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RESEARCH PAPER

Channeling Agent and Drug Release from a Central Core Matrix Tablet

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ABSTRACT

A new oral dosage form for controlled and complete release of drug after a predetermined lag time is described. The system, designed to exploit the relatively constant small intestine transit time, consists of a drug-containing core coated with a polymeric matrix formed by a channeling agent (NaCl, mannitol, and Emdex) and an inert polymer (Eudragit RS100). The lag time was found to be dependent on type and particle size of the channeling substances used. Also, rheological properties of the binary mixtures (channeling substance–polymer) can affect the lag time periods. On the other hand, the release kinetics were found to be influenced significantly by excipient type and particle size. Results obtained from in vitro dissolution testing demonstrated that this device potentially could be used to deliver drugs orally for up to once-a-day dosing at controllable rates.

Key Words: *Bimodal release; Lag time; Matrix tablet; Zero-order release.*

INTRODUCTION

A number of matrix systems have been developed to obtain sustained release of the active agent; several approaches, such as the modification of device geometry, have been proposed for the preparation of solid dosage forms to exhibit a constant release rate (1–4). Recently, Benkorah and McMullen (5) described the characteristics of a polymer device suitable for achieving a constant release rate of active principle. The device consisted of a round core with upper and lower faces inwardly tapered, coated by an impermeable film, and containing a cylindrical aperture to release the drug.

When zero-order kinetics are not desirable, devices that exhibit bimodal characteristics can be employed. Munday (6) prepared a matrix tablet able to compensate

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for the variations in the absorption rate from different regions of the gastrointestinal tract. Moreover, many studies have been carried out for drug delivery to a specific site within the gastrointestinal tract (7–11).

As an alternative to these approaches, we proposed a central core matrix tablet (12), which was recently patented (13). The device is formed by an inert polymer, which provides the matrix structure; a water-soluble substance, which forms a channel network during the dissolution process; and a central core formed by the drug embedded inside the matrix.

The position of the drug, inside the matrix, allows its release after a preset lag time. On the other hand, in accordance with Brooke and Washkuhn (1), this system releases the drug according to a zero-order kinetics delivery as long as it contains the drug because the matrix geometry keeps constant the relationship between the drug diffusion path and the effective area of the dissolution boundary.

Therefore, different release profiles can be obtained with this type of matrix by making simple changes, such as modifying some physical and chemical characteristics of the channeling agent (particle size, shape, solubility, and deformation properties). In particular, in this article, we deal with the influence of the nature of the channeling substance on the time lag periods. Also, the reactive dimension of these substances will be analyzed as a limiting factor for the drug release behavior.

EXPERIMENTAL

Materials

Methylene blue (Acofarma, Barcelona, Spain) was chosen as a model drug because of its solubility and pigment properties. This permitted observation of passage through the matrix tablet and into the dissolution medium. Lactose was used as the core binder. Sodium chloride, mannitol, and Emdex® were selected as water-soluble channeling substances, while Eudragit® RS100 was used as an inert polymer. Disodium hydrogen phosphate anhydrous and potassium dihydrogen phosphate were used to buffer the dissolution medium.

Drug Core Preparation

A syrup paste formed by methylene blue and lactose (50% w/w) was manually transformed into spherical granules. A hollow hemisphere mold was loaded with a 30-mg granule thus obtained, and a similar brass mold was placed over it to obtain the spherical core. A number of these spheres were prepared and stored in a desiccator.

Matrix Preparation

All components of the matrix were individually crushed and sieved (Retsch, type Vibro). Four granulometric fractions (50–100, 100–150, 150–200, and 200–250 μm) for the channeling agent and only one (150–200 μm) for Eudragit RS100 were selected.

A Malvern Mastersizer (Malvern, UK) particle size laser diffractometer was employed to measure the particle size distribution for the fractions selected. The focal length was 300 mm. The particles were suspended in ethanol during measurement, and the obscuration was adjusted between 10 and 30. After adding the sample, ultrasound was employed to break down cohesive aggregates. The appropriate fraction of the channeling substance and of the polymer were mixed in a V blender for 20 min to obtain binary mixtures in the ratio 50:50 for both components.

