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EVALUATION OF THE MECHANISM OF RELEASE OF A WATER SOLUBLE DRUG FROM A WAXY INERT MATRIX

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The main purpose of this study was to characterize and evaluate the release of a water soluble drug from a waxy matrix under relatively mild agitation conditions. Increasing the ratio of the waxy polymer in the matrix was effective in retarding the release of the drug. It was found that tramadol hydrochloride was released from a typical waxy matrix by a diffusion controlled mechanism. The amount of the drug dissolved was proportional to the square root of time according to Higuchi model. The commpression force was not a major factor affecting the release of the drug.

Keywords: *Wax matrix; Tramadol HCl; Controlled release*

Introduction

In a matrix system, the drug in its powder form and a matrix-forming agent are mixed and the mixture is shaped in a suitable form to control the release of the drug. Therefore, the design of the dosage form is an important factor in accomplishing this goal. Foster et al.(1) showed that the method of processing affects the release of the drug from a matrix system. The most commonly used matrix-forming agents are erodible, swellable, non-bioerodible, and waxy polymers. The use of wax appears to be of particular advantage due to its chemical inertness against other materials. In addition, waxy polymers have main uses in sustained-release systems especially for highly water-soluble drugs(2).

In this study, an investigation of the mechanism of drug release from a waxy polymer has been performed with a view to clarify the relationship between the compression force and the release characteristics of the drug. An objective of the study was to develop a method for logical characterization of the release properties and the mechanism of drug release from a waxy inert matrix. The work was carried out using tramadol HCl in a wax matrix of glyceryl behenate as a typical system.

Materials and Methods

Preparation of matrices

The matrices were prepared by hot fusion method where glyceryl behenate (Gattefosse Corp., France) was melted at 75°C. Tramadol HCl (The Advanced Pharmaceutical Industries Co., Jordan) was added with continuous stirring. The molten mass was allowed to cool down and solidify and then was ground and screened through a 1.25 mm sieve. The retained granules were compressed into flat-faced, beveled edge, 15.9 mm tablets using a Carver press. Three compression forces were tested which were 1, 3, and 5 tons.

Invitro release procedure

Dissolution of tablets subjected to different compression forces was tested. A rotating paddle dissolution apparatus (Erweka, Germany) with a stirring rate of 75 rpm was used in the drug release studies and the temperature maintained at 37°C. The dissolution medium was 500 ml of phosphate buffer (pH 7.4). At specified time intervals 1 ml samples were withdrawn and assayed spectrophotometrically at 271 nm for drug content. The samples were immediately replaced by the same volume of fresh dissolution medium. Measurements were carried out in triplicate.

Results and Discussion

Increasing the ratio of glyceryl behenate in the matrix resulted with an increased retardation in the release of the drug. This was expected due to the lipophilic nature of glyceryl behenate since

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it is a waxy polymer (3). In this case, the dissolution medium will slowly penetrate the matrix resulting in a slow and sustained release of the drug over time. Different ratios of glyceryl behenate in the matrix were examined and we found out that the higher the ratio, the slower was the release of the drug.

Fig.1 shows the dissolution data for a matrix prepared at various compression forces. Examination of the data of various compression forces tested showed little difference. All of them showed a relatively fast initial release during the first hour which was then followed by a slower release. About 50% of the drug was released in 6-7hrs. Variations in the compression force did not produce variations in the release of the drug due to the fact that a minimal compression force would result in melting and fusion of the waxy polymer leading to complete coating of drug particles and hence slow release.

According to Schwartz and coworkers (4) it was assumed that drug release from a wax matrix obeyed either first-order or a diffusion controlled mechanism. An indication of the mechanism can be obtained by a plot of the logaritm of the drug percent remaining in the matrix against time. A linear plot would indicate a first-order release while the diffusion controlled mechanism would generate an S-shaped curve(4).

Extended studies upto 10 hours were performed on matrices containing drug and glyceryl behenate in a ratio of 1:3 compressed at 3 tons. The data obtained were used to investigate the mechanism of drug release. The logarithm of the percent of drug remaining in the matrix was plotted against time as shown in Fig.2. The result indicated a lack of fitness and conformance to first-order kinetics. Therefore, an attempt was made to determine whether the drug release could be described by the diffusion equation(**Eq.1**) proposed by Higuchi (5).

