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Design and evaluation of a new central core matrix tablet[1]

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Abstract

In this paper, a study of the influence that two formulation variables exert on the drug release process from a new controlled drug delivery system has been realized in order to obtain a constant release rate during a prolonged period of time, and a programmed drug release. The drug release profiles obtained for the different batches have shown an interesting relationship between the particle size of the channeling agent used and the length of the zero-order periods. Furthermore, it is possible to modify the lag-times by using different granulometric fractions of the channeling agent. Similar results have been obtained by changing the weight of the assayed tablets. © 1997 Elsevier Science B.V.

Keywords: Zero-order kinetic models; Lag-time; Programmed release; Inert matrix systems; Controlled release

1. Introduction

The main objectives of controlled release drug delivery systems are to ensure safety and to improve efficacy of drugs as well as patient compliance. So, they are designed to provide a therapeutic amount of drug on the specific-site of absorption, and then to maintain the desired drug concentration, (Longer and Robinson, 1990). This idealized objective constitutes the most important aspect of drug delivery, namely, *spatial placement* and *temporal delivery* of a drug.

In recent years, numerous controlled release systems using alternative routes, have been designed. However, the oral route still remains as the most desirable one. So, the bulk of research is directed to oral dosage forms: it allows to comply with the temporal aspect of drug delivery.

On the other hand, modelling of controlled release of a water-soluble drug from matrix systems has been widely investigated (Peppas and Ségot-Chicq, 1985; Ramos, 1990; Makoid et al., 1993). The use of drug delivery formulations based on porous or 'channelled' polymeric materials has led to re-evaluation of the existing models. In this sense, the mathematical description of the

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different designs proposed by Higuchi (Higuchi and Hiestand, 1963), allows us to assume that it is different designs proposed by Higuchi (Higuchi and Hiestand, 1963), allows us to assume that it is not possible to obtain a zero-order release kinetic with classical geometries (slab matrix or tablet) and using an inert polymer as matrix excipient (Higuchi et al., 1963). Numerous systems have been designed with the objective of obtaining a constant release rate over a period of time (Hsieh et al., 1983; Béchard and McMullen, 1988; Conte et al., 1993; Fassihi and Ritschel, 1993; Grosser et al., 1993; Benkorah and McMullen, 1994; Munday, 1996).

The existence of zero-order release periods in channelled dosage forms has been theoretically predicted by Gurny et al. (1982) and experimentally demonstrated by Potter et al. (1992) in compacts, and Caraballo et al. (1993, 1996) in tablets. This phenomenon can be attributed to the saturation of drug into the water filled pores of the matrix. Under these conditions, the dissolution rate becomes slower than the rate of diffusion and determines the release kinetics of the process.

In this work, an inert system has been designed. The release kinetic of such device, a matrix tablet containing a centralized drug core, was examined.

The different lag-times found are relevant to design a system which permits to release the drug along the gastrointestinal tract.

2. Experimental

2.1. Materials

The following were obtained from the indicated sources: Methylene blue (Acofarma®, Tarrasa, Barcelona) was used as a water-soluble model active substance. Sodium chloride (Acofarma®, Tarrasa, Barcelona) was used as a channeling agent, and Eudragit® RS 100 (Industrias Sintéticas Curtex, Barcelona) was chosen as a matrix forming material. Sodium chloride and the inert polymer were adequately crushed and sieved (Retsch, type Vibro) to obtain granulometric fractions between 50 and 250 μm for the water-soluble substance, and 150 and 200 μm for Eudragit® RS 100.

Table 1
Tablet formulations of different lots elaborated

Lot	Weight ± S.D. (mg)	NaCl particle size (μm)
1	677.3 ± 5.358	50–100
2	679.0 ± 5.007	100–150
3	680.5 ± 4.809	150–200
4	678.6 ± 5.035	200–250
5	528.5 ± 5.144	150–200
6	827.8 ± 5.312	150–200

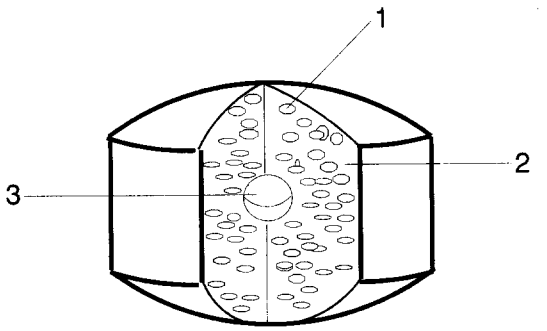

Fig. 1. Schematic drawing of the system designed: 1, Channeling agent; 2, Inert polymer; 3, Drug.

