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DISSOLUTION PROFILES OF LONG-ACTING QUINACRINE HYDROCHLORIDE PELLETS II

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ABSTRACT

Quinacrine hydrochloride is a well known drug used safely as an antimalerial agent and also could be used for permanent non-surgical female sterilization. In the present investigation the dissolution studies of the long-acting quinacrine hydrochloride pellets were carried by U.S.P. basket method. And it is seen that the drug release is prin-

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cipally through leaching and drug diffusion from the matrix. The plot of drug dissolved against time in the semilogaritmic presentation showed that the release kinetics is of first order.

INTRODUCTION

Surgical female sterilization, the most effective method of contraception for women who desire no additional children, requires trained personnel and adequate medical care facilities. The acquisition and maintenance of sophisticated equipment. Is also required unless minilaporotomy is used. These requirements can drain expensive and scarce medical resources, especially in the developing world. Kessel and Mumford estimate that only one fourth to one third of the potential demant for sterilization, excluding China, can be met by surgical methods in the 1980s. The development of a rapid, effective, safe, nonsurgical method that can be performed by paramedical personnel quinacrine sterilization, offers the best hope at meeting this demand. Various nonsurgical methods of sterilization have been investigated: systemic approaches, tubal plugs and chemical agents.

Investigation of chemical occlusive agents was reported as early as 1849 by Froriep (2). More recently, investigations have been conducted with such scarifying and necrosing agents as zinc, chloride, phenol, silver nitrate, salicylic acid, formaldehyde, methylcyanoacrylate and quinacrine.

Falb, et al. (3) developed a gelatin resorcinal-formaldehyde (GRF) adhesive system that provokes tissue in growth to form a permanent block of the tissue of the uterotubal junction; the adhesive biodegrades in three to six months.

Methyl cyanoacrylate (MCA) produces an irreversible Fallopian tube occlusion by causing tissue necrosis, inflammation and fibrosis; the adhesive biodegrades after four to five months (4). None of these delivery systems is yet perfected. Efficacy trials currently are being considered by the World Health Organization (5). The subject of chemical female sterilization has been reviewed recently by Richart (6).

The present investigation developed long acting quinacrine hydrochloride pellets for nonsurgical female sterilization and the invitro release of quinacrine hydrochloride from pellets was investigated. To obtain sustained release with a soluble drug in tablet formulations, it is necessary to provide a barrier to free solution and diffusion by dispersing the drug in a matrix of water insoluble materials (7). Fats, fatty acids, fatty alcohols, waxes and plastics have been used as matrix materials (8-13).

In the past few years the release rate of drugs from composites with polymer has been investigated invivo and invitro (14,15).

EXPERIMENTAL

Materials

Quinacrine Hydrochloride Dihydrate[1], Cholesterol[2], Carnaubawax[3], Magnesium Stearate[4] were used as received.

Methods

Pellet Formulations

The materials were mixed in a mortar by geometric dilution and wet granulated with chloroform. The granulation was dried at 37°C for four hours under vaccum. The granulation was screened through a 35 mesh and onto a 100 mesh screen. The fine particles were regranulated and 1% magnesium stearate was added before compression. The pellets were finally compressed[5] using flat faced 1/8 inch punches and die set. The particle size distribution of the granulation (150-500 μm) was held constant in the formulation. The formulation of long acting quinacrine hydrochloride tablets is shown in Table 1 (7).

Table 2 shows the values for quinacrine hydrochloride content in the granulations and intact tablets as well as the hardness and weight. The pellets weight showed complience with the U.S.P. limits. The average difference was between ± 2.28%.

Pellet hardness was determined, using a Strong Cobb Hardness Tester. The content uniformity and assay of the quinacrine hydrochloride tablets were analyzed according to methods presented in the U.S.P. XX (16).

Table 1

Formulation of Long Acting Quinacrine HCl Pellets

Ingredient	Concentration (mg)
Quinacrine Hydrochloride	25
Cholesterol	25
Carnauba Wax	3.125
Magnesium Stearate	0.53.

Table 2

Quinacrine Hydrochloride Content, Hardness and Weight of Cores

Quinacrine Hydrochloride Core (mg)	Hardness	Weight (mg)	Content Uniformity (mg)	Assay (mg)
25	23[a]	53.7[b]	23.51[c]	24.213[d]

[a] Strong Cobb Hardness Tester (unit) average of 50 determinations.

