acid–chloroform–methylene chloride on Column 2. Aspirin eluted first, followed by salicylamide, phenacetin, caffeine, and acetaminophen. Since most analgesic combinations do not contain all five compounds, slight changes may be made in the mobile phase to reduce the elution time to less than 20 min.

The same chromatographic system can be used for rapid quantitative determination of free salicylic acid. Modifying the mobile phase accomplished the separation of free salicylic acid in analgesics containing aspirin (Fig. 7). This method of separation and detection, with minimum sample preparation, proved to be more rapid than literature methods.

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Timed-Release Tablets Containing Quinine Sulfate

NICOLAS H. CHOULIS [x] and HARRY PAPADOPOULOS [x]

Abstract □ The release rates of quinine sulfate from slowly eroding, timed-release tablets prepared with various amounts of a swellable gum, carbomer, and cellulose acetate hydrogen phthalate at different compaction pressures were attained. For the dissolution test of the prepared tablets, the method described in NF XIII was followed. The concentration of the released quinine sulfate was determined spectrophotometrically.

Keyphrases □ Quinine sulfate timed-release tablets—release rates, effect of carbomer and cellulose acetate hydrogen phthalate concentrations □ Carbomer—effect on timed release of quinine sulfate from slowly eroding tablets □ Timed-release quinine sulfate tablets—effect of carbomer concentration on release rate

It has been reported that continuously effective therapeutic drug levels can be achieved over a period of time by incorporating the medicament in a solid, edible, pharmaceutically and medically acceptable vehicle, consisting of a copolymer of glyoxal and partially degraded gelatin, and by compressing the resulting mixture into a tablet. The copolymer was claimed to swell and decompose slowly in the presence of aqueous solutions, liberating the active ingredient gradually (1). A process for the preparation of slowly eroding tablets, involving the compression of a medicinal agent and a hydrophilic swellable gum was described (2). This process was based on the discovery that a gelled zone is formed on the surface when such a tablet comes in contact with aqueous media, which delays entry of water into the interior of the tablet. The incorporation of water-insoluble medicament in a gel, formed from cellulosic gums in organic solvents, was used to produce stable tablet products with delayed release (3).

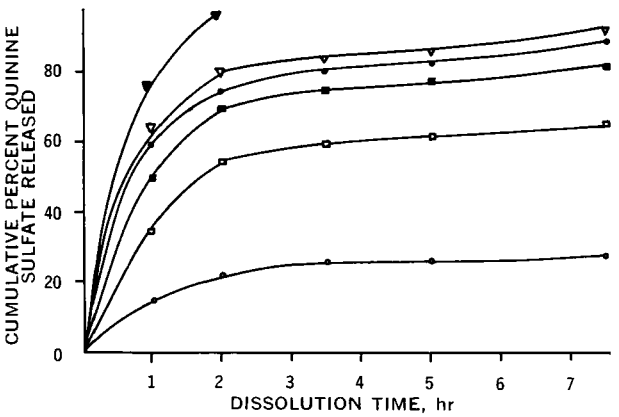

Figure 1—*Drug release rates from timed-release tablets containing decreasing amounts of carbomer. Key:* ○, *Formulation 1.1;* □, *Formulation 1.2;* ■, *Formulation 1.3;* ●, *Formulation 1.4;* ▽, *Formulation 1.5; and* ▼, *Formulation 1.6.*

Compressed tablets were prepared having sustained-release characteristics which contained, in addition to the medicinal agent, a water-insoluble, cross-linked polymer of acrylic acid and a particular, very slightly water-soluble, basic magnesium or calcium compound (4). The sustained mechanism for these polymer-containing tablets was thought to derive from the formation of a protective barrier of gelled material at the tablet surface due to the swelling of the polymer.

The complexity of factors influencing the release of medicament for this category of tablets did not allow the development of an expression to correlate the release rate with physicochemical parameters. It was

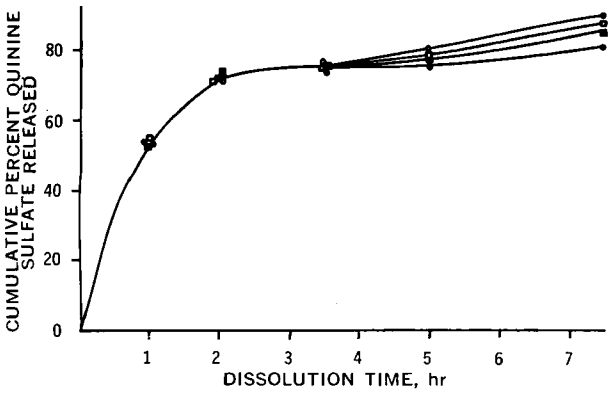

Figure 2—*Drug release rates from timed-release tablets containing increasing amounts of quinine sulfate and 40% carbomer. Key:* ○, *Formulation 2.1;* □, *Formulation 2.2;* ■, *Formulation 2.3; and* ●, *Formulation 2.4.*

reported that Higuchi's relationship adequately describes the dissolution process for tablets containing hydrophilic gums, although they cannot be considered as true matrix systems (5, 6).

