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Evaluation of cross-linked amylose press-coated tablets for sustained drug delivery

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Abstract

Based on the physico-chemical properties of cross-linked amylose (CLA), a hydrophilic polymer, we were able to design dry-coated tablets for time-independent and complex drug release. To make the cores, CLA was mixed with the model drug in different proportions and then compressed. The cores were coated manually, consisting of either pure CLA or a mixture of CLA with a small proportion of solute. Diltiazem HCl and acetaminophen were the model drugs used. CLA dry-coated tablets behave as reservoir systems where the outer gel layer acts as a solution-diffusion membrane, through which transport occurs by a process of dissolution of the permeating drug in the polymer at one interface and diffusion down a gradient in thermodynamic activity. After the drug has established a uniform concentration gradient within the outer membrane (lag time), drug release is linear for the range of constant thermodynamic activity in the core. For the same core composition, decreasing the coating thickness or incorporating small amounts of NaCl in the shell shorten the release lag time and increase the release rate. By varying the drug to CLA ratio in the core we are able to optimize the release profiles. Zero-order release profiles with or without a time delay were developed. Tablets for complex delivery (staircase profile) were also devised. © 1997 Elsevier Science B.V.

Keywords: Compression coating; Controlled release; Cross-linked amylose; Hydrophilic matrix; Acetaminophen; Diltiazem HCl

1. Introduction

For many years, one of the major axes in pharmaceutical research was the synthesis of new active ingredients capable of delivering therapeutic improvement. Though this continues to be a

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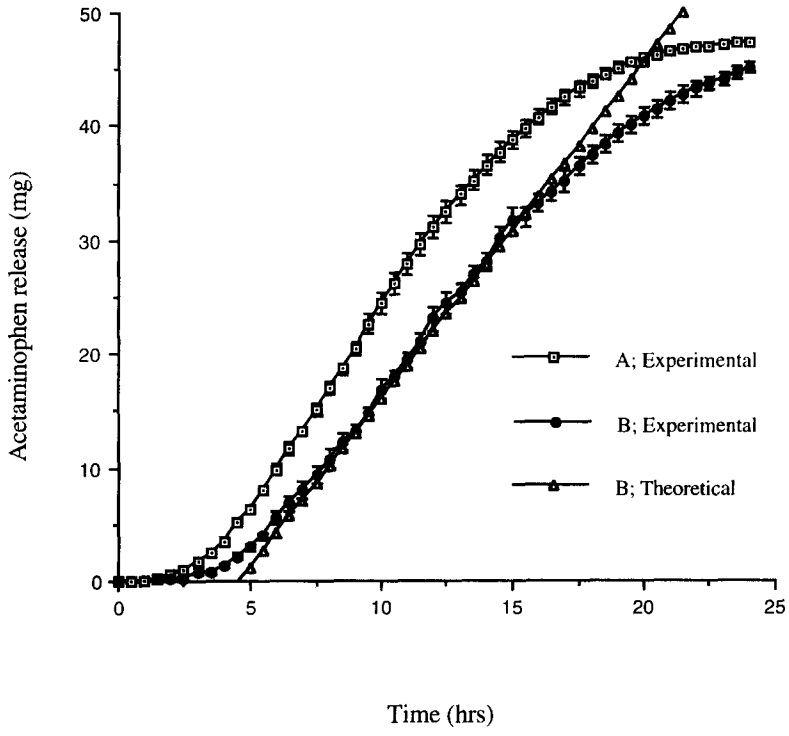

Fig. 1. Influence of coating thickness on drug release from press-coated tablets containing 50 mg of acetaminophen and 50 mg of CLA-8 in the core. The coating consisted of either 200 mg (A) or 250 mg (B) CLA-8.

fundamental trend, increased attention is being given to controlling drug administration characteristics or even their pharmacological activity (Ségot-Chicq et al., 1985).

Among the many oral dosage forms designed for controlled release of drugs, tablets are of major interest in the pharmaceutical industry because of their highly efficient manufacturing technology.

Amylose is a natural substance obtained from starch. It is essentially a linear polymer of glucopyranose units with α-D-(1 → 4) linkages (Banks and Greenwood, 1975). Cross-linked amylose (CLA) is a novel excipient for controlled release of drugs in solid dosage forms (Lenaerts et al., 1991). CLA is produced by the reaction of amylose with epichlorohydrin in an alkaline medium. Different degrees of cross-linking can be obtained by varying the ratio of epichlorohydrin to amylose in the reaction vessel (Mateescu et al., 1991, 1993).