[b] Average of 20 determinations.

[c] Average of 10 pellet individual analysis

[d] Determinations from powder obtained from 20 pellets.

Dissolution Procedure

The U.S.P. XX rotating-basket method (17) was employed for investigating drug release from the cores. One pellet was placed in the basket, which was immersed in 1000 ml of distilled water previously warmed to 37°C. The basket was rotated at 100 rpm and the water bath[6] was maintained at 37 ± 0.5°C for 25 hours. The samples were assayed hourly using a flow cell and spectrophotometer[7].

Quinacrine Hydrochloride Assay

The samples were assayed from the dissolution medium by measuring its absorbance at 425 nm against a water blank.

RESULTS AND DISCUSSION

This investigation studied the effect of cholesterol and carnauba wax, individually incorporated in an inert solid matrix, on drug release in an in vitro system. Cholesterol exists in the animal and human organism as the free sterol and as cholesterol esters of fatty acids.

The major factors influencing drug distribution in a sustained-release matrix (core) and drug release from the core include the particle size and drug solubility as well as core hardness and composition. Generally, the drug is physically incorporated into a wax matrix and compressed.

The mechanism of drug release from the wax matrix type core involves leaching by the dissolution medium that contacts the embedded drug. In addition to dissolving "surface"

drug, the fluid can enter the core through pores, cracks and intergranular spaces and dissolve the drug. Drug diffusion through the matrix is either nonexistent or insignificant (18,12).

Drug dissolution from time-released tablets results from slow and continuous core erosion in which new surfaces are being exposed (19), or channels must be continually forming in the core so that the dissolution fluid penetrates the core and leaches out the drug.

In ideal cases the drug from long acting tablets is released at a constant rate, which seems that the release rate is of zero order. It is more usual, however, that the release rate is of first or even higher order. According to the results presented in Figure 1. Quinacrine is first released at a rather fast rate from the tablets in this conjunction. After about 2-3 hours of dissolution the release rate reaches a constant value and the curve becomes almost linear. It might be assumed that, after the quinacrine occurring on the tablet surface and it its outermost parts has been released, the procedure continues at a constant rate over a fairly long period of time. Apparently, a certain concentration of quinacrine will in such a situation remain nearly constant in the diffusion cells formed in the matrix. Thus, as the quinacrine dissolves, only a part of the amounts that diffuse out can be continuously replaced by undissolved quinacrine in the matrix. After these phases, where the slopes

