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THE USE OF PRECIROL® TO PREPARE SUSTAINED RELEASE TABLETS OF THEOPHYLLINE AND QUINIDINE GLUCONATE

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ABSTRACT

Tablets were made using theophylline, lactose and Precirol by a granulation technique, resulting in more than 12 hours release. Granulation and hot fusion methods were used to prepare admixtures of quinidine gluconate and Precirol at different ratios of Precirol: drug, 1:9, 3:7 and 1:1. Dissolution studies in 0.1N HCl showed drastic differences in the release of quinidine gluconate from tablets made by the two different methods; granulation method gave a faster release while the hot fusion method gave slower and incomplete release at higher Precirol content. The release rate decreases with higher Precirol content.

INTRODUCTION

Precirol® (Glycerol palmito-stearate) was used to prepare a matrix base for sustained release tablets of theophylline (granulation technique) and quinidine gluconate (granulation and hot fusion method). Precirol has been used for the preparation of

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sustained release dosage forms of vincamine[1], proxyphylline[2], ferrous sulfate[3] and sodium salicylate[4]. The purpose of this study was to examine the effects of Precirol on the in-vitro dissolution of theophylline and quinidine gluconate. Theophylline was chosen as an amphoteric drug whereas quinidine gluconate is a freely water soluble drug.

EXPERIMENTAL

Material: Materials used were: theophylline anhydrous USP (Desmo Chemicals Corp., NY), Precirol (Gattefosse Corp., NY), quinidine gluconate USP (Berlex Labs., NJ), lactose USP (J.T.Baker Chem. Corp., NJ), chloroform (J.T.Baker Chem. Corp., NJ), ethyl alcohol (U.S. Industrial Chem. Co., NJ), 0.1N HCl and phosphate buffer (pH 7.4).

Preparation of Theophylline Tablets:

Table 1 shows the different formulations of theophylline. An accurately weighed amount of theophylline was mixed with different amounts of lactose and Precirol in a glass mortar. Before mixing, all ingredients were passed through a 40 mesh sieve. Granulation was affected by addition of chloroform until a dough like mass was obtained, followed by drying and screening through a 16 mesh sieve. Tablets of approximately 0.3 gm. were prepared using a Carver press at 4000 lbs./in^2 pressure.

Preparation of Quinidine Gluconate Tablets:

Two different manufacturing methods were used to prepare tablets. Three different ratios of Precirol:drug, namely 1:9, 3:7 and 1:1 w/w, were used (Table 2).

Granulation Method:

Quinidine gluconate was mixed with different amounts of Precirol in a glass mortar, after both were passed through a 40 mesh sieve. Ethyl alcohol was added to form a wet mass which was dried and screened through a 16 mesh sieve. Tablets of approximately 0.3 gm. were made at 4000 lbs./in^2 pressure in a Carver press.

TABLE 1
Different Formulations of Theophylline Tablets Made by the Granulation Technique.

Formulation number	Theophylline % w/w	Lactose % w/w	Precirol % w/w
1	100	-	-
2	50	45	5
3	50	42.5	7.5
4	50	40	10

TABLE 2
Tablet Formulations Containing Different Ratios of Precirol: Quinidine Gluconate (w/w) Prepared by Different Methods and Corresponding Time for 50% and 90% Dissolution of the Drug.

Formulation number	Method	Ratio	t_{50} hr.	t_{90} hr.
5	Granulation	0:1	-	0.34
6		1:9	0.5	0.8
7		3:7	1.1	2.2
8		1:1	3.0	6.0
9	Hot Fusion	1:9	1.8	5.0
10		3:7	6.0	>24
11		1:1	>24	>24

Hot Fusion Method:

Precirol was melted with constant stirring in a beaker maintained at 55 °C in a water bath. Quinidine gluconate was incorporated and the system was allowed to cool down to room temperature. The resulting mass was screened through a 16 mesh sieve. Tablets of approximately 0.3 gm were made at 4000 lbs./in^2 pressure in a Carver press.

Dissolution Studies:

Dissolution studies were performed using the USP XXI basket apparatus at 100 rpm with 0.1N HCl and phosphate buffer (pH 7.4) as the dissolution media (900 ml). Ten milliliter aliquots were withdrawn, filtered and assayed spectrophotometrically at 271 nm for theophylline and 250 nm for quinidine gluconate.