Four binary mixtures of sodium chloride (50%) and Eudragit® RS 100 (50%) were prepared in a V blender for 10 min. Different granulometric frac-

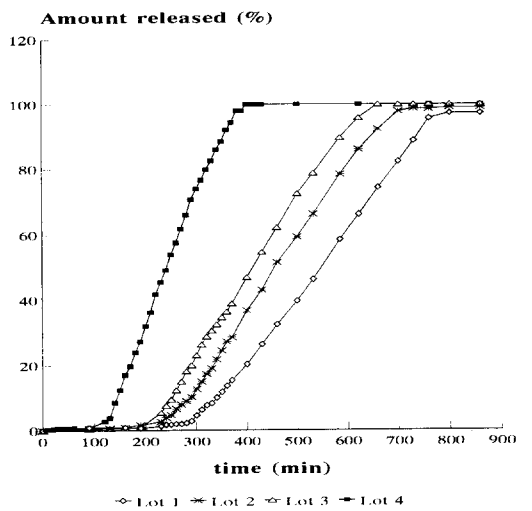

Fig. 2. Amount of drug released vs. time for tablets prepared with different NaCl particle size and 150–200 μm Eudragit® RS 100 particle size.

Table 2
Lag-time values corresponding to the lots indicated

Lot	1	2	3	4	5	6
Lag-time (min) ± S.D.	270 ± 10.0	230 ± 17.3	213 ± 11.5	123 ± 5.8	62 ± 2.9	290 ± 17.3

tions of the channeling agent were employed, whereas the particle size of the inert material was kept constant (150–200 μm).

The different binary mixtures formulation and their corresponding tablet weights can be observed in Table 1.

2.2. Preparation of matrix tablets containing central cores

The elaboration of matrix tablets is carried out in an eccentric machine (Bonals A-300), without any further excipients, using 9 mm biconvexes cylindrical punches.

An amount corresponding to the half one request to elaborate the matrix is added and the core is placed carefully in the center of the void compression. Then, the other half of the powder is added. Tablets of different weights are elaborated manually, and they are prepared to the maximum compression force accepted by our formulations.

In Fig. 1, a scheme of this matrix system is represented. The matrix systems elaborated were checked for diameter, height and weight.

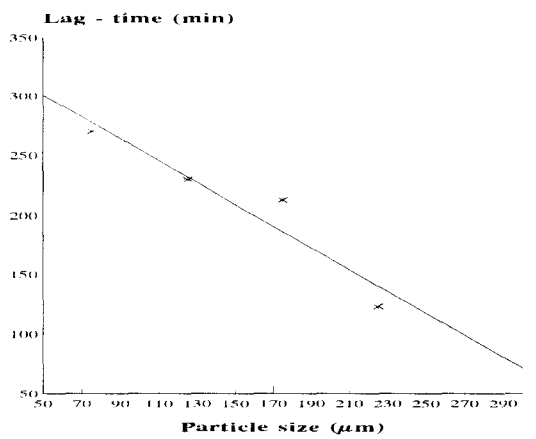

Fig. 3. Relationship between sodium chloride particle size and lag-time data.

2.3. In vitro dissolution testing

Dissolution studies of formulations were performed using the USP 23 paddle method (Turu Grau, model D-6). Purified water (700 ml) at 37 ± 0.5°C was employed as dissolution medium. The rotational speed was kept constant at 50 rpm. Samples of 2 ml were withdrawn at various time intervals and analyzed, without dilution, using an ultraviolet spectrophotometer (Hitachi, model U-2000) at 274 nm.