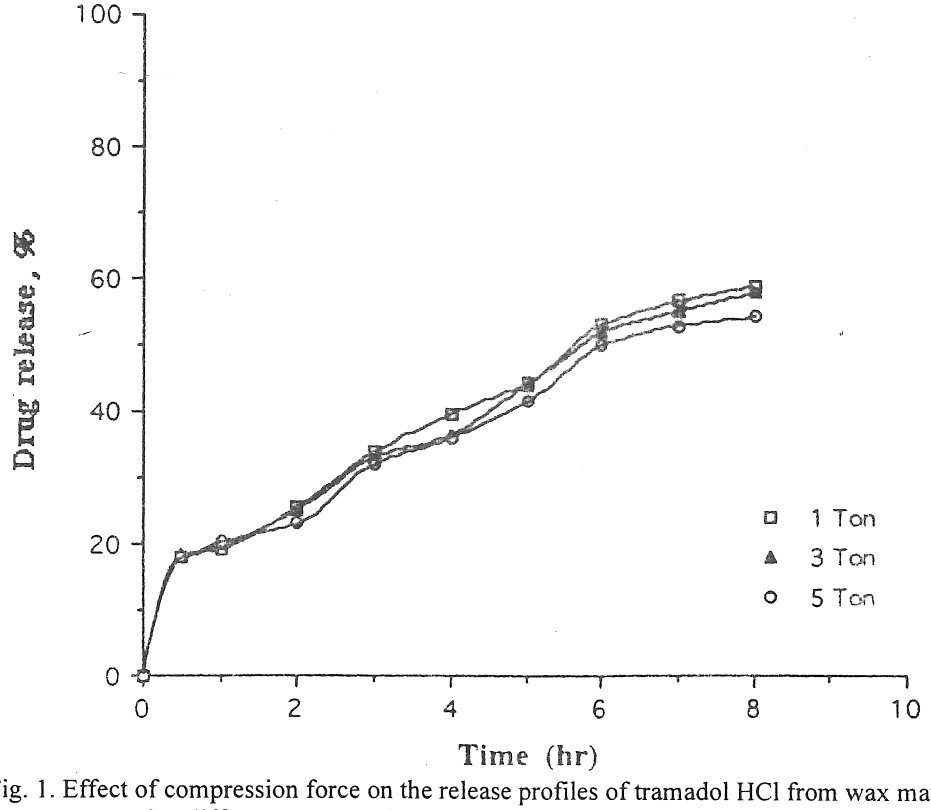

Fig. 1. Effect of compression force on the release profiles of tramadol HCl from wax matrix tablets prepared at different compression forces

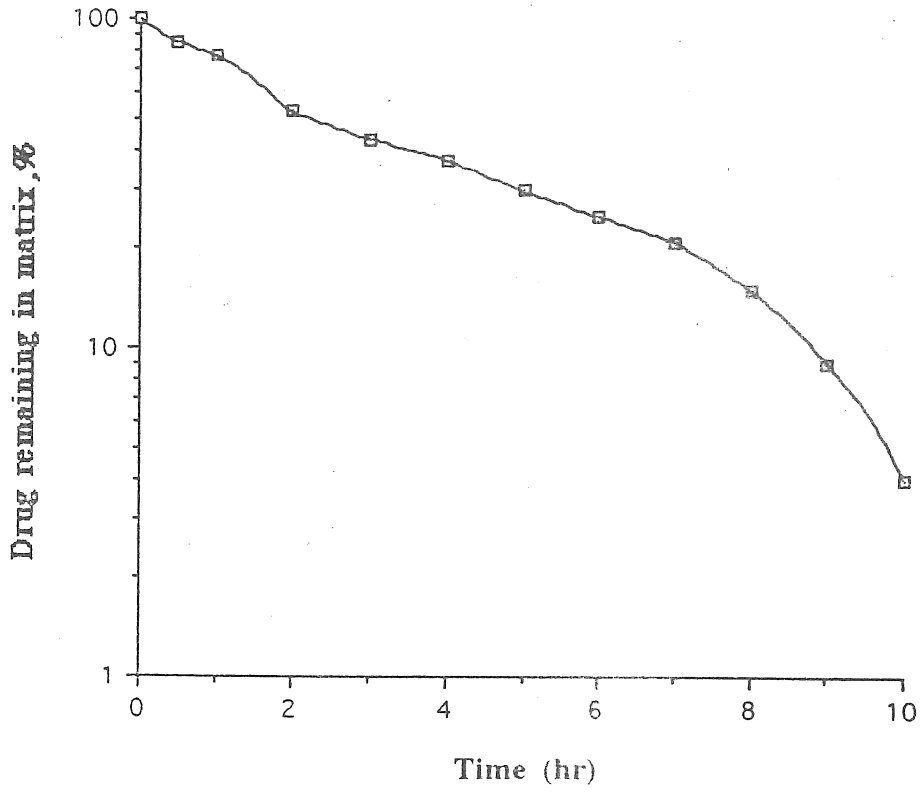

Fig.2. Release of tramadol HCl from a wax matrix (compression force 3 Tons)