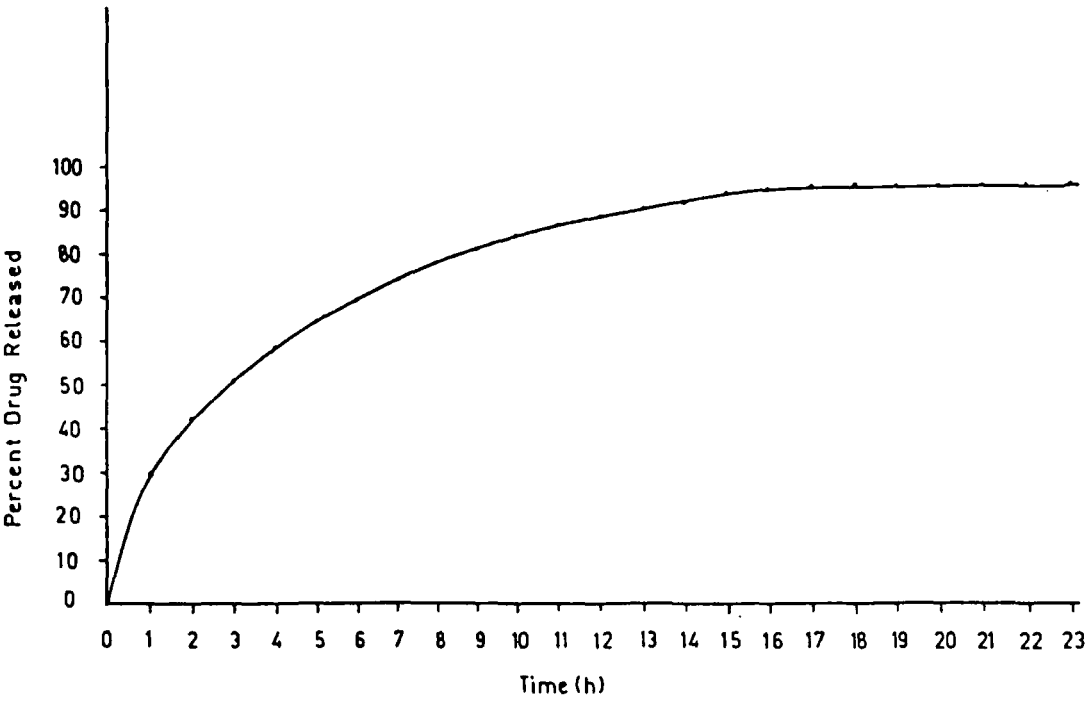

FIGURE 1

Release Profile of Quinacrine Hydrochloride Pellets.

are not constant in time, but first increase and then become constant, the release is at last decreasing. This last phase apparently leads to a situation in which all the solid drug in the matrix is dissolved.

According to Higuchi (20) the release rate is linear as a function of the square root of time when only one surface takes part in the dissolution. The pellets prepared for the present study were in rather good conformity with Higuchi's formula (Figure 2). The curves presented as a function of the square root of time are nearly linear although in this case quinacrine was released from all surfaces of the pellets.

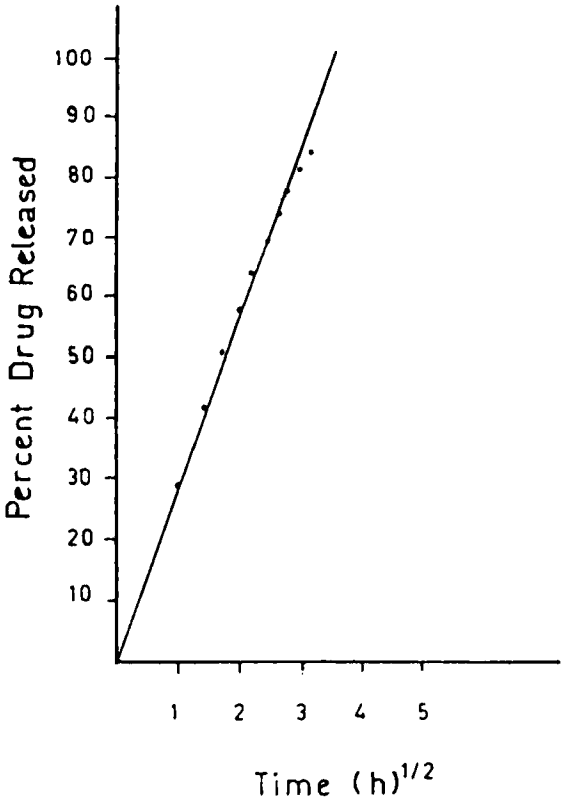

FIGURE 2

Drug Released Percent as a Function of the Square Root of the Time.

If the amount of undissolved drug is plotted against time in the semilogaritmic presentation, we can get straight lines, if the kinetics is of first order (Figure 3).

The quinacrine released from pellets can be affected by regulation of the compression force in tabletting, and swelling capacity of the matrix and air in the pores and the capacity of its chains.

Drug release is principally via a leaching mechanism, and drug diffusion through the matrix is either nonexistent

