Effect of Hydrophilization of Hydrophobic Drugs on Release Rate from Capsules

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Abstract □ The release of poorly soluble hydrophobic drugs from capsules can be improved significantly by the creation of a hydrophilic surface by intensive mixing of the hydrophobic drug with a small amount of a solution of a hydrophilic excipient. This technique was introduced previously for the production of microgranules. The data presented indicate that the hydrophilic material is mechanically distributed over the hydrophobic surface. The creation of hydrophilic capillaries in a capsule or tablet allowed the rapid penetration of the dissolution fluid, resulting in a dispersion of well-wetted particles, so that the maximum surface area of the powder was exposed to the dissolution medium. Moreover, hydrophilization of hydrophobic drugs has the important benefit that the release rate from capsules is independent of the surface tension of the dissolution medium.

Keyphrases □ Hydrophobic drugs—release rate from capsules, effect of hydrophilization □ Drug release—hydrophobic drugs from capsules, effect of hydrophilization □ Hydrophilization—of hydrophobic drugs, effect on release from capsules

Several methods for increasing the dissolution rate of poorly water-soluble drugs are available (1–4). A common approach is to reduce the drug's particle size to expose a greater surface area to the dissolution medium. This approach is, however, not without difficulties. Reducing the particle size leads to increased particle–particle interactions, and the resulting agglomerates may have an effective surface area smaller than anticipated.

If the drug is hydrophobic, particle-size reduction may give greater problems with wetting and liquid penetration into tablets and capsules. Since liquid penetration is the first step in the disintegration and dissolution of tablets and capsules, the overall process may be penetration rate limited. To overcome these problems, diluents and disintegrants are employed (5, 6), or the fine material may be granulated, which will aid in its wetting and promote liquid penetration (7). However, this method apparently would defeat, to some extent, the original object of size reduction.

In an ideal situation, the drug would be released from the dosage form as discrete, well-wetted particles, so that the maximum surface area afforded by the powder would be exposed to the dissolution medium. For hydrophobic materials, such a situation may be difficult; but it may be possible to achieve if the surface properties of the material are changed from hydrophobic into hydrophilic by coating the hydrophobic particles with a hydrophilic material. Such a coating should aid in the penetration of fluid and the wetting of individual particles but should not unduly retard the dissolution rate of the drug.

Coating of particles may be achieved by fluidization techniques (8–11), but problems may arise if the powder is cohesive. In this study, a technique described by de Jong (12) was used, in which a powder and a small amount of binder solution are mixed intensively in a kneading machine or high-speed mixer. The rigorous mixing inhibits agglomeration, resulting in a fine free-flowing powder. Although this method was originally developed for microgranule production, it is claimed that the powder is coated with the binding agent, so hydrophobic substances can be rendered hydrophilic. This study applied this technique to increase the dissolution rate of a hydrophobic, relatively insoluble drug from hard gelatin capsules.

EXPERIMENTAL

Materials—Hexobarbital[1] (Ph. Ned. grade) was chosen as the test drug because it is relatively insoluble in water and exhibits a high contact angle of 88° (13). Prior to use, it was ground in a rotor mill[2] with a 500-μm screen and passed through a centrifugal classifier[3] to remove fines with a particle size under 10 μm. The binders chosen were methylcellulose[4] and hydroxyethylcellulose[5]. Both binders are soluble in water but completely insoluble in alcohol. Hydroxyethylcellulose was passed through a rotor mill[2] fitted with a 200-μm screen. The milled and classified hexobarbital, methylcellulose, and milled hydroxyethylcellulose exhibited mean particle sizes, based on air permeability measurements[6], of 17, 30, and 32 μm, respectively.

Methods—*Treatment of Powders*—Dispersion of the binder over the drug surface was carried out in a small high-speed mixer[7]. Hexobarbital (50 g) was placed in the mixer, 3 ml of an aqueous solution of the binder was added, and the mixer was run for either 2 or 4 min at ~9000 rpm. The mixing was interrupted every 0.5 min to mix, with a spatula, material from deadspots in the mixer.

