	—	5
9	—	80	+	-	10	5	—	5
10	—	40	-	+	10	45	—	5
11	—	60	-	+	10	25	—	5
12	—	80	-	+	10	5	—	5
13	—	40	-	+	10	50	—	—
14	—	60	-	+	10	30	—	—
15	—	80	-	+	10	10	—	—
16	—	50	+	-	10	35	—	5
17	—	50	+	-	10	—	35	5

Table 2

Tablet Formulations (v/v)

Lot	Eudragit RL (%)	Eudragit RS (%)	Eudragit L	Eudragit S	Carteolol (%)	Emcompress (%)	Mannitol (%)	ε_0	Lubricant Mixture (%)
1	48.7	—	+	-	10.0	19.7	—	19.4	2.4
2	67.0	—	+	-	9.2	10.1	—	11.5	2.2
3	78.0	—	+	-	8.0	1.8	—	10.5	1.9
4	49.8	—	-	+	10.2	20.2	—	17.4	2.4
5	65.3	—	-	+	8.9	9.8	—	13.9	2.1
6	78.3	—	-	+	8.0	1.8	—	9.9	1.9
7	—	50.3	+	-	10.3	20.4	—	16.7	2.4
8	—	67.6	+	-	9.2	10.1	—	11.0	2.2
9	—	80.1	+	-	8.2	1.8	—	8.1	1.9
10	—	49.6	-	+	10.2	20.1	—	17.9	2.4
11	—	67.8	-	+	9.3	10.2	—	10.6	2.2
12	—	79.7	-	+	8.2	1.8	—	8.4	1.9
13	—	48.8	-	+	10.0	22.0	—	19.2	—
14	—	65.6	-	+	9.0	11.8	—	13.7	—
15	—	78.1	-	+	8.0	3.5	—	10.4	—
16	—	56.9	+	-	9.3	14.4	—	17.0	2.2
17	—	54.1	+	-	8.9	—	25.5	2.6	2.1

thresholds have been obtained. This fact suggests a great advantage for the application of the principles of percolation theory.

Furthermore, the capability of the proposed model to explain the influence of several formulation factors over the biopharmaceutical properties of the formulations has been evaluated in the present study. The formulation factors considered in this study are percentage and nature of polymer, type of wetting liquid, and percentage and nature of filler.

Influence of the Nature and Percentage of Polymer

When the release profiles obtained from matrices containing 40%, 60%, and 80% w/w of polymer (Figs. 2-4, respectively) are compared, it is clear that tablets containing 40% w/w of polymer (Fig. 2) show a different release behavior, their release profiles being much more sensitive to the nature of the wetting liquid employed. Per contra, in lots containing either 60% w/w or 80% w/w of polymer, the influence of the nature of wetting liquid is almost canceled. These facts are very difficult to explain on the basis of "classical theories." However, percolation theory provides a reasonable explanation for these behaviors, allowing a much better knowledge of these multicomponent matrix systems.

According to the postulates of percolation theory, this change is due to the fact that there is a percolation

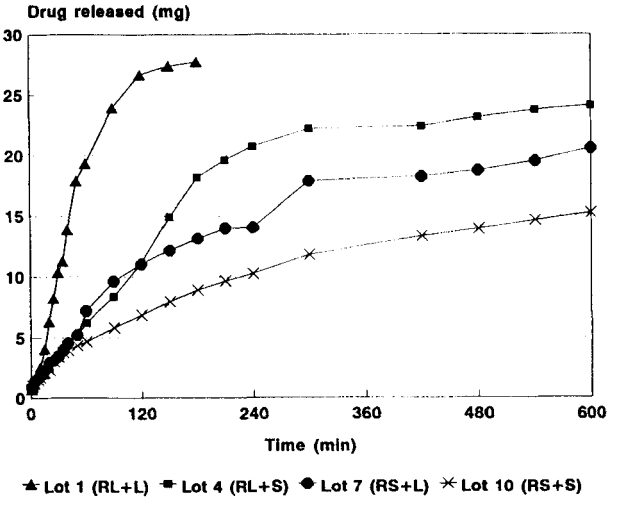

Figure 2. Release profiles of tablets containing 40% w/w of polymer (RL + L: tablets prepared with Eudragit RL as polymer and Eudragit L as wetting liquid; analogously for RL + S, RS + L, RS + S).