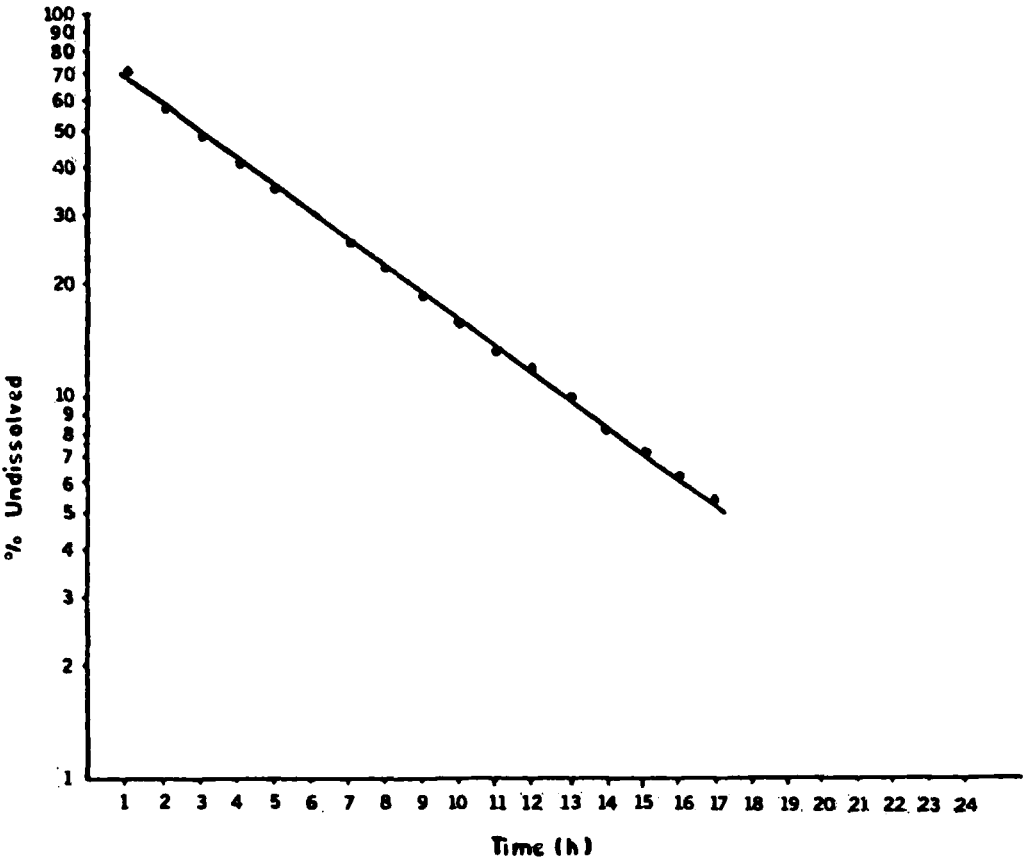

FIGURE 3

The Plots of the Logarithm of Undissolved in Time.

or insignificant. Either the core must be slowly and continually eroding so that new surfaces are being exposed or channels must be continually forming in the core so that the dissolution fluid penetrates the core and leaches out the drug.

The desired drug dissolution from the long acting portion over 10 hour assuming no initial release, is depicted by the dotted line in Figure 1.

Table 3

RELEASE OF QUINACRINE HYDROCHLORIDE FROM PELLETS

Time(hours)	Percent Released	Total Recovered (mg)	Remains (mg)
1	29.83		
2	42.16		
3	51.16		
4	58.51		
5	64.56		
6	69.82		
7	74.35		
8	78.08		
9	81.69		
10	84.23		
11	86.84		
12	88.17		
13	90.44		
14	91.69		
15	92.73		
16	93.81		
17	94.64		
18	95.21		
19	95.46		
20	95.78		
21	95.99		
22	96.14		
23	96.44		
24	96.5	23.365	0.848

Values reported are the average of five pellets

According to the aim of the study (7) in 13 hours on by about 90% of the quinacrine hydrochloride had been released in the case of quinacrine hydrochloride pellets studied, and even after a time of as much as 24 hours the cummulative quantity that had been released was only about 96.5% of the total quinacrine hydrochloride contents of the pellets. During the time of 24 hours covered by the experiment the pellets did not disintegrate in the dissolution medium. Figure 1 shows the release of quinacrine hydrochloride from the core prepared with cholesterol and carnauba wax.

The data in Table 3 show that total release is not possible. A certain percentage of drug will always be coated very effectively with a solid matrix impermeable to the dissolution fluid. Consequently, total release may be difficult to achieve.

An in vivo study is needed to correlate with the in vitro dissolution method. The dissolution method utilized is by no means indicative or predictive of the attainable blood levels, and some correlation between in vitro drug release and invivo performance is required.

ACKNOWLEDGEMENTS

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FOOTNOTES

1. Sigma Chemical Co., St. Louis, MO.
2. Amend Drug and Chemical Company.
3. Z.D. Gilman Inc.
4. Mallinckrodt.
5. Stokes Model E Single-Punch Tablet Machine.
6. Brookfield model water bath.
7. Hitachi model spectrophotometer.

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