Tablet Preparation

The formulations were tableted on an eccentric machine (Bonals, A-300) using concave punches (9-mm diameter). Half of the binary mixture (325 mg) was placed into the bottom punch. The core was then carefully placed into the center of the base. Finally, the remaining powder was added. Biconvex tablets were obtained. Each tablet weighed 680 ± 5 mg and contained 15 mg of drug.

Dissolution and Drug Release Studies

Release tests were performed using the USP paddle apparatus (Turu Grau, model D-6, Barcelona, Spain). Experimental conditions were 900 ml of dissolution medium at 37°C ± 0.5°C and 50 rpm. The tablets were first placed into a medium simulating a gastric fluid (pH 1.2). After a 60-min interval, the medium was substituted by a different solution simulating an intestinal fluid (pH 7.5 ± 0.5 Sorensen phosphate buffer).

The release of the model drug was assayed spectrophotometrically (Hitachi, model U-2000) at 608 nm. All release studies were carried out in triplicate.

RESULTS AND DISCUSSION

The delivery system was designed as a drug core enclosed in a matrix formed by Eudragit RS100 as the inert

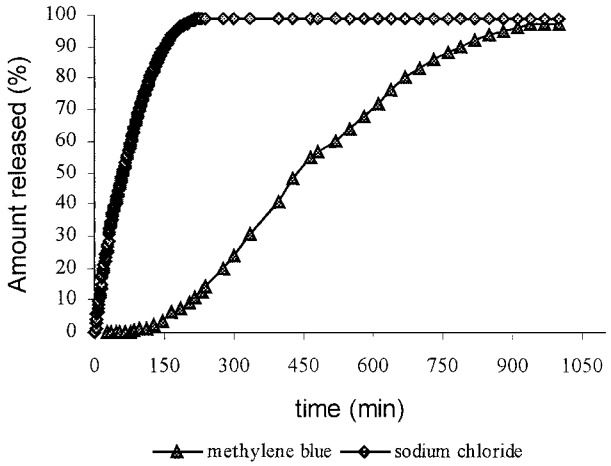

Figure 1. Release profiles obtained for the drug and the channeling agent in the same tablet. The quantitative valoration of both substances was simultaneous. Sodium chloride particle size was 100–150 μm.

polymer and a channeling substance (sodium chloride, mannitol, or Emdex). On contact with the aqueous medium, the soluble component begins to dissolve (Fig. 1). During a lag time, which coincides with the release of the channeling agent, the fluid penetrates through the channels created inside the matrix, reaching the drug placed in the central core. The dissolved drug then diffuses out toward the external medium. Results demonstrate that the drug starts to be released when more than 80% of the channeling component is dissolved.

The dissolution and release mechanism of the channeling agent can be fitted with the Higuchi equation (14), by which the amount released per square centimeter of tablet surface is linearly related to the square root of time (15). According to the release profiles, it can be appreciated that the drug diffusion occurs under a constant concentration gradient until the end of the process. This fact was corroborated by making a transverse section of the matrix before and after the release process (Fig. 2). No observable drug particles were present in the tablet after the release process, indicating that sink conditions were maintained throughout the dissolution process.

Two dependent variables that affect the release profiles are discussed here as a function of different physicochemical properties of the channeling agent, the time lag periods, and the zero-order periods.

Effect of the Channeling Substance on the Delay of the Time Lag Periods

The proposed system combines geometry with the principles of dissolution and diffusion to modulate the time lag periods of the model drug. The different formulations used in this study are shown in Table 1, which shows the different channeling agents used for the matrix preparation. Figure 3 shows the release profiles from systems containing 50% inert polymer and the different channeling substances (sodium chloride, mannitol, or Emdex) using the granulometric fractions selected.