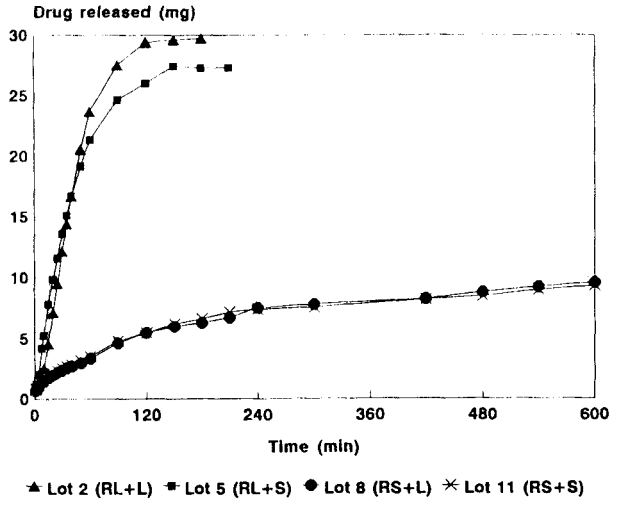

Figure 3. Release profiles of tablets containing 60% w/w of polymer (RL + L: tablets prepared with Eudragit RL as polymer and Eudragit L as wetting liquid; analogously for RL + S, RS + L, RS + S).

threshold between 40% and 60% w/w of resin (52.7–65.6% v/v of insoluble phase). This percolation range is in agreement with that reported in a previous study (12): 52.2–65.6% v/v.

So, for the lots containing 40% w/w of the polymer, the insoluble phase does not percolate the whole tablet.

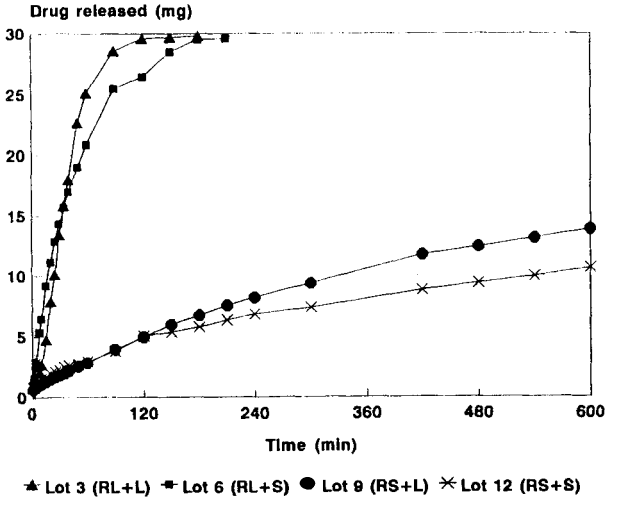

Figure 4. Release profiles of tablets containing 80% w/w of polymer (RL + L: tablets prepared with Eudragit RL as polymer and Eudragit L as wetting liquid; analogously for RL + S, RS + L, RS + S).

Therefore, these tablets containing an insoluble phase infinite cluster exhibit release profiles which are strongly dependent of the polymer nature. So, tablets containing an insoluble phase infinite cluster basically composed by Eudragit RS (an insoluble, hydrophobic, and nonswelling polymer) showed slow and incomplete drug release (Figs. 3 and 4). However, those matrices containing an insoluble phase infinite cluster with Eudragit RL (insoluble but more swelling than Eudragit RS) exhibit a fast and complete drug release (see Figs. 3 and 4).

On the other hand, lots without insoluble phase infinite cluster (Fig. 2), show different release behaviors as a function of their polymer nature. In these matrices (40% w/w of polymer) the insoluble phase, which is mainly composed by the polymer, is isolated in form of finite clusters. The effect of the insoluble phase being isolated in finite clusters is an increase in the drug release rate for matrices prepared with Eudragit RS and a decrease in those containing Eudragit RL.

This different behaviour is due to the fact that the infinite cluster of Eudragit RS (hydrophobic and nonswelling) makes difficult the water penetration inside the tablet: tablets containing 40% w/w of Eudragit RS show a faster release rate than those containing 60% or 80% w/w of this polymer.

Nevertheless, the existence of an infinite cluster of Eudragit RL (insoluble, but swelling in presence of water) produces a quicker water uptake and a faster drug release (water penetrates more slowly through the soluble substances). Therefore, tablets containing 40% w/w of Eudragit RL show a lower drug release rate than those containing 60% or 80% w/w of this polymer.