CLA tablets are prepared by direct compression and are highly resistant to mechanical stress in the dry state (Dumoulin et al., 1994a). When in contact with aqueous fluids, water diffuses into the matrix with subsequent formation of an outer gel layer. Progressive water sorption leads to significant swelling of the matrix (Moussa and Cartilier, 1995). No significant variation in the in vitro dissolution profiles was observed with increasing compression force over the whole range of 0.15 to 5.5 T (Lenaerts et al., 1992). With degrees of cross-linking below 11, the swollen polymeric matrix does not undergo any erosion in vitro resulting in a dense and homogeneous rubbery matrix. Depending on the degree of cross-linking of the matrix, different degrees of swelling are obtained (Lenaerts et al., 1991; Moussa and Cartilier, 1996).

In the formulation of CLA simple matrices one is limited by the charge of drug to incorporate in the tablet as well as the choice of release profiles.

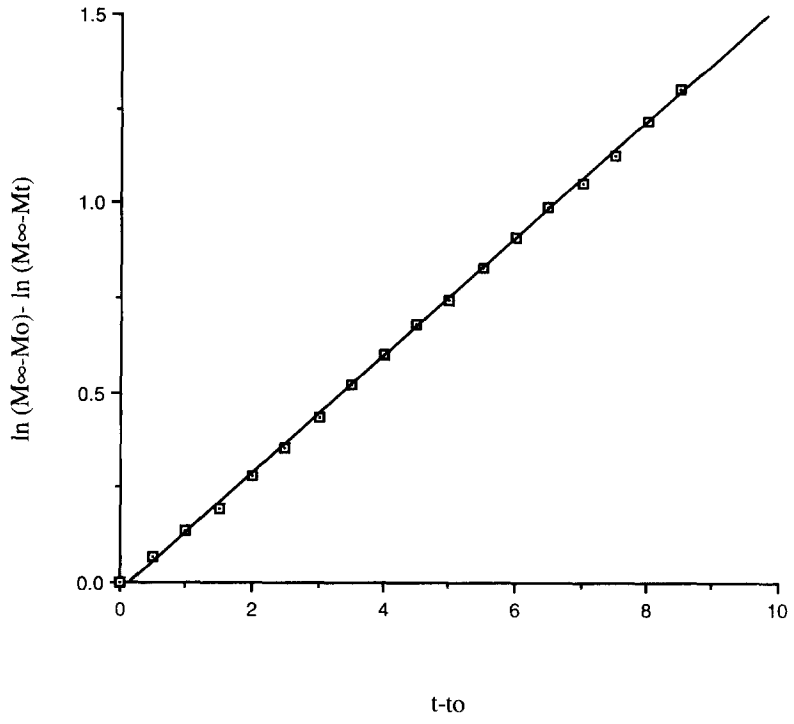

Fig. 2. Plot of $\ln(M_\infty - M_t) - \ln(M\infty - M_0)$ as a function of $-(t - t_0)$ for tablets consisting of 50 mg of acetaminophen and 50 mg of CLA-8 in the core, and 250 mg CLA-8 in the coating ($M_0 = 31.97$ mg, $M_\infty = 50$ mg, and $t_0 = 15.5$ h).

Our aim was, therefore, to evaluate in vitro release performances of CLA press-coated tablets as systems for sustained drug delivery and understand the mechanisms of release.

2. Materials and methods

2.1. CLA synthesis

Corn Amylose (300 g, Amylose Hylon VII, National Chemical Starch) and sodium hydroxide (1.8 l, 1.0 N, 54°C) were mixed in a planetary mixer (Hobart Model N-50, USA). After homogenization (15 min), epichlorohydrin (15.3 ml) was slowly added with continuous homogenization (15 min). The CLA gel was then neutralized with acetic acid and washed 3 times through a Büchner funnel with a solution of water/acetone (60:40 v/v). In the final step, the resulting solid gel was washed and dried with pure acetone over a Büchner filter (Dumoulin et al., 1994b). The polymer was then exposed to air (72 h) and stored in hermetic glass bottles. By convention, this polymer is referred to as CLA-6, with 6 being the number of g of epichlorohydrin added per 100 g of amylose. CLA-8 was synthesized under exactly the same conditions except for the amount of epichlorohydrin added.

Granulometric fractions between 75 and 250 μm were used to prepare the tablets. An extensive study of the influence of CLA particle size upon the in vitro dissolution profiles from CLA simple matrices has already been done (Zolia, 1994). No significant variation in drug release profiles was observed between granulometric fractions in the range of 45 to 250 μm.

