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[x] To whom inquiries should be directed.

# Correlations between Physical and Drug Release Characteristics of Polyethylene Glycol Suppositories

**IAN W. KELLAWAY and CHRISTOPHER MARRIOTT** [x]

**Abstract** □ The mechanical strength and elastic moduli of blocks of polyethylene glycol with a range of molecular weights were determined. A rotating-basket dissolution test was used to measure the release characteristics of prednisolone from similar blocks. The effects of blending bases of different molecular weight and of the addition of water also were determined. Linear relationships were found for the mechanical strength, molecular weight, and release rate, but no simple relationship could be observed for the elastic moduli.

**Keyphrases** □ Polyethylene glycol suppositories—relationships between physical characteristics (mechanical strength, molecular weight, and elastic moduli) and drug (prednisolone) release rates □ Suppositories, polyethylene glycol—relationships between physical characteristics and drug release rates □ Drug release characteristics of polyethylene glycols—relationship to polymer molecular weight, mechanical strength, and elastic moduli

Polyethylene glycols are among the most widely used of the hydrophilic polymer suppository bases. Drug liberation occurs as a result of base dissolution into the aqueous environment of the rectum, differing radically from the classical lipophilic bases which melt at body temperature and act as a lipid reservoir from which drug molecules partition prior to absorption.

Salicylate release from polyethylene glycol bases has been examined by several workers (1–5). High plasma levels of salicylic acid and sodium salicylate have been achieved (1) and the *in vitro* release of two different salicylates did not differ significantly (2). To achieve rapid drug release, polyethylene glycols have been recommended for aspirin formulations whereas cocoa butter (theobroma oil) is the base of choice for both sodium salicylate (4) and choline salicylate (3). The use of polyethylene glycols in some instances has produced similar plasma levels to an equivalent oral dose (4, 5). It has been suggested that salicylate liberation and absorption from polyethylene glycol suppositories may be influenced by salicylate–polyethylene glycol complexation (6–8).

Studies on drugs incorporated into a polyethylene glycol matrix include those on acetaminophen (9), iodoform and 2,4,6-triiodophenol (10), thiazinamium and indomethacin (11), chloramphenicol (12, 13), sulfonamides (14), antipyrine (phenazone) and sodium barbital (15), diphenhydramine and its hydrochloride salt (16), oxytetracycline (17), and other antibiotics (18). When selecting a suppository base, it is generally true that lipophilic drugs are best formulated in hydrophilic bases (19) and water-soluble compounds are best formulated in lipophilic bases (20) for rapid and complete release.

Rheological investigations of suppository bases have been confined to the molten or semisolid state (21–25) and determinations of "hardness" of the solid bases (4, 26–29). Baichwal and Lohit (25) ob-

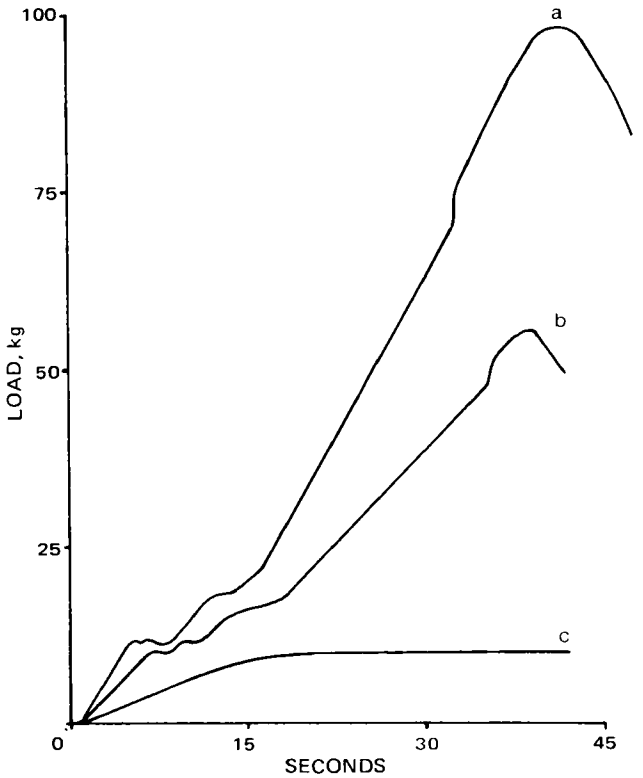


**Figure 1**—*Transmitted load-time curves for: (a) polyethylene glycol 6000, (b) 60% polyethylene glycol 6000 and 40% polyethylene glycol 1000, and (c) polyethylene glycol 1000. The rate of strain was 60 mm hr*$^{-1}$.