As Tables 1 and 2 show, lots containing 50% w/w of resin were prepared and studied in order to calculate more closely the insoluble phase percolation threshold. On the basis of the release profiles obtained from these tablets (see Fig. 5), it can be concluded that in these cases, the insoluble phase percolates the whole tablet and limits the release of the carteolol charge. So, assuming the previous considerations, the percolation threshold for the insoluble phase is found to be between 52.7% and 56.2% v/v (see Tables 1 and 2), considering formulations containing both Emcompress and mannitol as fillers.

Influence of the Percentage of Filler

As has been reported in a previous paper (2), the dose of carteolol was fixed in advance at 30 mg. There-

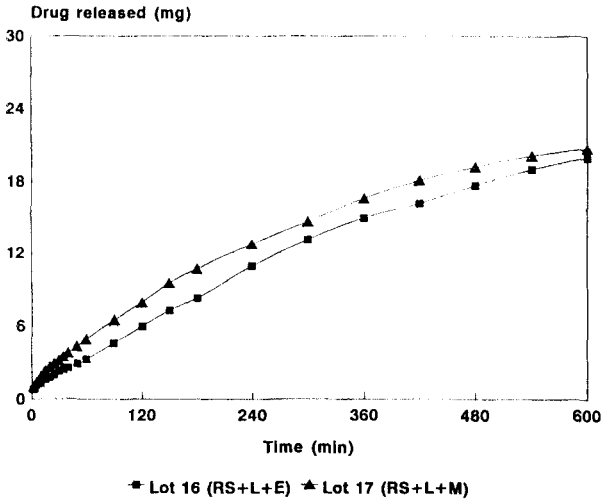

Figure 5. Release profiles of lots 16 and 17 (RL + L + E: tablets prepared with Eudragit RL as polymer, Eudragit L as wetting liquid, and Emcompress as filler; RL + L + M: tablets prepared with Eudragit RL as polymer, Eudragit L as wetting liquid, and mannitol as filler).

fore, the filler percentage is the formulation factor which will more strongly determine the percolation of the soluble phase.

Percolation of the soluble phase is very important, since it determines whether a complete release will be achieved or, per contra, a fraction of drug will remain encapsulated by the insoluble phase, forming finite clusters.

However, the complete release of carteolol hydrochloride from tablets containing Eudragit RL does not imply the existence of a soluble phase infinite cluster from the very start of the release process, because of the swelling characteristic of this polymer. This circumstance produces an increase in the tablet porosity as well as in the tablet volume. Consequently a change in the percolation thresholds is obtained while the dissolution process progresses. Therefore, in order to study when the soluble phase percolates the whole tablet, only lots containing nonswelling polymer (Eudragit RS, in our study) have been considered.

In the previous study (12) including a part of these formulations (lots 1–3 and 10–15), it was found that the percolation threshold of the soluble phase fell within the range 48.2–51.2% v/v.

In the present work, this percolation threshold has been found to be able to explain successfully the release behavior of the new studied formulations. In this manner, considering all the studied formulations containing Eudragit RS as matrix support material (lots 7–17), it has been found that those containing a soluble phase fraction equal to 48.2% v/v or less (lots 7–12 and 14–17; see Table 2) do not result in complete drug release (see Figs. 5–8). Nevertheless, lot 13 (51.2% v/v of soluble phase; see Table 2) includes a soluble phase infinite cluster yielding a complete release of carteolol.

The volume fraction of the soluble phase has been considered to be equal to the total porosity of the ma-

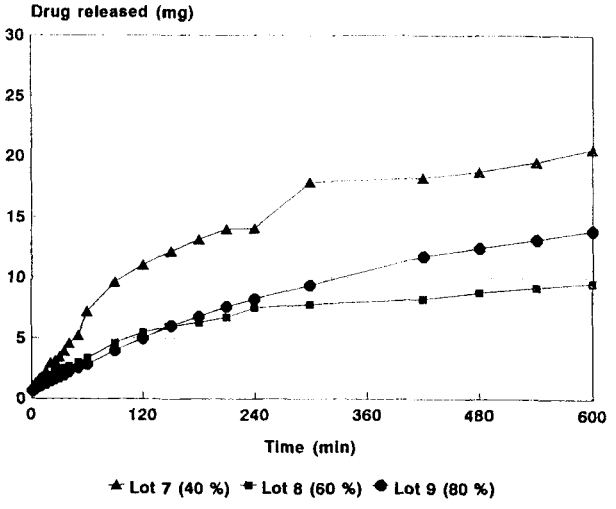

Figure 6. Release profiles of tablets prepared with Eudragit RS as polymer and Eudragit L as wetting liquid. The percentage refers to the Eudragit RS w/w concentration in the matrix.