In order to examine batch-to-batch variability, the release of a standard drug and water uptake studies are carried out. For example, the equilibrium water uptake values for CLA-4 simple matrices (average of 5 tablets/batch) obtained from three different batches were 0.28 ± 0.01, 0.30 ± 0.02 and 0.31 ± 0.01 g. According to Bon-

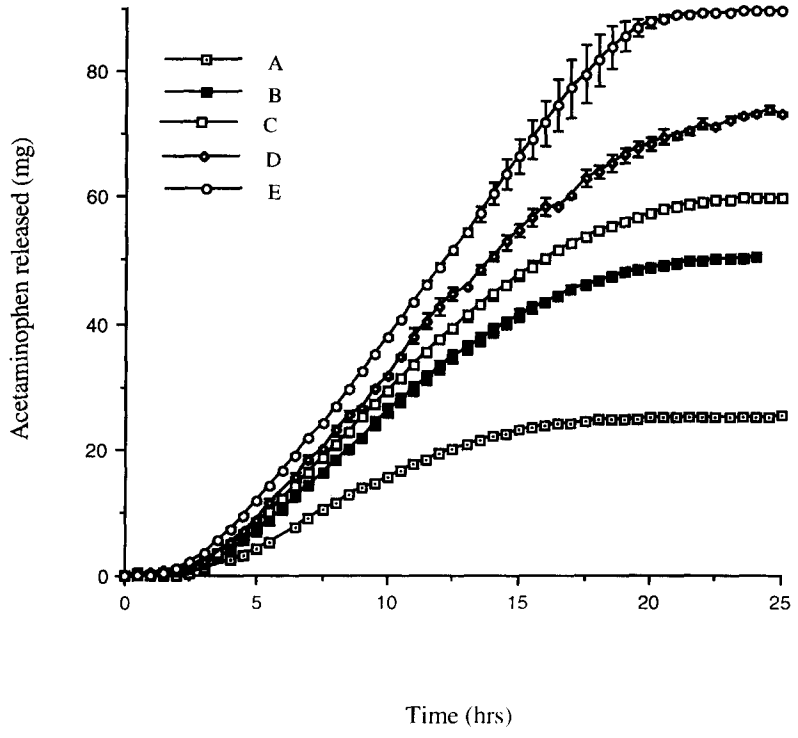

Fig. 3. Drug release from press-coated tablets containing different fractions of acetaminophen and CLA-8 in the core. Acetaminophen constituted either 25 (A), 50 (B), 60 (C), 75 (D) or 90% (E) of core weight (100 mg). The coating consisted of 200 mg CLA-8.

ferroni t-tests, we find no significant difference in the water uptake values from the three batches ($P < 0.05$).

2.2. Tablet preparation

Each dry-coated tablet consisted of a core and a shell. Several formulations were prepared in this study. The weight of the core was kept constant at 100 mg for all formulations. The weight of the shell was either 200 or 250 mg. The active ingredients were mixed with CLA in a Turbula shaking mixer (30 min, 25 rpm).

The dry-coated tablets were compressed using a hydraulic press (Specac, England). The core of each tablet was coated manually by carefully placing it in the center of a powder bed. The remaining powder belonging to the shell was spread over the core and base. Concave punches 8 mm in diameter and a compression force of 2 T were used to prepare the cores, while 12.8-mm concave punches and a 2 T force produced the final coated form.

2.3. In vitro drug release

The dissolution of acetaminophen (Mallinckrodt, USA) and diltiazem hydrochloride (DLTZ) (Marion Merrell Dow, Canada) was studied in dissolution test apparatus 2 (Model 72, Hanson Research, USA) equipped with a paddle system (USP XXIII). The tests were conducted in distilled water (1 l for DLTZ and 900 ml for acetaminophen) at 37°C and 50 rpm in triplicate. Drug release was followed spectrophotometrically (Diode Array 8452A, Hewlett Packard, USA) by continuous recording (234 to 242 nm for DLTZ and 234 to 252 nm for acetaminophen) in a closed loop system with a peristaltic pump at a flow rate of 8 ml/min.

2.4. Water uptake

A gravimetric method was used to record water uptake with measurements registered in triplicate. At the appropriate time interval, each tablet was taken from solution with forceps, briefly patted with lint-free cleaning tissues to remove the solution wetting its surface, and weighed (Ofner III and Schott, 1986).