Table I—Characterization of Polyethylene Glycols $CH_2(OH)(CH_2OCH_2)_mCH_2OH$

| Polyethylene Glycol | $m$ | Molecular Weight Range | Mean Molecular Weight | Melting Point |
|---|---|---|---|---|
| 400 | 8—10 | 380—420 | 400 | <10° |
| 1000 | 20—23 | 950—1050 | 1000 | 33.3—33.4° |
| 1540 | 28—36 | 1300—1600 | 1450 | 43.1—43.3° |
| 4000 | 69—84 | 3100—3700 | 3400 | 57.4—57.6° |
| 6000 | 115—160 | 6000—7500 | 6750 | 60.7—61.0° |

served that drug release from cocoa butter (theobroma) bases was inversely related to the consistency, expressed as a viscosity index. Sharova *et al.* (29) found that breaking strength increased with molecular weight for polymers of polyethylene oxide.

The purpose of this study was to examine drug release characteristics from polyethylene glycols in relation to polymer molecular weight and as a function of breaking load and elasticity of the bases.

## EXPERIMENTAL

**Preparation of Suppositories**—Polyethylene glycols 400, 1000, 1540, 4000, and 6000 were used[1]. Cylindrical "suppositories," 15 mm in diameter and length and approximately 3 g in weight, were prepared by pouring the molten base into a brass mold mounted on a glass plate. Prednisolone BP, micronized[2] (0.625%, w/w), was dissolved in the molten base to produce blocks for drug release testing; water, if required, was added immediately prior to pouring. All blocks were removed from the molds 1 hr after pouring and stored in well-closed containers at 5°. The blocks were allowed to attain room temperature prior to testing.

**Prednisolone Release Determinations**—A rotating-basket dissolution apparatus was used and enabled determinations at 37 ± 0.2° to be made simultaneously on four independent blocks. Each block was placed vertically in a basket rotating at 125 rpm. Two liters of distilled water was used as the dissolution medium for each block, and 5-ml samples were withdrawn every 120 sec from a fixed point in the medium. Each sample was analyzed for prednisolone content at 247 nm in a UV spectrophotometer[3].

**Breaking Load and Elasticity Determinations**—The blocks were placed face on in a compression unit against a 100-kg load cell[4] at 22 ± 0.5°. Compression was carried out at a constant strain rate of 60 mm $hr^{-1}$. The breaking load was measured as the transmitted force in kilograms at failure, and the elastic modulus was determined from the initial slope of the stress–strain curve (Fig. 1). Division of the load by the area of the block face produces the stress, and the corresponding strain can be derived by dividing time by the recorder speed. The elastic modulus can then be calculated from the ratio of stress to strain:

$$\text{elastic modulus } (Nm^{-2}) = \frac{\text{load (kg)}}{\text{area of block } (m^2)} \times \frac{\text{recorder speed } (m\,sec^{-1})}{\text{seconds}} \quad \text{(Eq. 1)}$$

A recorder[5] speed of 200 mm $min^{-1}$ was used for all compression tests. A minimum of three tests was performed on each formulation.

Table II—Effect of Pouring Temperature on the Breaking Load of Polyethylene Glycol 6000

| Pouring Temperature | Breaking Load, kg |
|---|---|
| 60° | 93 |
| 65° | 96 |
| 70° | 96 |
| 75° | 96 |
| 80° | 96 |
| 85° | 96 |

## RESULTS AND DISCUSSION

The release of prednisolone from polyethylene glycols 1000, 1540, 4000, and 6000 is shown in Fig. 2. Unlike the curves for salicylate release (4), no linear region was observed. Since semilogarithmic plots were also nonlinear, the release of prednisolone from

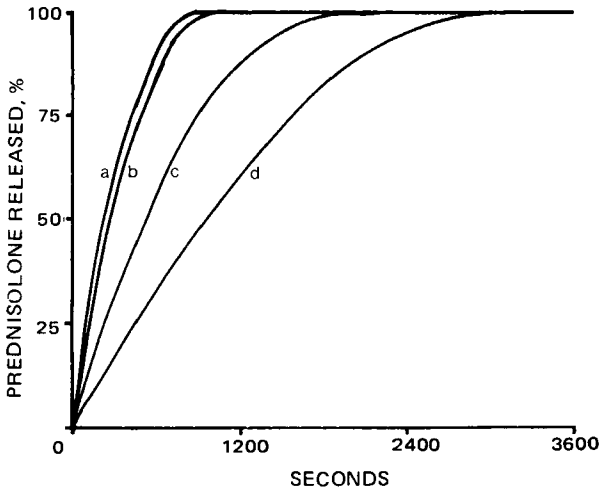


**Figure 2**—*Release curves of prednisolone from: (a) polyethylene glycol 1000, (b) polyethylene glycol 1540, (c) polyethylene glycol 4000, and (d) polyethylene glycol 6000 at 37°.*

