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IN VITRO AND IN VIVO EVALUATION OF SUSTAINED-RELEASE AND ENTERIC-COATED MICROCAPSULES OF DICLOFENAC SODIUM

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ABSTRACT

This work examines the release of diclofenac sodium from ethylcellulose (EC) microcapsules made up of different drug to polymer ratios. The release process was found to follow the Higuchi square root equation and not the zero-order or first order equations. However, for drug to polymer ratio of 1:1, a critical time (θ) was reached beyond which the release rate was lower than that predicted on the basis of the Higuchi square root equation. Dissolution experiments in 0.1N HCL revealed that less than 1.5% of the encapsulated drug was released in 6 h. This finding indicates the suitability of the EC microcapsules for enteric-coated preparations. The in vitro release of diclofenac sodium from microcapsules of different drug to polymer ratios was compared with that from a commercial sustained-release product. A distinct similarity between the release profile of the commercial product with that obtained for the 1:2 drug to polymer microcapsules was noted. The in vivo work included determination of the serum drug profile following oral administration of the microcapsules and the commercial product to rabbits. The obtained serum concentration time profile of the EC microcapsules exhibited a sustained-release pattern similar to the commercial product and consistent with the in vitro results.

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INTRODUCTION

Microencapsulation as a technique for the production of oral sustained-release dosage forms is well established (1). It involves the coating of the individual drug particles in a shell of inert polymeric material, through which the enclosed drug would diffuse at a controlled and predictable rate to the surrounding medium. Several microencapsulating materials have been reported including albumin (2), acryloylchloride-lysine (3), gelatin (4), crosslinked hemoglobin (5), and invertase (6). Ethylcellulose (EC), however, has been one of the most widely used coating materials. It has been used to produce microcapsules of several drugs, such as sodium salicylate (7), salicylic acid (8), phenobarbital sodium (9), theophylline (10), and nifedipine (11).

In studying the release of drugs from polymeric systems, it is important to characterize the kinetics of the release process from these systems. This involves determination of the mechanism of release and the kinetic model which best describes this release process. For EC, the overall release mechanism of drugs encapsulated in this polymer is thought to involve the permeation of the solvent into the microcapsule, dissolution of the drug, and diffusion through the microcapsule to the surrounding fluid through EC coat (10). The release from polymeric matrix systems such as EC is usually quantitatively described by the Higuchi square root equation (12) derived to describe the release of drugs embedded within a matrix system where the release process is diffusion controlled.

This work attempts to produce a sustained release as well as an enteric-coated microcapsules of diclofenac sodium through encapsulating it in EC microcapsules. Such microcapsules would reduce the gastric irritant action of the drug and produce sustained levels in the blood. This would reduce the frequency of dosing and minimize the toxic effects of the drug and hence improves patient compliance. The work therefore included: I) *in vitro* release characterization of microcapsules made up of different drug to EC ratios and analyzing the data obtained using different kinetic models, II) *in vitro* release studies of diclofenac sodium from a commercially available sustained-release product, and III) determination of the serum drug profiles in rabbits following the oral administration of the formulated microcapsules and the sustained-release product.

EXPERIMENTAL

Materials

Diclofenac sodium was kindly provided by Dar Al-Dawa Development and Investment Co., Amman, Jordan. Disodium hydrogen phosphate and EC were obtained from Sigma Chemical Company, U.K.

Preparation of the Microcapsules

The required amount of drug was dispersed in an EC solution in cyclohexane. The dispersion was then heated to 80°C and allowed to cool slowly at a controlled stirring rate to 40°C. The mixture was then cooled on an ice bath to 25°C and stirred for 20 minutes. The microcapsules were then separated from the solution by vacuum filtration on a Buchner funnel. The filtered

microcapsules were then washed with cyclohexane to remove any empty polymer coats. The microcapsules were then collected, oven-dried at 50°C for 30 minutes and stored in a desicator until used.

Assay For the Microcapsules Total Drug Content

In order to determine the total drug content of the microcapsules, 200 mg of the microcapsules were accurately weighed and triturated. The powder was then suspended in 100 ml of 0.1 N NaOH and filtered to separate the shell fragments. The diclofenac sodium content was determined spectrophotometrically at 277 nm. This was repeated three times for each sample. The three determinations of diclofenac sodium resulted in 98-101% of the expected values.