3. Results and discussion

In the formulation of CLA dry-coated tablets, we would expect the outer layer to hydrate in contact with water to form a gel layer. This film would thus act as a solution-diffusion membrane, through which transport occurs by a process of dissolution of the permeating drug in the polymer at one interface and diffusion down a gradient in thermodynamic activity. The core of the tablet would be the drug reservoir. Hence, if the thermodynamic activity of the drug is kept constant within the core, we should expect that a steady state will be established during which the release rate will be constant. Since drug release predominantly occurs through the axial sides of the tablet, we can approximate our system to a sandwich geometry. Assuming sink conditions (Crank, 1970), the release rate of a reservoir device would then be

$$dM_t/dt = D \cdot S \cdot K \cdot C_d/h \quad (1)$$

where M_t is the mass of drug released, dM_t/dt is the steady-state release rate at time t, S is the surface area of the device (both surfaces, edge effects are ignored), D is the diffusion coefficient of the diffusant, K is the partition coefficient, C_d is the internal drug concentration, and h is the membrane thickness. DK/h correspond to the membrane permeability (P).

At the initial stage, however, if no drug was already incorporated in the coating, a certain time (lag time, t_L) would be required for the drug to establish a uniform concentration gradient within the membrane separating the core from the outer medium. t_L is the point of intersection of the extrapolated steady-state portion of the release line to the time axis. For a slab or sandwich geometry, the lag time is given by

$$t_L = h^2/6D \quad (2)$$

and Eq. (1) can be integrated and rewritten as:

$$M = D \cdot S \cdot K \cdot C_d \cdot (t - t_L)/h \quad (3)$$

Even in the case where unit thermodynamic activity of the drug within the reservoir was initially established, continual loss of drug or dilution by imbibed water causes the drug activity and hence the release rate to fall exponentially with time (Baker and Lonsdale, 1974). We would, hence, observe a first-order drug release that can be expressed as

$$\ln(M_\infty - M_0) - \ln(M\infty - M_t) = k \cdot (t - t_0) \quad (4)$$

where t_0 is the time at which drug activity begins to decrease, M_0 is the cumulative amount of drug released during steady-state conditions, M_∞ is the mass of drug released as time approaches infinity, k is the first order release rate constant, and $M_0 \leq M_t \leq M_\infty$.

If CLA dry-coated tablets are to behave as a reservoir system, we should expect an initial lag time (if no drug initially in the shell), followed by a linear drug release that shifts into a first-order process with a decreasing C_d.

3.1. Effect of coating thickness on drug release

In order to understand the mechanism of drug release from CLA dry-coated we studied first the effect of coating thickness on acetaminophen release profile. Different coating thicknesses were obtained by varying the amount of material in the shell. By extrapolating the steady-state portion of release line A (Fig. 1) to the time axis using regression analysis we determined the lag time (3.19 h). Knowing t_L and h (0.18 cm, experimentally obtained) we calculated $SDKC_d$ from the corresponding slope (0.621 mg·cm·h^{-1}). Our objective was to use Eq. (3) to predict acetaminophen release profile for another membrane thickness and compare it to the experimental data. In order to predict the release from other tablets with a membrane thickness of 0.21 cm, we need to compute the lag time. The latter

Table 1
Influence of the amount of acetaminophen in the core on the release lag time

Drug load (%)[a]	Lag time (h)	Error (h)
25	3.11	0.09
50	3.13	0.06
60	3.12	0.03
75	3.19	0.07
90	3.04	0.04

[a] The total weight of the core was 100 mg. The coating consisted of 200 mg CLA-8.

was calculated based on Eq. (2) where $t_{Lb}/t_{La} = (h_b/h_a)^2$ (assuming D independent of h) and found to be 3.34 h. By doing so, we can see if we can predict drug release profile based on steady state conditions, and if so, determine the point at which deviation from linearity occurs. Fig. 1 shows the predicted and experimental release profiles for a membrane thickness of 0.21 cm. We can clearly see that the two curves superpose for a period of 10 h. The deviation point of the two lines ($t_0 =$ 15.5 h) should indicate that C_d is not constant anymore and we should expect an exponential decay in drug release rate. To verify this assumption, we plotted the left-hand side of Eq. (4) as function of $(t - t_0)$. If drug release follows a first order process we should then expect a linear relationship, with the slope corresponding to the release rate constant k. In fact, as seen in Fig. 2, the plot is linear and the value of k obtained by linear regression is 0.16 h^{-1}.