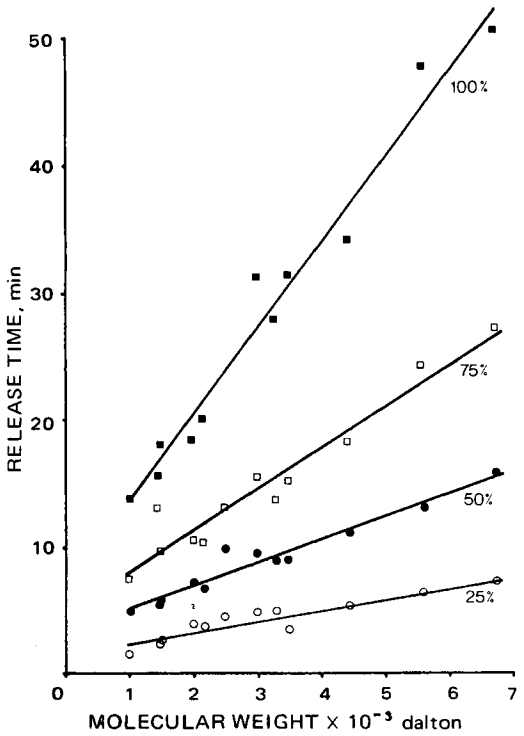


**Figure 3**—*Release times ($t_{25}$, $t_{50}$, $t_{75}$, and $t_{100}$) as functions of base molecular weight.*

[1] Koch-Light Laboratories Ltd., Colnbrook, Bucks, United Kingdom.
[2] The Boots Co. Ltd., Nottingham, United Kingdom.
[3] Cecil model CE272, Cecil Instruments Ltd., Cambridge, United Kingdom.
[4] DC 12/C, Transducers (C.E.L.) Ltd., Reading, United Kingdom.
[5] Metrohm Labograph E478, Metrohm AG, Ch-9100 Herisau, Switzerland.

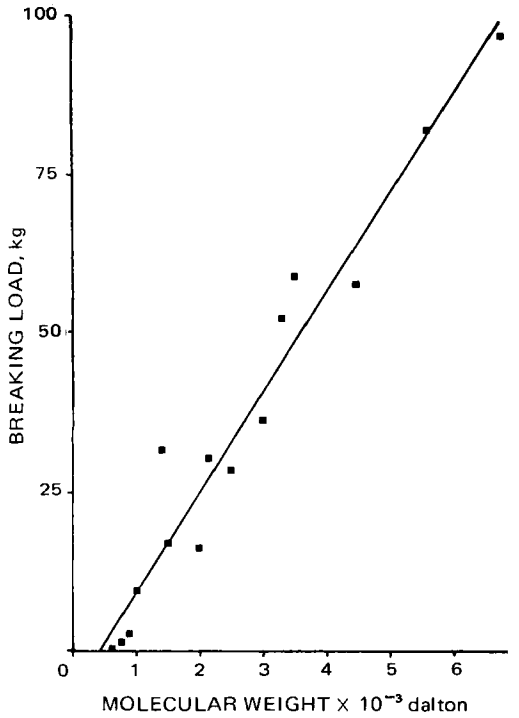


**Figure 4**—*Breaking load as a function of base molecular weight.*

polyethylene glycol suppositories follows neither zero-order nor first-order kinetics.

The times for release of 25, 50, 75, and 100% ($t_{25}$, $t_{50}$, $t_{75}$, and $t_{100}$, respectively) of the prednisolone were determined graphically from the dissolution–time plots. When these times were plotted against the "average" molecular weights (Table I), significant linear relationships ($p > 0.999$) were obtained (Fig. 3). Extrapolation to the ordinate was not undertaken, since release times corresponding to liquid polyethylene glycols would have dubious practical significance. Figure 3 includes data for the "pure" compounds and bases formulated by blending polyethylene glycol 1000 with both 4000 and 6000.