In the present investigation the effect of the amount of a swellable gum, namely carbomer, on the release of quinine sulfate from slowly eroding, timed-release tablets is examined.

EXPERIMENTAL

Materials—Quinine sulfate[1], cellulose acetate hydrogen phthalate[2], and carbomer[3] were used. All other chemicals were analytical or USP grade, obtained from standard sources.

Procedures—Slowly eroding, timed-release tablets were formulated with a swellable gum, carbomer, to retard drug release. By adjusting the proportion of the gum, quantitative release of quinine sulfate was attained. Several formulations were prepared (Tables I–III).

The ingredients of each formulation, having the desired particle size less than 60 mesh, were mixed for 15–20 min with a twin-shell mixer[4]. Any aggregates formed during mixing were broken down with a spatula, thus producing additional shear mixing. Weighed amounts of the mixture of powders were compressed into tablets

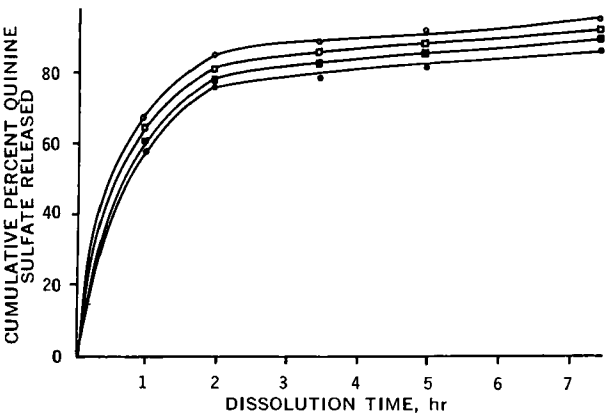

Figure 3—*Drug release rates from timed-release tablets containing increasing amounts of quinine sulfate and 25% carbomer. Key:* ○, *Formulation 3.1;* □, *Formulation 3.2;* ■, *Formulation 3.3; and* ●, *Formulation 3.4.*

[1] Fisher.
[2] Eastman.
[3] Commercially available as Carbopol 934, B. F. Goodrich.
[4] Patterson-Kelley Co.

Table I—Formulations of Timed-Release Tablets[a] Containing Various Proportions of Carbomer

Formulation Number	Ingredients	Amounts, parts %
1.1	Carbomer	75
	Quinine sulfate	25
1.2	Carbomer	50
	Cellulose acetate hydrogen phthalate	25
	Quinine sulfate	25
1.3	Carbomer	40
	Cellulose acetate hydrogen phthalate	35
	Quinine sulfate	25
1.4	Carbomer	30
	Cellulose acetate hydrogen phthalate	45
	Quinine sulfate	25
1.5	Carbomer	25
	Cellulose acetate hydrogen phthalate	50
	Quinine sulfate	25
1.6	Carbomer	20
	Cellulose acetate hydrogen phthalate	55
	Quinine sulfate	25

[a] Tablets were prepared by direct compression with a compaction force of 4000 lb.

by compression in a 13-mm diameter set of die and punches lubricated with magnesium stearate.

For the dissolution test of the prepared tablets, the method described in NF XIII (7) was modified as follows. One tablet was placed in each 90-ml screw-capped bottle containing 60 ml of pH 1.2 dissolution fluid, previously warmed to 37°. The bottles were capped tightly, placed in the clamps of the rotating-bottle apparatus, and rotated at 40 ± 2 rpm in a water bath maintained at 37 ± 0.5°.

At the end of 1 hr, the apparatus was stopped and the bottles were removed. The pH 1.2 dissolution fluid from each bottle was decanted through a 40-mesh metal screen; as much residue was retained in the bottle as possible. Any residue remaining on the screen was returned to the original bottle, and 60 ml of pH 2.5 dissolution fluid was added. The decanted pH 1.2 dissolution fluid was retained for assay.

The process was repeated at the end of 2, 5, and 7.5 hr using pH 4.5, 7.0, and 7.5 fluid, respectively.

