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FORMULATION OF LONG-ACTING QUINACRINE HYDROCHLORIDE PELLETS IN DIFFERENT MATRICES I

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ABSTRACT

In this study, quinacrine hydrochloride, which is a very soluble drug in water was selected as the active ingredient to formulate a long-acting dosage form. The prolonged release form is obtained by incorporating the drug in an inert solid matrix. Since it is believed that if the correct matrix and hardness is chosen the drug release can be controlled. The effect of different fatty acids, fatty alcohols, polymers and waxes individually or in combinations were investigated.

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INTRODUCTION

For over a decade, zipper and associates evaluated the transcervical instillation of quinacrine hydrochloride for effecting permanent sterilization. His initial animal studies (1) indicated that quinacrine selectively produced significant morphologic changes in the reproductive tract and caused permanent tubal fibrosis and tubal occlusion in the rat. In clinical trials, he evaluated various doses, concentrations, solvents for the suspension and instillations of the most effective schedules of quinacrine (2, 3) . With three instillations of the most effective schedules of quinacrine, there were low pregnancy rates. Other investigators substantiated the findings (4, 5, 6, 7) .

He hypothesized that quinacrine disrupts the epithelium of the intramural portion of the tube without altering the histology of the endometrium (8) .

Quinacrine is a well-known drug used safely as an antimaterial agent in hundreds of thousands of persons. The drug is easy to obtain in all parts of the world. The present investigation formulated long-acting quinacrine hydrochloride pellets.

Formulation methods used to obtain the desired drug release rate from sustained or long-acting dosage forms include (a) increasing the particle size of the drug or the dosage form, (b) embedding the drug in a matrix, (c) coating the drug or dosage form containing the drug, and (d)

chemically reacting the drug with materials such as an ion exchange resin. A matrix, for our purpose is usually a hydrophobic material. For example, if the drug is highly soluble, it may be necessary to incorporate it into a matrix which has a large particle size (tablet), use a hydrophobic matrix material (fatty acid, fatty alcohol, or wax), and use a method of manufacture that yields fine, highly tortuous pores (solidification from a melt or compression into a tablet of very low porosity) . There are many examples of matrix formulations in the literature, some considerably more complex than they need to be. It is often possible to obtain the desired drug availability rate from matrix formulations that contain only one or two added ingredients (9 - 18) .

The aim of our study is to formulate an inert solid matrix of quinacrine hydrochloride and to study the effect of different fatty acids, fatty alcohols, polymers and waxes on drug release. The object of the formulation was to release 80 - 90 % of the active principal in approximately 800 minutes.

EXPERIMENTAL

Materials

Quinacrine Hydrochloride Dihydrate[1], Cholesterol[2], Tristearin[3], Stearyl alcohol[4], PEG 20.000[5], Carnauba Wax[6], Cetyl ester wax[7], and Magnesium Stearate[8] were used as received.

Pellet Preparation

Three methods of incorporating the drug into the matrix were explored:

(1) The drug and other ingredients were mixed and granulated with chloroform and compressed into a pellet.

(2) The drug and other ingredients were mixed and granulated with chloroform and compressed into a slug and then regranulated and compressed into a pellet.

(3) The drug and other ingredients were dissolved in chloroform and the solvent was evaporated. The wett mass was granulated and compressed into a pellet.

The granulations were dried at 37°C for four hours under vacuum. The granulation was screened through a 35 mesh and onto a 100 mesh. The fine particles were re-granulated. The particle size distribution of the granulations (150 - 500 μm) were held constant for all formulations. Finally, 1% of magnesium stearate was added to the granulation before compression. The pellets were finally compressed[9] using flat faced 1/8 inch punches and die set. Pellet hardness was determined, using a Strong Cobb Hardness Tester.

Dissolution Procedure

The U.S.P. XX rotating-basket method (19) was employed for investigating drug release from the pellets. 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 r.p.m. and the water bath was maintained at 37 ± 0.5°C for 25 hours. The samples were assayed hourly using a flow cell and spectrophotometer.

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

The formulations for the preparation of long-acting quinacrine hydrochloride pellets are shown in Table 1. Pellet hardness, percent release and release time are shown in Table 2.

Formulations 3, 7 and 10 are the same formulations but were prepared by different methods. Formulation 7 and 10 have almost the same hardness but the percent released is 21 hours for formulation 7 and 13 hours for formulation 10. This means that if we change the manufacturing conditions we can get different results. In formulation 3 if we increase the hardness, we can get 96 - 97% release in 12 - 13 hours. This time is the same as formulation 10 but there is a big difference from formulation 7.

In manufacturing large quantities it is difficult to use method 2 and 3 (b, c), therefore, method 1 is preferred. If we add to the formulation a very small amount of Carnauba wax as in formulation 6, we can get much longer release time, 24 hours . Even the pressure is the same as formulation 3.