The molecular weights of the blends were calculated as weight averages according to:

$$\bar{M}_w(\text{blend}) = \frac{N_1M_1^2 + N_2M_2^2}{N_1M_1 + N_2M_2} \qquad \text{(Eq. 2)}$$

where $M_1$ and $M_2$ are the "average" molecular weights of the two polyethylene glycols, and $N_1$ and $N_2$ are the numbers of moles of each in the blend. Therefore, it appears feasible that any desired release rate of prednisolone from polyethylene glycol suppositories can be achieved by the selection of a suitable base or blend of bases to produce the appropriate mean molecular weight.

**Table III—Effect of Storage Time on the Breaking Load of Polyethylene Glycol 1540**

| Storage Time, hr | Breaking Load, kg |
|---|---|
| 2 | 33 |
| 5 | 31 |
| 21 | 32 |
| 43.5 | 32 |
| 72 | 32 |
| 120 | 32 |

Collins *et al.* (30) suggested that the appearance and mechanical properties of polyethylene glycol suppositories are dependent upon the temperature of pouring and recommended the use of a temperature just above the congealing point to prevent glazing of the surface. Krowczynski (31), however, using 24 different bases, concluded that the preparative technique had no effect on the drug release characteristics. To examine the effect of the preparation procedure on breaking strength, polyethylene glycol 6000 blocks were prepared by pouring the base at different temperatures above the congealing point. The results (Table II) indicate that the breaking strength is independent of pouring temperature, except when this temperature is close to the congealing point. It is possible that crystallization may be occurring prior to pouring, giving rise to a nonhomogeneous polymer matrix within the block interior.

Aging effects were monitored in blocks of polyethylene glycol 1540 stored at 5° in well-closed containers for between 2 and 120 hr. No significant differences could be observed in the breaking loads over this aging period (Table III). All other tests, however, were carried out on blocks that had been aged for between 4 and 24 hr.

Figure 4 illustrates the linear relationship that existed between the breaking load and mean molecular weight of the base. Bases with molecular weights less than 1000 were produced by blending polyethylene glycol 1000 with polyethylene glycol 400. The computed line intersects the abscissa at a molecular weight corresponding closely to the transition between solid and liquid polyethylene glycols at 22°. Therefore, knowledge of the approximate molecular weight serves as a useful guide to base hardness.

When the elastic moduli of the bases were calculated from the compression tests, no simple linear correlation with molecular weight was evident. This finding may be due to the relatively in-