For the chemical assay of quinine sulfate, aliquots of the samples were appropriately diluted and the pH's of the final solutions were adjusted to either 1.2 or 7.5. The concentration of quinine sulfate was then determined spectrophotometrically at 345 nm (for

Table II—Formulations of Timed-Release Tablets[a] Containing Various Proportions of Quinine Sulfate, Group I

Formulation Number	Ingredients	Amounts, parts %
2.1	Carbomer	40
	Cellulose acetate hydrogen phthalate	50
	Quinine sulfate	10
2.2	Carbomer	40
	Cellulose acetate hydrogen phthalate	40
	Quinine sulfate	20
2.3	Carbomer	40
	Cellulose acetate hydrogen phthalate	20
	Quinine sulfate	40
2.4	Carbomer	40
	Cellulose acetate hydrogen phthalate	10
	Quinine sulfate	50

[a] Tablets were prepared by direct compression with a compaction force of 4000 lb.

Table III—Formulations of Timed-Release Tablets[a] Containing Various Proportions of Quinine Sulfate, Group II

Formulation Number	Ingredients	Amounts, parts %
3.1	Carbomer	25
	Cellulose acetate hydrogen phthalate	65
	Quinine sulfate	10
3.2	Carbomer	25
	Cellulose acetate hydrogen phthalate	55
	Quinine sulfate	20
3.3	Carbomer	25
	Cellulose acetate hydrogen phthalate	35
	Quinine sulfate	40
3.4	Carbomer	25
	Cellulose acetate hydrogen phthalate	25
	Quinine sulfate	50

[a] Tablets were prepared by direct compression with a compaction force of 4000 lb.

solutions of pH 1.2) and 331 nm (for solutions of pH 7.5), using the appropriate medium as the blank.

RESULTS AND DISCUSSION

The relationship between the amount of carbomer included in the tablets and the release rates obtained with the dissolution test is shown in Fig. 1. The proportion of carbomer in the tablets ranged from 75% for Formulation 1.1 to 20% for Formulation 1.6. Release rates from tablets containing 10–50% quinine sulfate are shown in Figs. 2 and 3. The amount of carbomer included in Formulations 2.1–2.4 was 40%, while 25% was used for Formulations 3.1–3.4.

The release rates did not differ substantially for compaction pressures from 1000 to 5000 lb/1.3266 cm^2. However, higher pressures decreased considerably the release rates, probably due to entrapment of drug within the matrix. Pressure of 4000 lb/1.3266 cm^2 for matrixes containing carbomer produced tablets of sufficient hardness without hindering the release of drug. The lubricant magnesium stearate might retard tablet dissolution slightly; replacement with magnesium lauryl sulfate is possible, but its toxicity has not yet been established (8).

The mechanism of drug release of the eroding type could be explained by the fact that the formation of a hydrated and gelled zone on the surface acts as a barrier to the further penetration of the liquid into the tablet interior (9). As the gelled zone slowly dissolves in the medium, a fresh surface is exposed to the liquid, with subsequent formation of a new gelled zone. Drug is liberated from this zone through a combination of diffusion and attrition processes. Part of the drug is diffused through the swelled area while the remainder is liberated when the hydrated zone is dissolved.

In Fig. 1 the release of drug from timed-release tablets containing carbomer is shown. The amount of carbomer has a marked influence on the release of drug; as the proportion of carbomer decreases, the release rate increases. This effect would be expected since the swelled zone is more susceptible to attrition as the proportion of the gum decreases. Therefore, the proportion of carbomer can be adjusted so that all drug is released in 7.5 hr (Formulation 1.5). However, the release pattern is similar to that of matrix tablets; *i.e.*, most of the drug is liberated during the initial period of the dissolution process. It was also found that when the proportion of the gum was 20% or less (Formulation 1.6), rather rapid disintegration occurred within 2 hr (Fig. 1).

As a filler or diluent, cellulose acetate hydrogen phthalate was used to enhance the permeability of the hydrated area at higher pH values. This use was based on the property of cellulose acetate hydrogen phthalate to be insoluble in acidic environment but soluble in media of pH 5 or higher. It was postulated that this effect could counterbalance the increased viscosity of carbomer gel at higher pH values (10). The proportion of drug in the tablets containing 40% carbomer (Formulations 2.1–2.4) had a negligible effect on release rates expressed as percentages (Fig. 2). However, the absolute amounts of drug released will be proportional to the total drug content. Similar results were obtained when the proportion of carbomer was 25% (Formulations 3.1–3.4, Fig. 3). No significant differences in drug release were observed when the drug and carbomer contents were kept constant and the quantity of cellulose acetate hydrogen phthalate was varied at a given pH (pH 5 or higher).

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