Dissolution Studies

Dissolution experiments of pure or microencapsulated diclofenac sodium were carried out using 100 mg of the pure drug or an amount of the microencapsulated drug equivalent to 100 mg pure drug in a USP dissolution apparatus (Erweka, DT-D6, W. Germany) maintained at 37°C. 500 ml of phosphate buffer (pH 7.4) or 0.1 N HCL (pH 1.2) were placed in the one liter flask. A stirring rate of 100 rpm was maintained throughout the experiment. Samples (5 ml) were withdrawn at designated time intervals and immediately replaced with a fresh dissolution medium. The samples were then filtered through a 0.22 um membrane filter unit (Millipore Ltd., U.K.). The diclofenac sodium concentration was repeated three times and the average values were taken. In all cases standard deviation was less than 3%. The same procedure was followed to measure the release from the commercial product Diclogesic (100 mg capsules, Dar Al-Dawa Development and Investment Co., Jordan).

Animal Experiments

For the assessment of the sustained-release pattern of the experimental formulation *in vivo*, adult male New Zealand rabbits, 3-5 kg, were used. Food was not given to the rabbits for 12 h prior to and during the experiment, but water was allowed *ad libitum*. A dose of 50 mg of diclofenac sodium in the form of either EC granules or peads of a commercial sustained-release product (Diclogesic R) suspended in 30 ml of water were administered by gastric intubation. Blood samples (1.5 ml) were collected just prior to drug administration and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h post administration. The blood was obtained from the marginal ear veins and allowed to clot (1 h) prior to centrifugation. The obtained serum was stored frozen until assayed. The serum samples were assayed for diclofenac sodium using an HPLC procedure as described by El-Sayed et (13). The data of the *in vivo* experiments are expressed as mean ± s.e.m.

RESULTS AND DISCUSSION

In general, the release kinetics of sustained-release preparations can be described by the use of one or more of three kinetic models comprising the zero-order equation (8), the first-order equation (14, 15) and the Higuchi square root equation

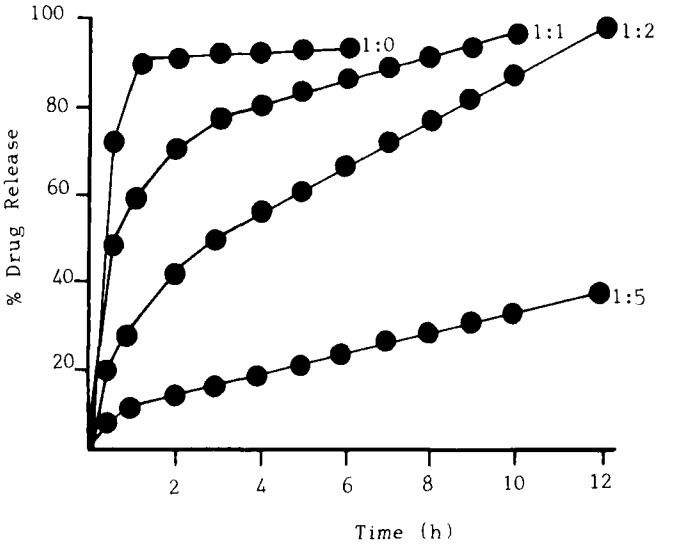

FIGURE 1.

Release profiles of diclofenac sodium from microcapsules made of different drug to EC ratios at pH 7.4 plotted according to zero-order equation.

(12). The applicability of all these equations to the release data of diclofenac sodium form EC microcapsules was tested in this work.

The dissolution rate profile of diclofenac sodium at pH 7.4 from EC microcapsules made up of different drug to EC ratios is shown in Figure 1, plotted in accordance with the zero-order equation. The release curves as indicated from the figure were not zero-order in nature. The release curves, however, showed tow distinct regions; an initial region in which the release of the drug occurs at a relatively fast rate and a terminating region in which reduction in the release rate is obtained as indicated from the negative deviation of the profile from linearity. The time at which leveling of the curve takes place, decreases as the percentage of the drug in the microcapsule increases. The decrease in release has been attributed to the progressive fall in concentration gradient across the matrix through which the drug diffuses to the exterior (9). Figure 1 also indicates that the sustained action increases as the polymer ratio in the microcapsule increases. For example whereas the 1:1 microcapsules release about 75% of their drug contents in 2 h, the 1:2 and 1:5 drug to EC microcapsules release respectively 40% and 15% of their drug contents at this time. This high release rates from 1:1 EC to drug microcapsules could be attributed to the presence of uncoated drug particles (16), since at this ratio the amount of EC might be insufficient to coat all the drug articles present as compared to lower ratios.