3. Results and discussion

The results can be interpreted on the basis of the Percolation Theory Stauffer, 1985. In this sense, Leuenberger et al. (1987) have concluded that for matrix tablets formulated with two different materials, the site percolation constitutes an interesting model which permits to explain phenomena associated to the dosage form. In this three-dimensional system, a lower and upper percolation thresholds can be defined. Between both of them, the two components form a connecting structure, i.e. they form infinite cluster. Below and above the percolation threshold one component of the binary mixture forms isolate clusters, and the other one spans the system (Leuenberger and Leu, 1992).

In recent years, this theory has been applied to study the release mechanism and the biopharmaceutical properties of inert matrix tablets. In previous works (Fernández-Hervás, 1994, Fernández-Hervás et al., 1995, 1996a,b,c, it has been demonstrated that the infinite network is kept for binary mixtures constituted with 50% for sodium chloride and Eudragit® RS 100, and the release rate is determined by the diameter of the channel.

Table 3
Study of correlation between the particle size of NaCl vs. the lag-times obtained

Coefficient of determination: 0.90529	Estimated constant term: 357.246
Multiple correspondence coefficient: 0.9515	S.E. of estimate: 24.330

Source of variance	D.F.	Sum of squares	Mean of squares	*F*	*P*
Regression	1	11316.1	11316.1	19.116	0.0485
Residuals	2	1183.9	591.9		
Total	3	12500			
Regression coefficient	Standard coefficient		S.E.	*T*	*P*
−0.9909	−0.9515		0.2266	−4.3722	0.0485

3.1. Study of lag-times as a function of sodium chloride particle size and the weight of the matrix system

As an example, Fig. 2 shows the dissolution profiles obtained for the lots prepared with different granulometric fractions, and 650 mg of weight. The influence of particle size of the channeling agent in the release process is evident. Thus, when the smaller granulometric fraction is selected, slower release rate of methylene blue is obtained.

An increase in the channeling agent particle size arises larger diameter channels in the matrix system. When the sodium chloride particle size is increased, the dissolution medium can achieve the drug core more easily, dissolving the drug particles and allowing a faster release rate. On the other hand, the release process takes place at a constant rate during a long period of time, due to the location of the drug core within the tablet and the saturation of the channels. Initially, there is a period of time in which only the channeling agent is released to the dissolution medium.

The values of these lag-time periods are shown in Table 2. It can be observed that these lag-times

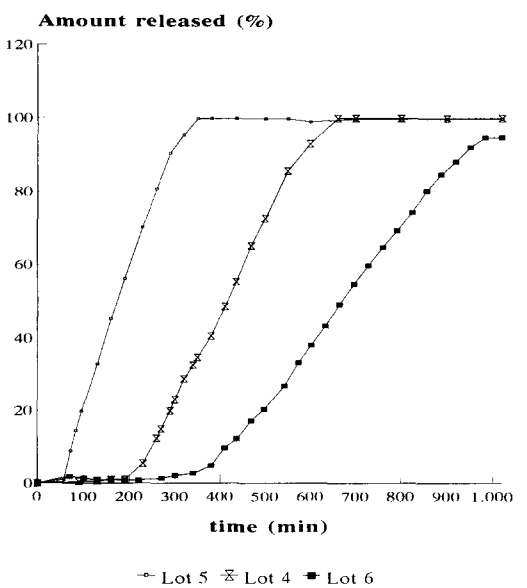

Fig. 4. Amount of drug released vs. time for tablets prepared with different weight tablets: 500, 650 and 800 mg.

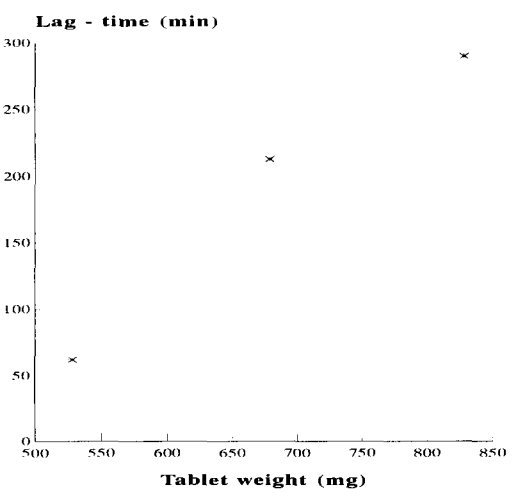

Fig. 5. Relationship between tablet weight and lag-time values.