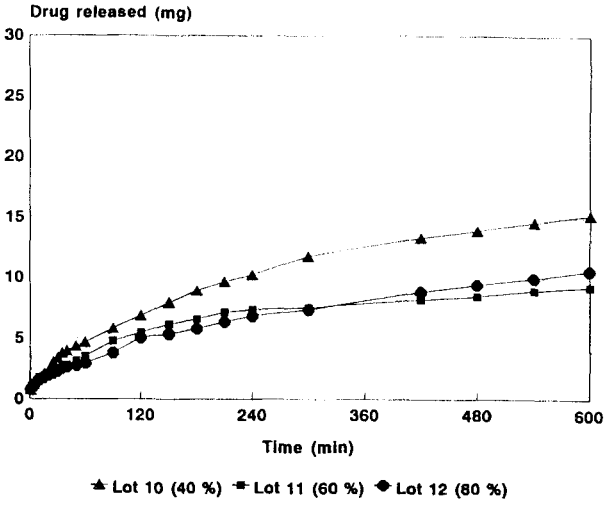

Figure 7. Release profiles of tablets prepared with Eudragit RS as polymer and Eudragit S as wetting liquid. The percentage refers to the Eudragit RS w/w concentration in the matrix.

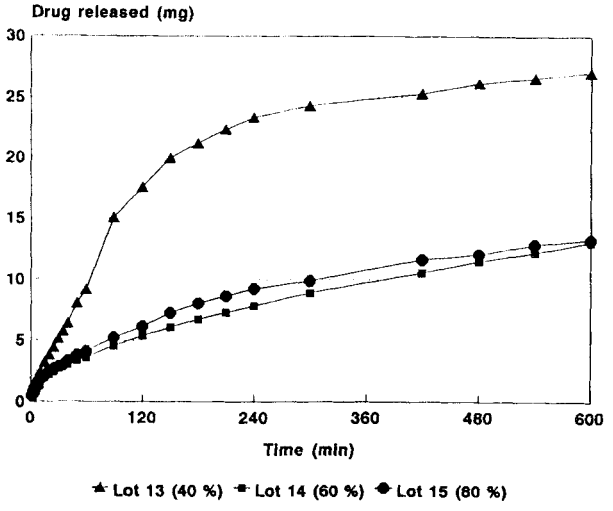

Figure 8. Release profiles of tablets prepared with Eudragit RS as polymer and Eudragit S as wetting liquid without lubricant mixture. The percentage refers to the Eudragit RS w/w concentration in the matrix.

trix (7,9,10,12) (initial porosity plus porosity due to the dissolution of the soluble substances). From the obtained results, percolation thresholds of the different components of the formulation seem to be quite invariable. No significant changes in percolation thresholds have been found when the tablet volume was kept constant.

Influence of the Nature of the Filler Substance

Emcompress has been considered to belong to the soluble phase. Nevertheless, Emcompress has a pH-dependent solubility, and a pH gradient method has been used in the release studies.

Therefore, in order to study the influence of the nature of the filler substance, matrix tablets containing mannitol (a freely water-soluble substance) as filler have been prepared (lot 17; see Tables 1 and 2), and their release profiles have been compared with those obtained from tablets elaborated with Emcompress as filler in the same weight/weight concentration (lot 16).

As Fig. 5 shows, there are no important differences in these profiles, the total amount of carteolol released at the end of the assay being only 3% greater when mannitol is used. This situation can be attributed to the fact that the soluble phase in formulations containing mannitol is 3% v/v higher in the case of Emcompress.

Therefore, two different conclusions can be obtained from these results. First, it has been demonstrated that Emcompress has a sufficient solubility in all the pH range employed so as to be considered included in the soluble phase. Second, the nature of the filler substance does not exert a great influence over the release profiles of inert matrices if the filler used has a sufficient solubility.

Influence of the Nature of the Wetting Liquid Employed

As indicated in the section on polymer nature and percentage, the influence of the wetting liquid becomes evident only when the tablets do not contain an insoluble phase infinite cluster (see Fig. 2). This influence involves an increase in the release rate when Eudragit L is used as wetting liquid because of its higher hydrophilicity in comparison with Eudragit S.

On the contrary, the influence of the nature of the insoluble phase becomes very strong, masking the influence of the different hydrophilicity of the wetting liquid employed, for tablets containing an infinite cluster of the insoluble phase.