From the results obtained above, we find that CLA dry-coated tablets behave as reservoir systems where the outer gel layer acts as a solution-diffusion membrane, through which transport occurs by a process of dissolution of the permeating drug in the polymer at one interface and diffusion down a gradient in thermodynamic activity. The release mechanism of soluble drugs can be summarized as follows: after a lag time during

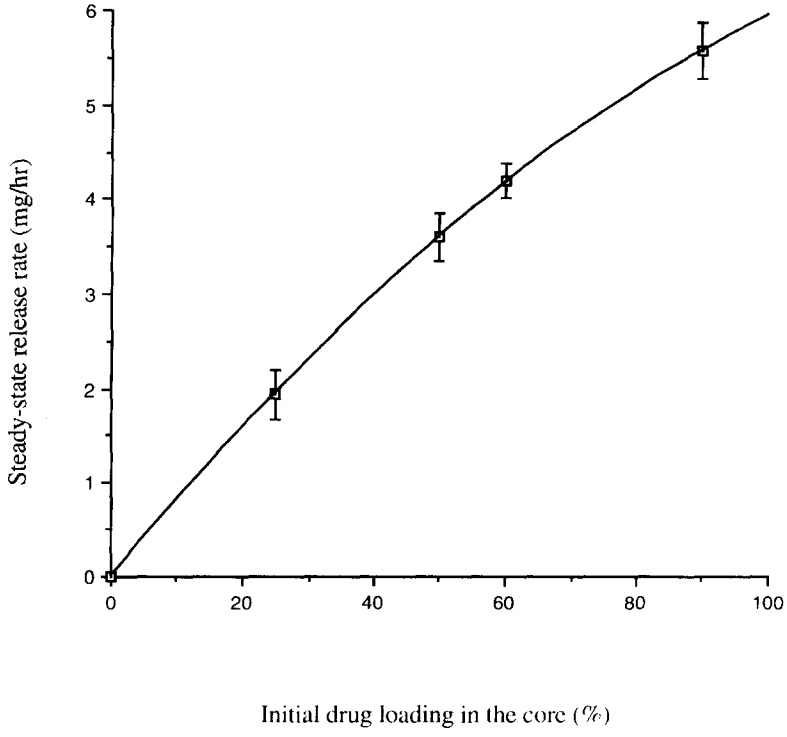

Fig. 4. Plot of the steady-state release rate (V_{SS}) as a function of drug loading (%) in the core (total weight of 100 mg). Tablet coating consisted of 200 mg CLA-8.

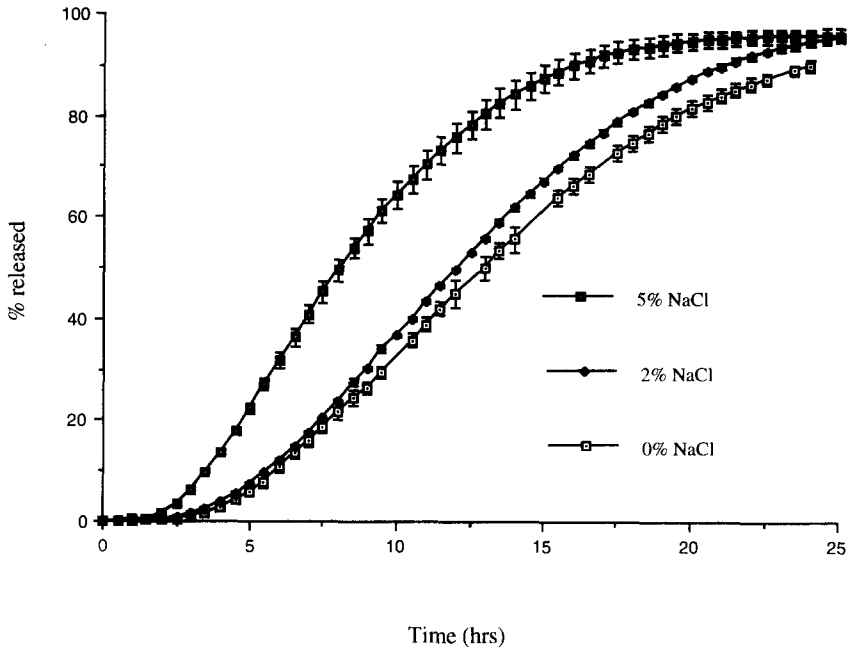

Fig. 5. Drug release from press-coated tablets containing 50 mg of acetaminophen and 50 mg of CLA-8 in the core. NaCl was added to CLA-8 in the coating in different proportions (0%, 2% or 5% NaCl of the 250 mg coating).

which the drug establishes a uniform concentration gradient within the outer membrane, drug release is linear as long as the thermodynamic activity of the drug in the core is constant. After a certain while, due to continual loss of drug, the internal drug concentration begins decreasing. This leads to a shift in the mechanism of drug release from zero-order to a first-order process.