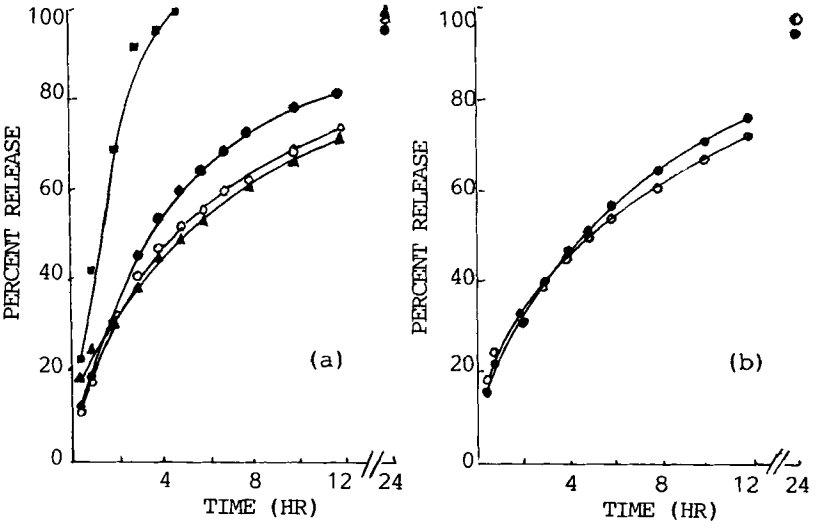

FIGURE 1
Dissolution Profiles of Theophylline from Tablets Made by the Granulation Method
(a) Using Different Concentration (w/w) of Precirol (in 0.1N HCl). Key: ■ - Pure Theophylline Tablet, ● - 5%, ○ - 7.5%, ▲ - 10%.
(b) Using 10% w/w Precirol in Different Media. Key: ● - 0.1N HCl, ○ - Phosphate Buffer (pH 7.4).

RESULTS AND DISCUSSION

Release Characteristics of Theophylline:

Inspection of Figure 1(a) shows that release rates of theophylline from tablets containing 7.5% and 10% Precirol are similar, whereas the release rate from tablets containing 5% Precirol is faster. Most of drug was released in less than 5 hours from the theophylline tablets made without Precirol. Theophylline release was delayed more than 12 hours with a simple granulation process at low Precirol concentration. Figure 1(b) shows that the release of theophylline from tablets containing 10% Precirol is independent of pH, similar results were obtained in both 0.1N HCl and phosphate buffer (pH 7.4). At 24 hours all formulations showed 100% release.

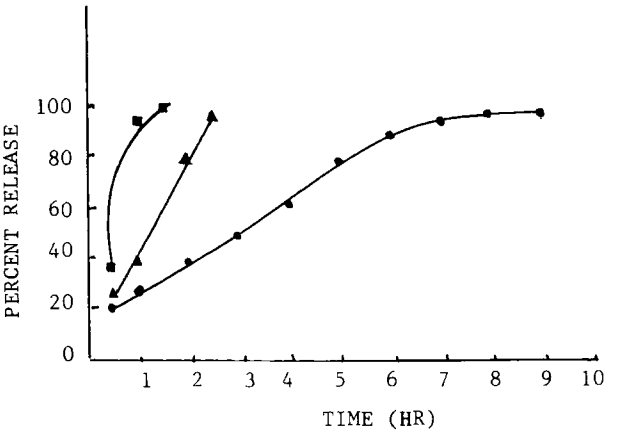

FIGURE 2
Dissolution Profiles of Quinidine Gluconate in 0.1N HCl form Tablets Made by the Granulation Method Using Different Ratios of Precirol: Quinidine Gluconate. Key: ■ - 1:9, ▲ - 3:7, ● - 1:1.