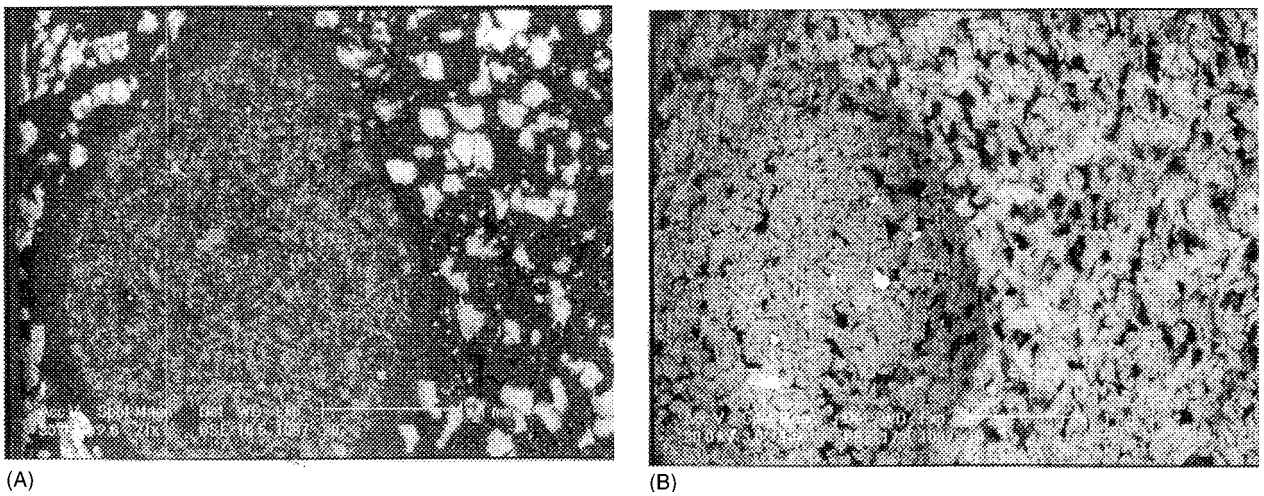

Figure 2. Microphotograph corresponding to a transverse section of a matrix tablet formed using sodium chloride as the channeling agent: (A) before the release process; (B) after the release process.

Table 1

Compositions of the Formulations Used

Channeling Substance		Tablet	
Type	Mean Diameter ± SD (mm)	Weight ± SD (mg)	Thickness ± SD (mm)
Sodium chloride	87.25 ± 2.09	668.11 ± 5.36	8.30 ± 0.10
	140.6 ± 2.68	662.66 ± 5.01	7.64 ± 0.31
	201.9 ± 3.51	671.30 ± 4.81	7.28 ± 0.10
	240.92 ± 1.85	678.90 ± 6.04	7.27 ± 0.08
Mannitol	60.33 ± 1.11	673.86 ± 4.13	9.66 ± 0.09
	109.53 ± 2.21	671.42 ± 6.67	9.64 ± 0.22
	183.39 ± 2.59	671.93 ± 6.91	9.54 ± 0.30
	249.63 ± 3.12	674.23 ± 3.93	9.45 ± 0.07
Emdex	67.61 ± 0.89	67.61 ± 0.89	9.42 ± 0.06
	122.69 ± 2.74	122.69 ± 2.74	9.23 ± 0.04
	185.46 ± 1.48	185.46 ± 1.48	9.14 ± 0.10
	258.97 ± 3.25	258.97 ± 3.25	9.02 ± 0.02

Eudragit RS100 with a mean particle size of 150–200 μm was used for all the batches.

Graphically, the lag time values were calculated from the intercept on the time axis of the straight lines interpolating the experimental data (see lines in Fig. 3). The results demonstrate that the nature of the channeling agent significantly affects the drug release delays (Table 2). The matrices containing sodium chloride display a more prolonged time lag than those containing mannitol and Emdex.

The results were interpreted as follows. The production of a matrix from a particulate mass requires the formation of many strong interparticulate bonds. According to Duncan-Hewitt and Papadimitropoulos (16), the applied compaction stress decreases the tablet porosity by increasing the particle-particle contacts, and a plastic deformation produces relatively large areas of interparticle contacts where adhesion can occur. In addition, as Down has demonstrated (17), in the case of sodium chloride, limited fractures of the crystals occur as a result of high localized stresses created during particle rearrangement. As compression continues, further stress cracks are created together with extensive plastic flow of the crystals. The interparticle adhesion makes difficult the entry and diffusion process between the solute and the dissolution medium. As a consequence, the exit of drug from the device is delayed.