In addition, we showed that by assuming a slab or sandwich geometry we can predict the influence of coating thickness on the lag time as well as the profile of the steady-state portion of the release line.

3.2. Effect of drug loading in the core on acetaminophen release

If CLA dry-coated tablets act in fact as reservoir devices, the amount of drug which must be released from the device should not influence the time to reach steady-state, since the release lag time would only depend on D and h. Tablets with different ratios of acetaminophen to CLA-8 in the core were, therefore, prepared with the total weight of core kept constant at 100 mg. The influence of acetaminophen loading in the core on the release profiles is shown in Fig. 3. By extrapolating the steady-state portion of the release lines to the time axis using regression analysis, we determined the corresponding lag time values. As seen in Table 1, no significant difference exists between the lag time values irrespective of the amount of drug incorporated in the core. This implies that CLA dry-coated tablets do, in fact,

Table 2
Influence of the amount of NaCl in the shell on the degree of water uptake

NaCl in the shell (%)[a]	Degree of water uptake (%)	90% CL[b] (%)
0	368	9
2	382	13
5	395	21

[a] The core consisted of 50 mg acetaminophen and 50 mg CLA-8. The coating (250 mg) contained CLA-8 and NaCl in different proportions.
[b] $n = 3$.

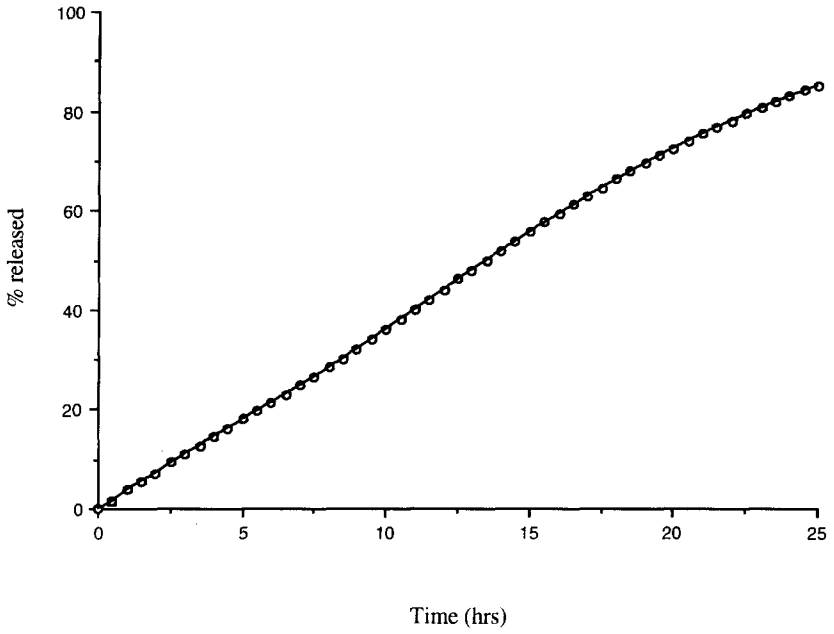

Fig. 6. Drug release from press-coated tablets containing 62.5 mg of acetaminophen. The core contained 50 mg of acetaminophen and 50 mg of CLA-6. The coating consisted of 12.5 mg acetaminophen and 237.5 mg CLA-6.

act as reservoir systems with drug release being controlled by the outer gel membrane.

On the other hand if we replace C_d in Eq. (1) by $F \cdot L_i$, we obtain the following expression:

$$dM_t/dt = D \cdot S \cdot K \cdot F \cdot L_i/h \quad (5)$$

where L_i is the amount of drug initially incorporated in the core (expressed as wt of drug/wt of core), and F is the proportionality coefficient. Hence a plot of the steady-state release rate (V_{ss}) as a function of L_i should allow us to evaluate the corresponding variation in C_d. If a linear relationship is obtained between V_{ss} and L_i, then C_d is directly proportional to L_i. This implies that C_d is still below the C_s of the drug. In order to verify that, the steady-state release rate was plotted as a function of L_i. V_{ss} was obtained experimentally. It corresponds to the plateau region of the rate of release curve. As seen in Fig. 4, the relationship between V_{ss} and L_i is not perfectly linear and is best fitted by a second order polynomial equation ($V_{ss} = -0.009 + 0.085L_i - 0.0002L_i^2$, $R^2 = 1.00$). The observed gradual decrease in V_{ss} with increasing L_i can be explained by the decrease in the dissolution rate of acetaminophen as C_d approaches C_s. We may, hence, conclude that with the current core dimensions, the C_d of soluble drugs incorporated in the core does not reach C_s even for a 90% drug loading. In other words, we can increase quasi-linearly the release rate of water soluble drugs from our system by increasing the initial drug loading in the core.