Table 4
Zero-order release parameters

Lot	Onset(min)	End(min)	Rate(% min^{-1})	r	n	F	P
1	330	730	0.2022	0.9994	15	11470.4	<0.0001
2	270	660	0.2269	0.9992	19	10826.1	<0.0001
3	230	580	0.2438	0.9996	21	21503.1	<0.0001
4	130	320	0.4084	0.994	20	15642.1	<0.0001
5	80	290	0.3694	0.9995	9	6679.3	<0.0001
6	340	1020	0.1509	0.9969	21	3074.2	<0.0001

depend on several formulation factors, such as the particle size of the channeling agent and the weight of the tablet. This last variable is going to determine the distance that the drug would go through before it reaches the dissolution medium.

On the basis of these results, an inverse relationship between the sodium chloride particle size and the lag-times has been obtained (Fig. 3). The regression data are shown in Table 3.

As indicated above, the weight of the matrix system has also influenced the lag-times obtained in the release profiles. In order to verify these results, matrix tablets with the same particle size for the sodium chloride and the inert polymer (150–200 μm), have been prepared. In Fig. 4, the release profiles for different lots are shown. It is possible to appreciate that the release rate increases when the weight of the tablet decreases. This fact can be explained because the diffusion distance that the drug must go through to be released is shorter in smaller tablets. When the weight of the tablet increases, the length of the channels increases and so, the distance from the tablet surface to the drug core and from this to the dissolution medium becomes also higher, which implies an increase of the lag-time period. This effect can be appreciated in Fig. 4, where the drug included in tablets with 500 mg weight is released faster than the active substance incorporated in 800 mg matrix tablets. Therefore, a direct relationship between the weight of the tablet and the lag-time data has been found (Fig. 5).

3.2. Effect of sodium chloride particle size and the tablet weight on the release behaviour

In recent years, the existence of zero-order release periods has been described in inert matrix tablets by Caraballo et al. (1993). In our assays, the presence of these release periods can be attributed to the saturation of drug into the water filled pores of the matrix. Under these conditions, the dissolution rate becomes slower than the rate of diffusion and, hence it determines the release kinetics of the process. Therefore, the existence of a greater drug loading in the tablet implies a saturation concentration in the water-filled matrix pores; the presence of this phenomenon constitutes the main factor in order to obtain these periods.

In Table 4, the onset and the end of zero-order periods obtained for each lot, have been depicted. It is possible to appreciate a clear influence of the sodium chloride particle size and the weight of the matrix system over the drug release rate. Effectively, an inverse relationship between the channeling agent particle size and the onset of zero-order periods is observed. When the channeling particle size increased, the drug leaves the tablet pores more fastly. So, the constant release rate of drug is higher.

Analogously, when the weight of the tablet increases, the drug remains in saturation conditions into the tablet pores. The batches presenting the highest weight (lot 6) showed a slower release rate than the tablets with a weight of 650 or 500 mg. This result can be explained on the basis of the tablet dimensions, particularly the height of the tablet. When the height of the tablet increases, the diffusion distance is higher, the diffusion pro-

cess is slower and the drug is released at a constant rate during a more extense period of time (680 min).

In conclusion, the results which derive from the behaviour of this device in the dissolution test indicate that the system designed permits to target drugs to different parts of the gastrointestinal tract as a function of the lag-time achieved. However, further investigations have to be realized in order to improve the system, and to study other variables such as, solubility of the drug.

References

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.

Benkorah, A.Y. and McMullen, J.N. Biconcave coated, centrally perforated tablets for oral controlled drug delivery. *J. Control. Release*, 32 (1994) 155–160.

Caraballo, I., Fernández-Arévalo, M., Holgado, M.A. and Rabasco, A.M., Percolation theory: application to the study of the release behavior from inert matrix systems. *Int. J. Pharm.*, 96 (1993) 175–181.

Caraballo, I., Millán, M., Rabasco, A.M., Leuenberger, H., Zero-order release periods in inert matrices. Influence of the distance to the percolation threshold. *Pharm. Acta Helv.*, (1996) in press.

Conte, U., Maggi, L., Colombo, P. and La Manna, A., Multi-layered hydrophilic matrices as constant release devices (Geomatrix® systems). *J. Control. Release.*, 26 (1993) 39–47.