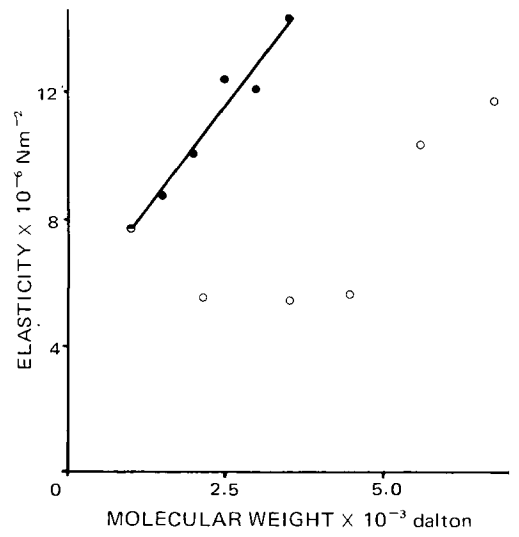


**Figure 5**—*Elasticity-molecular weight relationships for 4000–1000 blends (●) and 6000–1000 blends (○).*

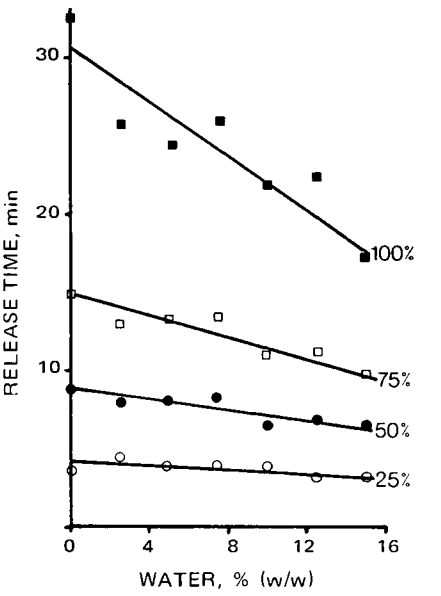


**Figure 6**—*Effect of water addition to polyethylene glycol 4000 on* $t_{25}$, $t_{50}$, $t_{75}$, *and* $t_{100}$.

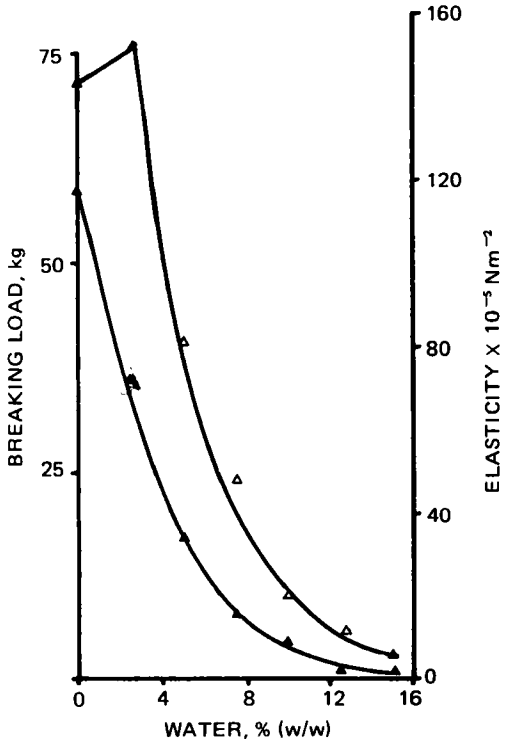


**Figure 7**—*Effect of water addition to polyethylene glycol 4000 on breaking load (▲) and elasticity (△).*

sensitive technique used. Figure 5 illustrates the effect of blending polyethylene glycol 1000 with polyethylene glycols 4000 and 6000; the former resulted in a linear plot, the latter in a curvilinear one. An explanation of the different behavior exhibited by 6000–1000 blends could involve differences in the matrix structure of polyethylene glycol 6000 when compared with those of the 4000 and 1000 bases. The observation that, with the nonblended bases, polyethylene glycol 6000 was the only compound to produce a clean fracture when compressed to failure may support this suggestion.

It is common pharmaceutical practice to add water to polyethylene glycols when they are used as suppository bases in an attempt to counteract the irritant action on the rectal mucosa occasionally encountered due to water removal by osmosis. The effect of the addition of water to polyethylene glycol 4000 on prednisolone release (Fig. 6), breaking load, and elastic modulus (Fig. 7) were examined. A linear decrease in release times with increasing water content was observed. Breaking load and elastic modulus were also found to decrease but in a nonlinear manner to the maximum water content of 15% (w/w). Concentrations exceeding this figure produced blocks that could not be ejected whole from the molds.

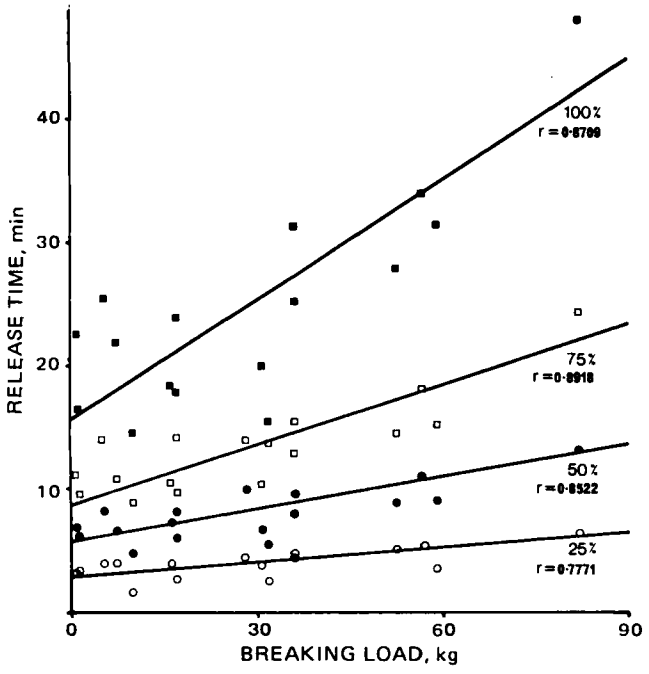


**Figure 8**—*Significant (>0.999) linear relationships existing for* $t_{25}$, $t_{50}$, $t_{75}$, *and* $t_{100}$ *as a function of breaking load.*