3.3. Effect of incorporating a water-soluble additive in the coating on acetaminophen release

Our aim was to shorten the release lag time without much affecting the drug release rate. So we thought that by integrating in small proportions an osmotic agent in the shell we may be able to speed up the hydration rate of the coating without much affecting the diffusion coefficient of the drug through the gel membrane. Three formulations containing varying amounts of NaCl in the coating were prepared. The resulting acetaminophen release profiles are shown in Fig. 5. No significant decrease in t_L was observed with a 2% NaCl concentration in the shell. On the other

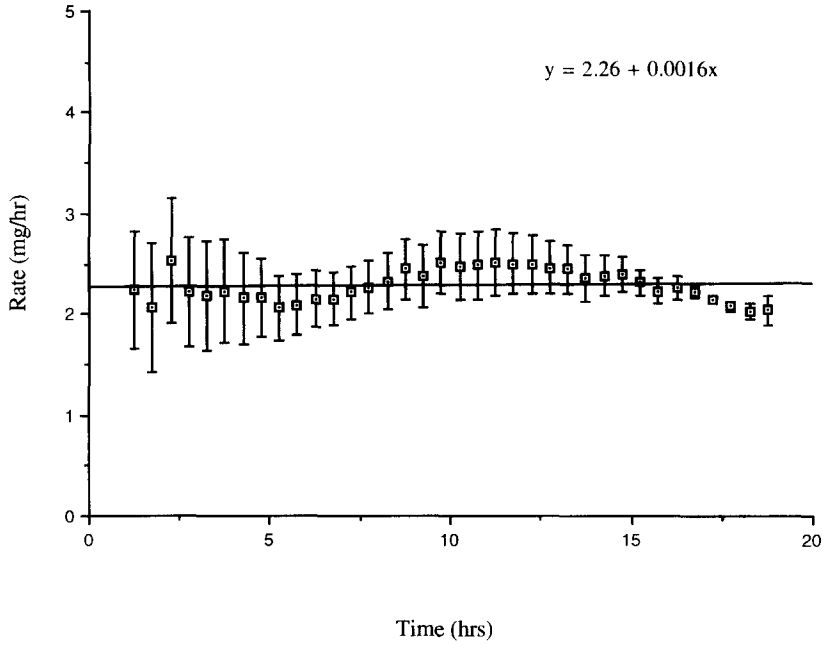

Fig. 7. Acetaminophen release rate from press-coated tablets containing 62.5 mg of drug. The core contained 50 mg of acetaminophen and 50 mg of CLA-6. The coating consisted of 12.5 mg acetaminophen and 237.5 mg CLA-6. The straight line was obtained by linear regression analysis.

hand an important shortening of lag time was obtained with the 5% NaCl formulation (Fig. 5). The general release profile was, however, considerably affected since the acetaminophen release rate was much faster than for tablets with 0 or 2% NaCl in the coating. A possible explanation could be that when 5% of the water soluble compound was incorporated in the coating, the initial flux of water sorbed into the coating was significant enough to interfere with the mechanism of gel formation in the coating. This led to a much more permeable outer gel layer and, hence, to a higher drug diffusion coefficient in the membrane. The water uptake values (Table 2) show that the total amount of water sorbed at equilibrium was considerably higher when 5% NaCl was incorporated in the shell.

3.4. Repartition of acetaminophen in the core and shell of CLA tablets

Now that the release behaviour of a water soluble drug incorporated in the core of CLA dry-coated tablets is mainly clear, we wanted to achieve a quasi-linear drug release with no lag time. We, therefore, decided to incorporate some drug in the shell. By properly selecting the core to shell repartition of acetaminophen, we were able to obtain a time-independent release. As seen in Fig. 6, by incorporating acetaminophen at a relative amount of 5% of shell weight, the release lag-time was reduced to zero without a burst-effect. As Fig. 7 shows, the drug release rate was constant (within the error limits) over a 15-h period. The horizontal line seen in Fig. 7 corresponds to the best-fit curve using linear regression analysis. It refers to the constancy of drug release that could be achieved with CLA press-coated tablets.