Release Characteristics of Quinidine Gluconate:

Granulation Method:

Figure 2 shows the release of quinidine gluconate from three different tablet formulations in 0.1N HCl. Tablets containing a 1:1 ratio of Precirol:drug, had a t_{50} value of 3 hours, the faster initial rate may be due to rapid dissolution of the drug from the tablet surface, with drug present in the deeper interstices being released slower. Figure 2 also shows that dissolution rate reduces as the Precirol content increases. During these dissolution studies, tablets were observed to gradually erode until the resulting small tablet disintegrated. Such behaviour may be a result of the high solubility of the quinidine gluconate in the acid medium. The surface dissolution of quinidine leads to the formation of pores which are more easily penetrated by the dissolution medium.

Hot Fusion Method:

Figure 3(a) shows release profiles in 0.1N HCl of quinidine gluconate from 3 different tablet formulations. The formulation containing 1:9 ratio was difficult to prepare, as the amount of the

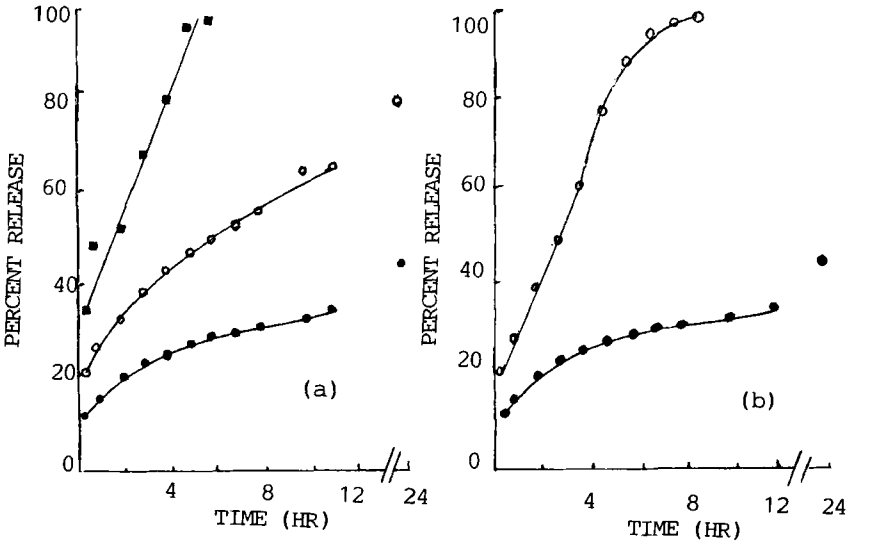

FIGURE 3
Dissolution Profiles of Quinidine Gluconate in 0.1N HCl from (a) Tablets Made by the Hot Fusion Method Using Different Ratios of Precirol:Quinidine Gluconate. Key: ■ - 1:9, o - 3:7, ● - 1:1. (b) Two Different Tablet Formulations Made by the Different Methods Using 1:1 Ratio of Precirol:Quinidine Gluconate. Key: O - Granulation Method, ● - Hot Fusion Method.

carrier was low compared to the amount of drug to be dispersed. Only part of the drug was able to be incorporated in the melted Precirol. The formulation appears to be a physical mixture for most of the drug, with the remainder embedded in the molten Precirol. However, this product gave more prolonged dissolution than obtained using the granulation method (Precirol:drug, 1:9). During dissolution, the tablets remained intact behaving as an inert matrix. The release was incomplete from formulations with 3:7 and 1:1 ratios of Precirol:drug, less than 50% released after 24 hours from the later. As Precirol content increases, dissolution rate decreases.

Figure 3(b) compares the release of quinidine gluconate in 0.1N HCl form tablet formulations made by the two different methods, with 1:1 Precirol:drug. There is a drastic difference in the

release. Table 2 shows that the values of t_{50} and t_{90}, in all cases, are lower for the granulation compared to the hot fusion method. The slower release is probably due to the lower matrix porosity and more effective coating of Precirol in the fusion method. This may be due to air driven out by heat in the fusion process, resulting in an effective enveloping of the drug particles by the melted Precirol. This reduction in porosity inhibits the eluting fluid form entering and drug from diffusing out. The granuation method results in faster release due to poorer coating by Precirol and an increased porosity. Also, surface dissolution of water soluble drug leads to rapid surface erosion or the formation of channels or pores, further facilitating diffusion of the drug.

A combination of the two methods of preparation may be used to obtain intermediate sustained release profiles. The relative ease of manufacture and the variety of release profiles attainable make Precirol a useful excipient for sustained release tablets.

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