However, only an elastic deformation was experienced by mannitol and Emdex particles (18,19). In these cases, the number of the particle-particle spaces increased, and the delay was shorter since the diffusion pathway was shorter.

On the other hand, the release profiles (see Fig. 3) of Emdex show practically no lag period. This excipient is highly water soluble (1 g/ml). When a tablet is wetted by the aqueous medium, Emdex particles rapidly dissolve, and the drug release process starts after 10 min.

Figure 4 shows the effect of the particle size of the water-soluble substance on the time lag modulation. An inverse relationship between these parameters can be observed: Large particles provide large channels in the matrix, facilitating the diffusion process of the drug toward the dissolution medium. The rheological properties of the powders were examined concerning their influence on the beginning of drug release. Figure 5 shows the relationship between the particle average (mean) diameter and the bulk density of the binary mixtures. This parameter is known to be affected by the size, as well as the shape, of the particles. In fact, in tablets of a constant volume, as the particle size decreases, the number of particles increases, and more particle-particle spaces generally are present in the matrix.

An increase in bulk density is expected as the particle size decreases (20), together with a consequent decrease in porosity. This was observed in the case of the 150–200 μm granulometric fraction, for both water-soluble materials and Eudragit RS100, which presented the highest bulk density. This behavior was observed

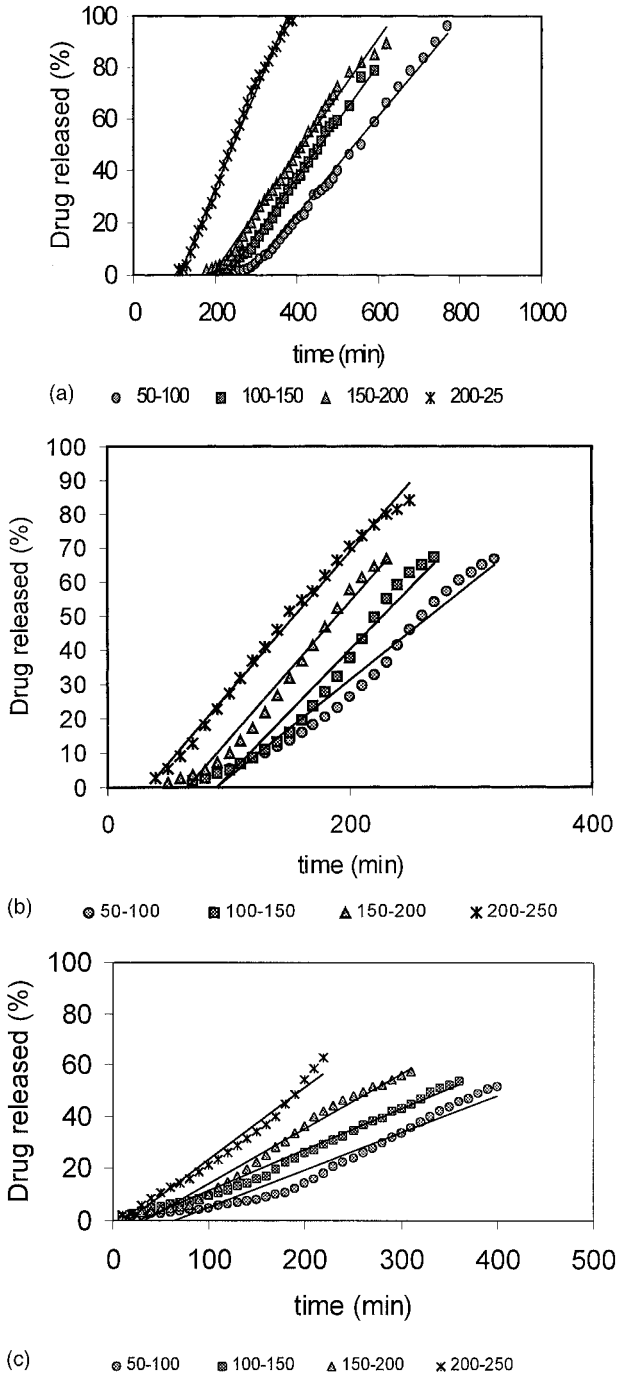

Figure 3. Amount of methylene blue (%) released versus time (min) for the batches indicated: (a) sodium chloride; (b) mannitol; (c) Emdex.

also for tablets manufactured with sodium chloride or Emdex.