In order to obtain a zero-order drug release the active ingredient should be added to the shell in small amounts only. This would prevent the drug to saturate the surface of the coating and, hence, avoid any burst-effect. It will also decrease its influence on gel layer formation and, thus, on the consequent drug release rate from the core.

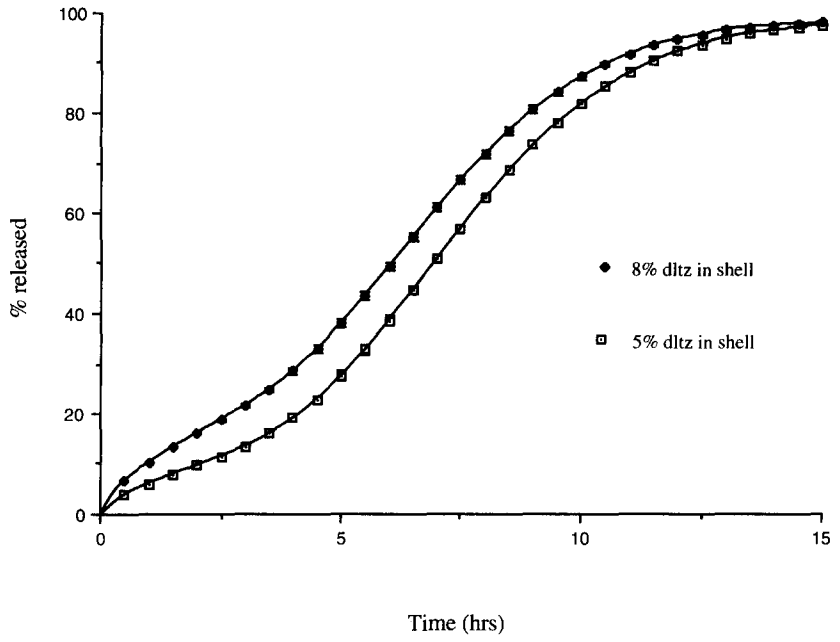

Fig. 8. DLTZ release from press-coated tablets containing 50 mg of drug and 50 mg of CLA-8 in the core. The coating (250 mg) contained DLTZ and CLA-8 in two different proportions (DLTZ: 5% or 8% of coating weight).

3.5. Bimodal drug release profiles

In cases where a disease has a marked diurnal rhythm, drug levels should vary during the day (Sirkiä et al., 1994). Asthma attacks, for example, usually take place early in the morning. Consequently, drug concentration should be highest when symptoms are most severe (Bogin and Ballard, 1992). It is also known that the morning hours between 04:00 and 08:00 h constitute a critical time for myocardial infarct and angina episodes (Thiffault et al., 1993). Hence, when a dosage form allowing increased drug release with time is administered in the evening, maximum drug levels may be expected the next morning.

We evaluated the potential of CLA dry-coated tablets for bimodal drug delivery. DLTZ was used as a model drug. Two formulations with different amounts of DLTZ in the coating were tested. In Fig. 8, the first phase of the release profiles corresponds to the release of drug incorporated in the shell following square-root-time kinetics. In the second phase the release of DLTZ occurs through diffusion of the drug from the core into the gel membrane with quasi-zero-order kinetics. Once DLTZ concentration in the core starts decreasing, drug release shifts into a first-order process. Each curve corresponds to the average of three assays. The very small error bars imply high reproducibility in the release profiles of CLA dry-coated tablets.

4. Conclusions

The CLA dry-coated tablet is formed of two compartments, an outer coating and an inner core. The outer layer is a gel-forming matrix layer. The core acts as a drug reservoir. In vitro studies in aqueous medium, have showed that the mechanism of drug release occurs by a process of dissolution of the permeating drug in the polymer at one interface and diffusion down a gradient in thermodynamic activity. The outer gel layer, thus, acts as a solution-diffusion membrane. When no drug is initially present in the coating, there exists a lag time during which the drug establishes a uniform concentration gradient within the outer

membrane followed by a linear drug release phase. After a certain while, due to continual loss of drug, the internal drug concentration begins decreasing. This leads to a shift in the mechanism of drug release from zero-order to a first-order process.

Acetaminophen steady-state release rate is controlled by core loading (2nd order polynomial relationship), coating thickness (linear relationship), and can be further tailored by the addition of soluble salts in the shell.

The release lag time is shortened by an increase in the diffusion coefficient of the drug in the gel layer (e.g. adding NaCl to the shell), or a decrease in the coating thickness.

By properly selecting the core to shell repartition of the active ingredient, zero-order as well as bimodal release profiles were obtained.

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