$$Q = \frac{\sqrt{D\epsilon}}{\tau}(2A-\epsilon Cs)Cst \qquad \textbf{(Eq.1)}$$

In the equation, **Q** is the amount of drug released per unit area of the matrix exposed to the solvent, **D** is the diffusion coefficient of the drug in the permeating fluid, ϵ is the porosity of the matrix, τ is the tortuosity of the matrix, **A** is the concentration of the solid drug in the matrix, **Cs** is the solubility of the drug in the dissolution medium, and **t** is the time. All of the mentioned terms in the equation except **t** can be combined in one term and that is **K** and the equation can be reduced to **Eq. 2** in which case **K** represents the rate constant of drug release.

$$Q = Kt^{1/2} \qquad \textbf{(Eq.2)}$$

Therefore, according to **Eq.2** a plot of the amount of drug released versus the square root of time should be linear which indicates a diffusion controlled mechanism. Fig.3 shows a plot of the data in this manner for matrices at different compression forces. A linear plot was obtained for times more than 1 hr. Thus, under mild agitation conditions, drug release did not appear to be affected by compression force over the range tested.

With the aid of **Eq.2**, the slope in Fig. 3, which is K, was evaluated where it gave a value of 0.891 $mg/cm^2min^{1/2}$ equivalent for the composite results of all runs. The factors affecting the release of the drug from the matrix were those factors comprising K which were; diffusion coefficient, porosity, tortuosity,

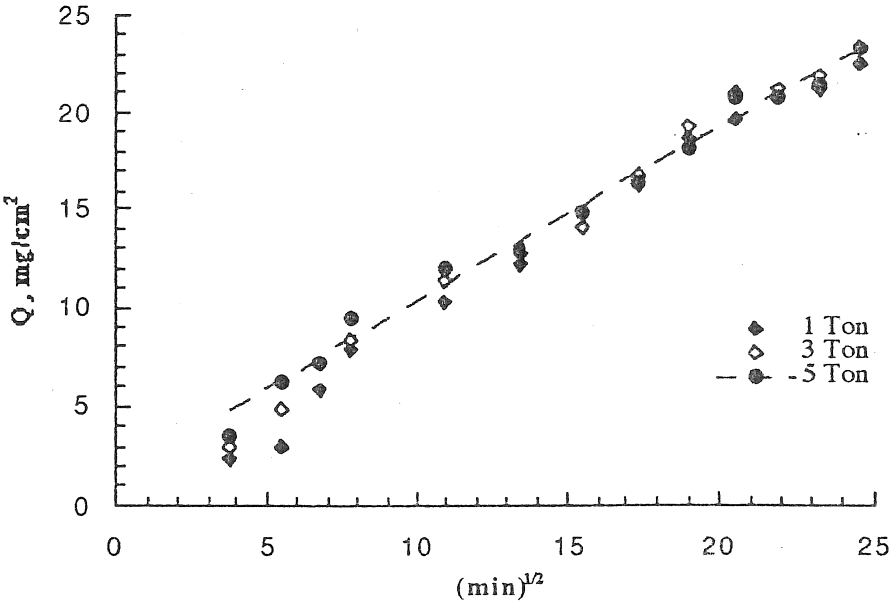

Fig.3. Amount of drug released versus the square root of time for matrices prepared at compression forces 1, 3 and 5 Tons

concentration of the drug in the matrix, and the solubility of the drug in the dissolution medium. The solubility of the drug in any dissolution medium is a constant. Therefore, drug release from a wax matrix can be altered by altering the factors comprising K. Hence, K is modified by a change in formulation such as increased or decreased wax content or a change in the diluent. For example, the compressional force was expected to change the porosity, and hence K. However, in this study, K was not significantly affected by any change in the compression force. Therefore, further characterization of K for various systems would give some general conclusions regarding drug release from a matrix as a function of formulation variables.

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