Effect of Water-Soluble Substance on Drug Release Behavior

In many experimental situations, the mechanism of drug diffusion deviates from the Fickian equation. In these cases, a general equation, proposed by Ritger and Peppas (21), can be used:

$$\frac{M_t}{M_\infty} = k \cdot t^n$$

where M_t/M_∞ is the fractional release of the drug, t is the release time, k is a constant related to structural and geometric characteristics of the release device, and n is the release exponent related to the release mechanism. This equation also may be used also for the device proposed because, in this case, the drug diffusion coefficient is concentration independent. Diffusion is one dimensional, that is, the aspect ratio of the channels (length/thickness or width/thickness) is at least 10/1. Finally, the equation has been proposed for use with systems in which drug diffusion occurs through the polymeric structure (network) and not from porous systems since the combined mechanisms will shift the release exponent toward smaller values.

The profiles obtained demonstrate that the methylene blue release approximates zero order in all cases. Data were analyzed using the exponential relationship previously presented, and the exponent n was determined (Table 3). Results demonstrate that a nearly constant release rate was achieved with these systems, and the existence of zero-order release periods was observed.

The onset and end of these periods have been calculated in accordance with previous papers (12). Results indicate that tablets containing sodium chloride allow a drug release at a constant rate for a longer time, while tablets containing mannitol show the smallest value for this time. On the other hand, it was observed that an increase in the channeling particle size produced a decrease in zero-order periods. By assuming near saturation of the dissolved portion and a constant diffusion rate, when the diameter of channels is reduced, the flux through them must also be reduced. This fact is explained because of the smaller surface area through which the drug must diffuse. Therefore, the relationship between the drug diffusional path length and its effective dissolution area remains constant for a longer time, using smaller particle sizes, because of a more stable diffusion layer. As the

Table 2

Lag Time Values, Regression Functions, and Correlation Coefficients r *Obtained*

Channeling Agent	Mean Diameter (μm)	Lag Time (min)	*r*
Sodium chloride	87.25 ± 2.09	279.99 ± 1.59	0.9911
	140.6 ± 2.68	229.99 ± 3.12	0.9908
	201.9 ± 3.51	193.70 ± 2.69	0.9922
	240.92 ± 1.85	112.00 ± 1.96	0.9945
Mannitol	60.33 ± 1.11	89.25 ± 1.12	0.9694
	109.53 ± 2.21	89.88 ± 2.31	0.9622
	183.39 ± 2.59	65.79 ± 2.58	0.9778
	249.63 ± 3.12	33.04 ± 3.01	0.9941
Emdex	67.61 ± 0.89	63.32 ± 1.58	0.9495
	122.69 ± 2.74	33.43 ± 2.63	0.9787
	185.46 ± 1.48	27.74 ± 3.05	0.9841
	258.97 ± 3.25	16.50 ± 1.79	0.9759

particle size increases, the surface area exposed to the medium, and consequently the diffusion layer, is less stable and requires a more gradient concentration profile.

CONCLUSIONS

The device proposed is a new pharmaceutical system designed to prevent the drug release until a predetermined lag time independent of normal physiological conditions. The system can be manufactured using conventional industrial equipment and with excipients that are widely used in the pharmaceutical industry.