Fassihi, R.A. and Ritschel, W.A. Multiple-layer, direct-compression, controlled-release system: in vitro and in vivo evaluation. *J. Pharm. Sci.*, 82 (1993) 750–754.

Fernández-Hervás, M.J., Aplicación de la teoría de la percolación y la geometría fractal al estudio del proceso de liberación en sistemas matriciales inertes. *Tesis Doctoral*, Facultad de Farmacia, Universidad de Sevilla, 1994.

Fernández-Hervás, M.J., Vela, M.T., Arias M.J. and Rabasco, A.M., Percolation theory: evaluation and interest of percolation threshold determination in inert matrix tablets. *Pharm. Acta Helv.*, 71 (1996a) 259–264.

Fernández-Hervás, M.J., Vela, M.T., Caraballo, I. and Rabasco A.M., Effect of drug particle size on the release behaviour of NaCl-matrix systems. *Eur. J. Pharm. Biopharm.*, 42 (3) (1996b) 208–211.

Fernández-Hervás, M.J., Vela, M.T., González-Rodríguez, M.L. and Rabasco, A.M., Use to the Percolation theory in order to explain the release behaviour from inert matrix systems. *Drug Dev. Ind. Pharm.*, 22 (1996c) 201–210.

Fernández-Hervás, M.J., Vela, M.T., Holgado, M.A., Del Cerro, J. and Rabasco, A.M., Determination of percolation thresholds in matrix-type controlled release systems: application of a resistance analysis technique. *Int. J. Pharm.*, 113 (1995) 39–45.

Grosser, A.E., Fitzsimons, M. and Salha, J. Model for a controlled-release drug delivery safety system with permeable and erodible coatings. *J. Pharm. Sci.*, 82 (1993) 1061–1063.

Gurny, R., Doelker, E. and Peppas, N.A., Modelling of sustained release of water-soluble drugs from porous, hydrophobic polymers. *Biomaterials*, 3 (1982) 27–32.

Higuchi, W.I. and Hiestand, E.N., Dissolution rates of finely divided drug powders I. Effect of a distribution of particle sizes in a diffusion–controlled process. *J. Pharm. Sci.*, 52 (1963) 67–71.

Higuchi, W.I., Rowe, E.L. and Hiestand, E.N., Dissolution rates of finely divided drug powders II. Micronized methylprednisolone. *J. Pharm. Sci.*, 52 (1963) 162–164.

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.

Leuenberger, H. and Leu, R., Formation of a tablet: a site and bond percolation phenomenon. *J. Pharm. Sci.*, 81 (1992) 976–981.

Leuenberger, H., Rohera, B.D. and Haas, C., Percolation theory—a novel approach to solid dosage form design. *Int. J. Pharm.*, 38 (1987) 109–115.

Longer, M.A. and Robinson, J.R., Sustained-release drug delivery systems. In Gennaro, A.R. and Chase, G.D. (Eds), *Remington's Pharmaceutical Sciences*, 18th edn., Bonnie Brigham Packer, Philadelphia, 1990, pp. 1676–1686.

Makoid, M.C., Dufour, A. and Banakar, U.V., Modelling of dissolution behaviour of controlled release systems. *S.T.P. Pharma*, 3 (1993) 49–58.

Munday, D.L. Bimodal in vitro release from polymeric matrix tablets containing centralised drug cores. *S.T.P. Pharma. Sci.*, 6 (1996) 182–187.

Peppas, N.A. and Ségot-Chicq S., Les dispositifs à libération contrôlée pour la délivrance des principes actifs médicamenteux. III. Modélisation des mecanismes diffusionnels. *S.T.P. Pharma*, 1 (1985) 208–216.

Potter, A., Proudfoot, S.G., Banks, M. and Aulton, M.E., Factors affecting dissolution-controlled drug release from a compacted dry powder mix. *Proc. 6th Int. Conf. Pharm. Technol., Paris, 2–4 June 1992*, pp. 90–99.

Ramos, M.T., Modelización de los procesos difusionales en sistemas matriciales inertes. *An. Real Acad. Farm.*, 56 (1990) 201–210.

Stauffer, D., *Introduction to Percolation Theory*, Taylor and Francis, London, 1985, pp. 3–103.