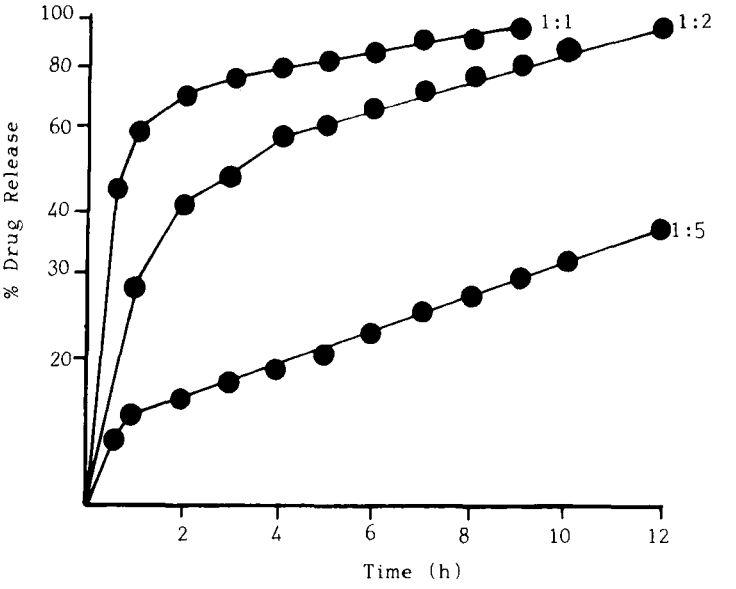

FIGURE 2.

Release profiles of diclofenac sodium from microcapsules made of different drug to EC ratios at pH 7.4 plotted according to first-order equation.

Figure 2 shows the release data plotted according to the first-order equation (logarithm of the amount released against time). None of the curves was linear suggesting that the release process was not dissolution controlled.

A plot of the data in accordance with the Higuchi square root equation is shown in Figure 3. In the case of the 1:1 EC to drug microcapsules, it is noted that the linearity of the amount released as a function of the square root of time applies up to a certain time, θ, which was about 1 h. For microcapsules made of 1:2 and 1:5 drug to EC, linearity was obtained throughout the duration of the experiment (12 h). It appears therefore that the Higuchi square root equation is only applicable for matrix systems containing relatively high proportion of the coating material. Deviation from the Higuchi equation when applied for matrices containing high proportions of water soluble materials have been reported by Fessi et al (17). Such deviations have been attributed to changes in the porosity and surface area of the matrix systems, and to the assumption that the concentration gradient in the penetrant liquid is linear. This latter assumption is contrary to what have been originally assumed in the derivation of the Higuchi equation. It is also possible that at time θ the amount of the drug remaining in the matrix is not sufficient to maintain a constant rate of drug diffusion from the matrix.

The release of drug from microcapsules made of 1:1 and 1:2 drug to EC in 0.1N HCl was investigated. The total amount of drug

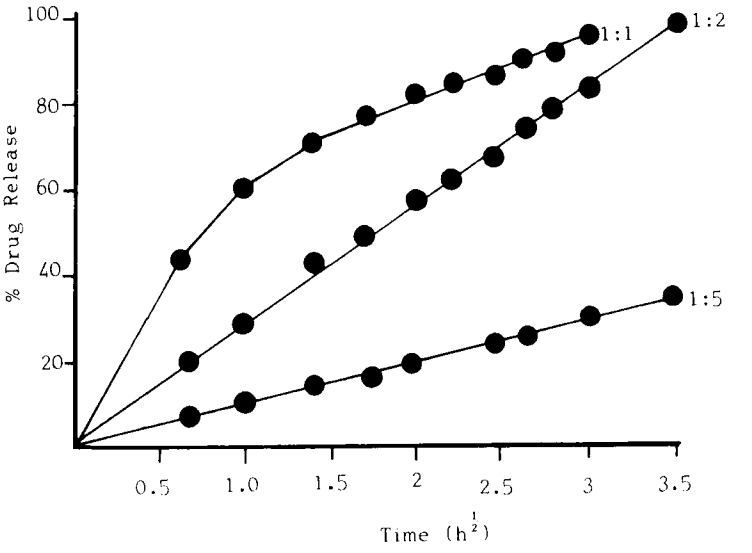

FIGURE 3.