Table 1

FORMULATIONS OF QUINACRINE HYDROCHLORIDE FOR LONG ACTING PELLETS

Formulations	Quinacrine (mg)	Cholesterol (mg)	Stearyl Alcohol (mg)	Tristearin (mg)	PEG 20.000 (mg)	Carnauba Wax (mg)	Cetyl Ester Wax (mg)	Magnesium Stearate (%)
1[a]	40	35	5					1
2[a]	40	40					5	1
3[a]	40	40						1
4[a]	40	40		5				1
5[a]	40	60						1
6[a]	40	40				5		1
7[b]	40	40						1
8[c]	40	35				5		1
9[c]	40	35			5			1
10[c]	40	40						1

[a] 1-6, formulations prepared by method 1.

[b] 7, formulation prepared by method 2.

[c] 8-10 formulations prepared by method 3.

Table 2

HARDNESS, RELEASE TIME AND PERCENT OF CUMULATIVE RELEASE OF QUINACRINE HYDROCHLORIDE FROM PELLETS PREPARED IN DIFFERENT MATRICES AND METHODS

Formulation	Hardness[b]	Percent Release	Time (hours)
1	7	96	10
1[a]	10	96	11
2	4	93	14
2[a]	5	93	15
3	20	96	12
3[a]	22	97	13
4	15	97	11
5	16	95	15
6	20	96.5	24
6[a]	23	97	25
7	11.5	98	21
8	11.5	96	25
9	11.5	95	12
10	10	95	13

[a] same formulation with different hardness.

[b] Strong Cobb Hardness Tester (unit).

On the other hand, formulations 1 - 6 were prepared by using the same methods, as well as formulations 8 - 10. In formulation 2 we couldn't get much higher pressure because cetyl ester wax has very poor cohesion characteristics. In formulation 4 Tristearin increased the tablets channelling, therefore, we got only 11 hours release time. Finally, even the hardness is not the same. We could get almost the same percent release in a very close time interval except formulation 6. Formulation 7 gave 98% release in a 21 hours, which means very long time for the drug release, but the method is not simple as the one prepared by formulation 1. The slow release profile from a matrix, when the pellets are prepared by the slugging method, probably can be attributed to the absence of channels in the dry-blended pellets.

Formulation 8 - 10, which are prepared by method 3, had almost the same hardness. In formulations 9 and 10, 95% released is the same in 12 and 13 hours. But in formulation 8 the 96% released took 25 hours. This means that the effect of three different matrices on the dissolution rate is cholesterol + carnauba wax > cholesterol > PEG 20,000 + cholesterol. Because PEG 20,000 is a much more soluble polymer than cholesterol and the cholesterol-wax matrix, it effects the channelling in pellets.

More drug was released at the end of 12 hours when the PEG 20,000 was used at the same concentration instead of another ingredient.

In this study two official waxes (cetyl ester wax and carnauba wax) and different fatty acids and fatty alcohols such as Tristearin, Stearyl alcohol, Cholesterol and hydrophilic polymer (PEG 20,000) have been used as matrix materials. It is possible to get longer time by increasing the pressure. High pressure increases pellet hardness and decreases pellet porosity. So we can affect drug release from the pellet by changing its diffusibility. On the other hand, diffusibility depends on matrix structure and tablet surface texture. Even at the low pressure we can get longer release time using Cholesterol, Tristearin and Stearyl alcohol than with the PEG 20,000. When we used Cholesterol and Tristearin together or Cholesterol and Stearyl alcohol, we got very similar results in formulations 1 and 4, but if we used only Cholesterol and increased the hardness (in formulation 3) or even similar hardness as seen as formulation 5. If we increased the Cholesterol amount, we got longer release time than in formulations 1 and 4. It has been seen that in formulation 6 the cholesterol matrix incorporated with wax matrix gave 96 - 97% release in 24 - 25 hours.

The data in Table 2 shows that total release is not practical. A certain percentage of drug will always be coated very effectively with a matrix film impermeable to the dissolution medium. In the dissolution tests the quinacrine hydrochloride pellets did not disintegrate during the total time of the test.

According to the results obtained from the study it is possible to use Cholesterol in preparing long acting pellets or tablets. Because Cholesterol has very good compressibility and is a nontoxic and biodegredable material, it can be a very good solid matrix even when using a soluble drug like quinacrine hydrochloride. The method is simple and easy to use in manufacturing. These dissolution test results showed that the quinacrine hydrochloride was released by a first order process, as suggested by the relationship between the amount of drug released and time. The first method and formulation 6 was selected to prepare long acting quinacrine hydrochloride pellets for investigation in nonsurgical female sterilization.

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FOOTNOTES

1. Sigma Chemical Co., St. Louis, MO.
2. Amend Drug and Chemical Company.
3. Sigma Chemical Co.,St. Louis, MO.
4. Ruger Chemical Company.
5. The Dow Chemical Company.
6. Z.D.Gilman Inc.
7. A.D.M.Company.
8. Mallinckrodt
9. Stokes Model E Single-Punch Tablet Machine

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