Optimization of the drug release rate from the proposed device requires an appropriate choice of excipients. Modulation of the lag time periods can be achieved by modifying the particle shape and size. The study suggests that constant release rates are reached with smaller chan-

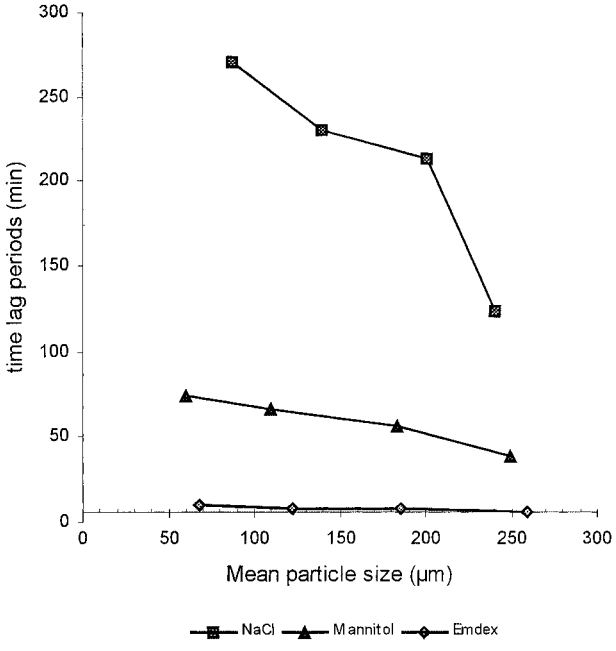

Figure 4. Relationship between the mean particle size of the channeling substance and the time lag periods obtained during the release process.

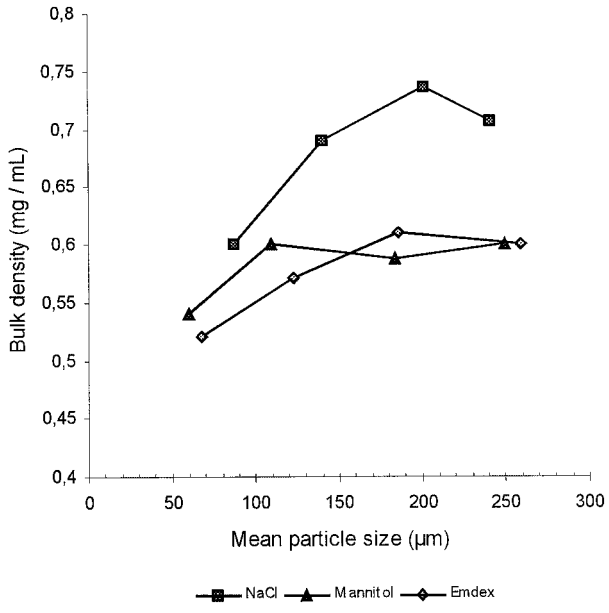

Figure 5. Effect of the mean particle size of the channeling substance on the bulk density.

Table 3

Kinetic Parameters and Zero-Order Periods

Water Soluble Substance		Kinetic Exponent *n*		Zero-Order Periods	
Type	Mean Diameter (μm)	*n*	*r*	Duration (min)	K (mg · min^{-1} · 100)
NaCl	87.25 ± 2.09	0.89 ± 0.0012	0.9620	400 ± 5.71	0.20
	140.6 ± 2.68	1.10 ± 0.0007	0.9991	390 ± 7.56	0.23
	201.90 ± 3.51	0.95 ± 0.0020	0.9990	350 ± 5.22	0.24
	240.92 ± 1.85	0.80 ± 0.0008	0.9549	190 ± 3.87	0.41
Mannitol	60.33 ± 1.11	0.95 ± 0.0005	0.9797	102 ± 7.41	0.40
	109.53 ± 2.21	0.91 ± 0.0010	0.9772	146 ± 8.52	0.55
	183.39 ± 2.59	0.94 ± 0.0041	0.9862	88 ± 3.25	0.49
	249.63 ± 3.12	0.95 ± 0.0011	0.9984	62 ± 1.99	0.43
Emdex	67.61 ± 0.89	0.99 ± 0.0008	0.9958	190 ± 7.51	0.19
	122.69 ± 2.74	0.97 ± 0.0012	0.9805	214 ± 5.64	0.19
	185.46 ± 1.48	0.99 ± 0.0051	0.9813	108 ± 5.88	0.28
	258.97 ± 3.25	1.00 ± 0.0007	0.9757	104 ± 4.96	0.25

k, release constant; *n*, kinetic exponent; *r*, correlation coefficient.

nel diameters, giving a better zero-order approximation over a longer period of time.

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