On the other hand, when all the studied formulations are considered, the values obtained for the percolation thresholds for soluble (48.2–51.2% v/v) and insoluble (52.7–56.2% v/v) phases were higher than the theoretical predictions of random percolation models (in a three-dimensional system, percolation usually occurs between 30% v/v and 40% v/v).

Nevertheless, as has been demonstrated in previous works (14), random percolation models cannot explain the influence of particle size over the percolation thresholds because these models need the existence of a regular underlaying lattice to be applied on a system. This problem can be solved by equating the dimensions of the lattice site to the dimensions of the minor particles and considering the coarser particles as clusters of the minor ones. This approach is developed in the correlated percolation model. This theory shows that the substance having the greater particle size needs a higher volume fraction to percolate the tablet.

Experimental results obtained using inert matrix systems containing KCl as drug model (10) have shown that the use of a smaller particle size results in a easier formation of an infinite cluster of this substance. Furthermore, a linear relationship has been found between percolation thresholds and particle size (14,15).

Therefore, the obtaining of these high percolation thresholds for both soluble and insoluble phases can be attributed to the existence of substances (such as carteolol hydrochloride and the lubricant mixture) having a very low particle size but in concentrations which

do not allow them to percolate the tablet themselves. Therefore, the principal components of both soluble and insoluble phases (Emcompress and Eudragit RL or RS) have a very high particle size compared to the rest of the components. Thus, due to a layering effect of the smaller particles on the coarser particles, random distribution of the components does not occur and the percolation thresholds can be shifted. These circumstances can be explained by using the correlated percolation model.

On the basis of these data, the application of percolation theory to the study of multicomponent matrix systems provides a better and more complete description of these systems. Furthermore, percolation theory appears to possess a great versatility, being able to yield a more rational interpretation of many different systems.

On the other hand, the characterization of a multicomponent system on the basis of percolation theory seems to be quite general. It has been observed that percolation occurred in similar ranges when some formulation factors were changed. This fact suggests a great advantage for the application of this theory to the rationalization of pharmaceutical dosage form design. So, additional studies are needed in this new field.

REFERENCES

1. M. A. Holgado, M. Fernández-Arévalo, I. Caraballo, A. M. Rabasco, and A. Fini, Pharm. Acta Helv., 67(Suppl.), 89 (1992).
2. A. M. Rabasco, M. A. Holgado, M. Fernández-Arévalo, and J. M. Ginés, Eur. J. Pharm. Biopharm., 37, 147 (1991).
3. M. A. Holgado, M. Fernández-Arévalo, J. M. Ginés, and A. M. Rabasco, Drug Dev. Ind. Pharm., 18, 911 (1992).
4. M. Fernández-Arévalo, M. A. Holgado, J. M. Ginés, and A. M. Rabasco, Int. J. Pharm., 95, 117 (1993).
5. H. Leuenberger, B. D. Rohera, and Ch. Haas, Int. J. Pharm., 38, 109 (1987).
6. H. Leuenberger, J. D. Bonny, and M. Usteri, in *Proceedings of Second World Congress Particle Technology*, Kyoto, 1990, p. 1.
7. J. D. Bonny and H. Leuenberger, Pharm. Acta Helv., 66, 160 (1991).
8. H. Leuenberger and R. Leu, J. Pharm. Sci., 81, 976 (1992).
9. J. D. Bonny and H. Leuenberger, Pharm. Acta Helv., 68, 25 (1993).
10. I. Caraballo, M. Fernández-Arévalo, M. A. Holgado, and A. M. Rabasco, Int. J. Pharm., 96, 175 (1993).
11. I. Caraballo, M. Fernández-Arévalo, M. A. Holgado, and A. M. Rabasco, Eur. J. Drug Metab. Pharmacokinet., 18(1 Suppl.), 130 (1993).
12. I. Caraballo, M. Fernández-Arévalo, M. A. Holgado, A. M. Rabasco, and H. Leuenberger, Int. J. Pharm., 109, 229 (1994).
13. A. M. Rabasco, M. A. Holgado, and M. Fernández-Arévalo, in *Abstracts Book of the 6th Symposium on Biopharmaceutics and Pharmacokinetics*, Bratislava, 1990, p. 23.
14. I. Caraballo, Teoría de la percolación: aplicación al diseño y caracterización de sistemas de liberación controlada de medicamentos, doctoral thesis, University of Seville (1994).
15. I. Caraballo, M. Millán, and A. M. Rabasco, Pharm. Res., 13, 387 (1996).