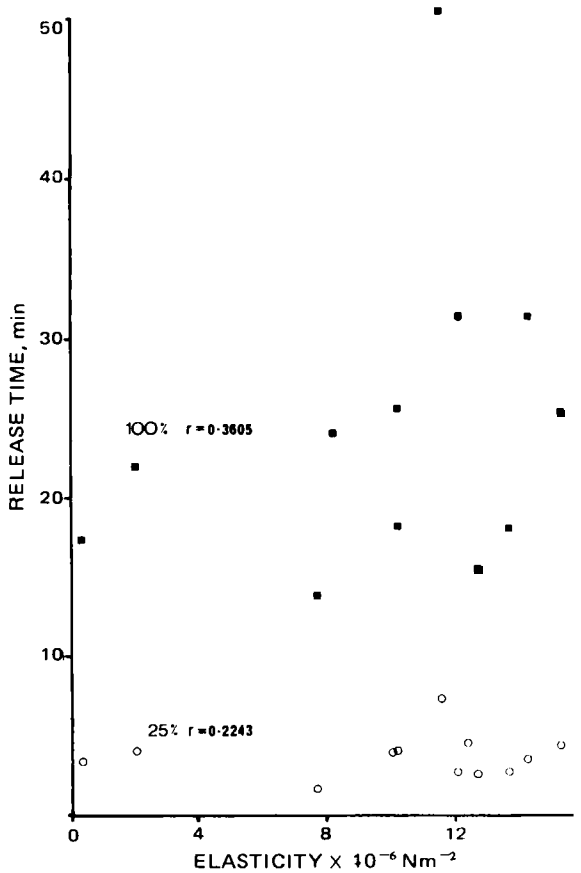


**Figure 9**—*Nonsignificant (<0.90) correlation between* $t_{100}$ *and* $t_{25}$ *and elasticity.*

It was also possible to relate prednisolone release times to the breaking load of the base when linear relationships were observed (Fig. 8). The significance of the correlation coefficient was >0.999 but was reduced to <0.90 when the elastic modulus was substituted for the breaking load (Fig. 9). Only 25 and 100% release data are included in this latter figure for the sake of clarity. It is considered that the relationship demonstrated between breaking load and release times may prove useful as a formulation guide for lipophilic drugs in polyethylene glycol suppository bases.

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[x] To whom inquiries should be directed.

# Comparison of IR Spectroscopic Analysis and X-Ray Diffraction of Aluminum Hydroxide Gel

**STEVEN L. NAIL [*], JOE L. WHITE [‡], and STANLEY L. HEM [*x]**

**Abstract** □ Data are presented which demonstrate that IR spectrophotometry is more sensitive than X-ray diffraction to structural changes occurring in aluminum hydroxide gel during aging. By examining changes in peak shape and position in the IR spectrum, evidence is seen for an increasing degree of order as the gel ages. The increased order may be responsible for the loss of acid reactivity observed during aging. IR analysis is also recommended for routine monitoring of aluminum hydroxide gels.

**Keyphrases** □ Aluminum hydroxide gel—monitoring of structural changes during aging, IR and X-ray diffraction methods compared, relationship to decreased acid reactivity □ IR spectrophotometry—monitoring, structural changes in aluminum hydroxide gel during aging, compared to X-ray diffraction method □ X-ray diffraction—monitoring, structural changes in aluminum hydroxide gel during aging, compared to IR spectrophotometric method

Aluminum hydroxide gel is an effective antacid, although many aspects of its structure and acid reactivity are not fully understood. The initial precipitate resulting from the reaction of a soluble aluminum salt with a base is probably a highly random structure. With aging, structural rearrangement occurs to form a more thermodynamically stable system. For example, a polymerization-like process may produce a highly ordered system resistant to attack by acid (1–4). The rate of this process has been related to many factors including pH of precipitation (5), type and concentration of ions present (6–8), temperature (9), and order of addition of the reactants (10). The end-product of the aging process is usually a crystalline form of aluminum hydroxide (1–4, 6–8, 11, 12). These crystalline structures are resistant to attack even by concentrated acid.

It has been demonstrated that aluminum hydroxide gels, which are essentially nonreactive as measured by the USP acid-consuming capacity test, retain an amorphous X-ray diffraction pattern (5). Since X-ray diffraction appears to be relatively insensitive to the structural changes occurring during aging that result in a diminished acid reactivity, a more sensitive method is needed to study these structural changes. The purposes of this report are to demonstrate the usefulness of IR spectrophotometry