Release profiles of diclofenac sodium from microcapsules made of different drug to EC ratios at pH 7.4 plotted according to the Higuchi square root equation.

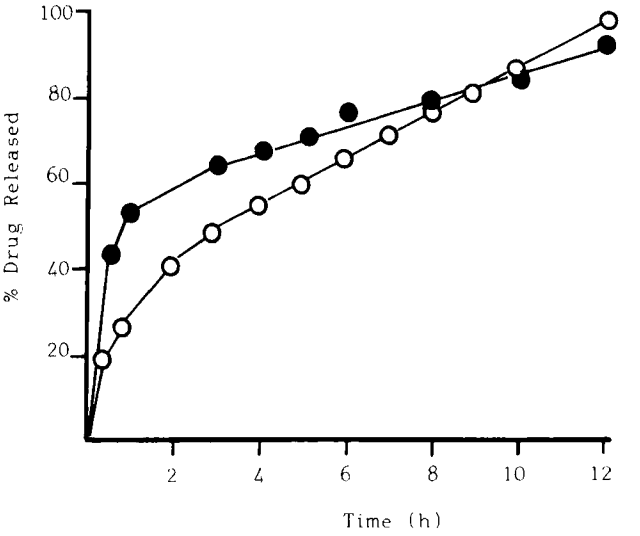

FIGURE 4.

Release profiles of diclofenac sodium at pH 7.4 from the commercial product, Diclogesic capsules (●), and the 1:2 drug to EC microcapsules (○).

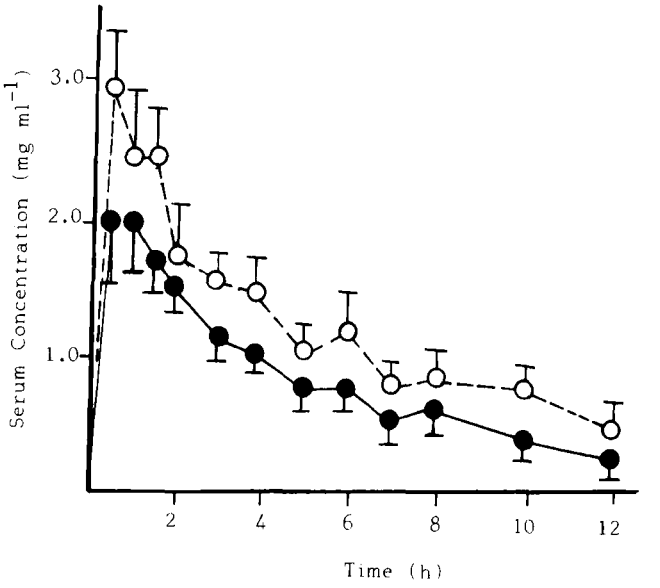

FIGURE 5.

Diclofenac sodium serum concentrations following oral administration of 50 mg of 1:2 drug to EC microcapsules to 5 rabbits (●) and 50 mg Diclogesic retard peads to 4 rabbits (O). The vertical bars represent s.e.m.

released in 6 h was less than 1.5% of the amount incorporated. This complies with the 10% release limit suggested by Chambles et al (18) for enteric-coated dosage forms. Thus, the microencapsulation of diclofenac sodium in EC provides an enteric-coated preparation for the drug.

In order to select the drug to EC ratio which might lend itself for further in vivo experimentation, the in vitro dissolution profiles of a commercially available sustained release product was obtained (Figure 4). It was noted that the drug release profile from microcapsules made up of 1:2 drug to polymer was similar to the profile of the commercial product. Therefore, this ratio was chosen to study the in vivo release of the drug EC microcapsules.

The mean serum profile of diclofenac sodium following oral administration of microcapsules (50 mg) and a sustained release product (Diclogesic retard, 50 mg) via gastric intubation to rabbits is shown in Figure 5. The two profiles are not significantly different from each other (assuming similar intrasubject variation following the two formulations). Further, the area under the concentration-time curves over 12 h calculated by the trapezoidal rule (19) were not found to be statistically different (10.80±1.81 and 14.34±1.81 ug.h/ml for EC microcapsules and Diclogesic, respectively) using the t-test for unpaired data. The elimination of diclofenac sodium following either product is

apparently very slow as reflected by the shallow slope of the terminal segments. This highly demonstrates that the 1:2 drug to EC microcapsules exhibits in vivo sustained -release properties comparable to a commercially available sustained-release product.

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