The material was dried in a tray drier at 50° for 1 hr and screened through a 200-μm sieve. Dry-mixed powders of hexobarbital and binder were prepared using a tumbler mixer[8], running at 90 rpm for 30 min. Hexobarbital was blended with the same amount of methylcellulose or

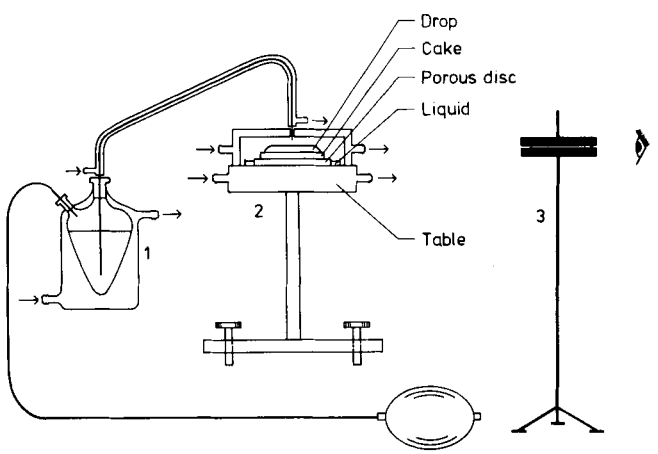

Figure 1—*Schematic diagram of the setup for the contact angle measurement. Key: 1, liquid reservoir water jacketed at 23 and 37°; 2, environmental chamber for drop formation; and 3, cathetometer.*

[1] Brocacef B. V., Maarssen, The Netherlands.
[2] Pulverisette 14002, Fritsch, Idar-Oberstein, West Germany.
[3] Multiplex 100 MZR, Alpine AG, Augsburg, West Germany.
[4] Celacol M20, British Celanese Ltd., Derby, England.
[5] Natrosol 250L, Hercules Inc., Wilmington, Del.
[6] Model 95, Fisher Scientific Co., Pittsburgh, Pa.
[7] MX 32, Braun AG, Frankfurt/M., West Germany.
[8] Turbula, W. A. Bachoven, Basel, Switzerland.

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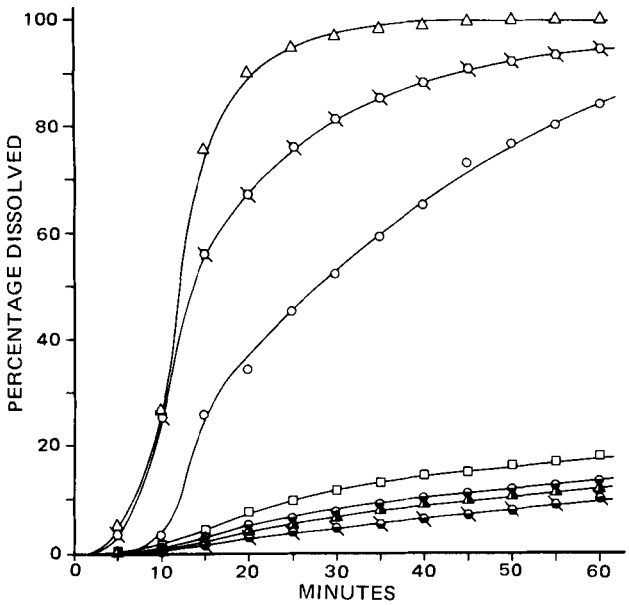

Figure 2—*Release from hard gelatin capsules of hexobarbital, untreated, treated, and mixed with methylcellulose. Key:* □, *untreated;* ◒, *0.06% physical mix;* ▲, *0.18% physical mix;* ◔, *0.30% physical mix; and* ○, △, *and* ◔. *treated for 2 min with 1, 3, and 5% binder solutions, respectively.*

hydroxyethylcellulose as was used for the coating procedure of the drug.

Capsule Filling and Dissolution—The pure drug, the treated drug, or the physical mixes of drug and binder were loosely packed by hand (250 mg) into No. 1 hard gelatin capsules[9], using a manually operated capsule-filling machine[10]. No compression of the powder was made.

Dissolution was carried out in a water-jacketed 1-liter beaker containing 900 ml of distilled water maintained at 37°. The capsule was held in a spiral of stainless steel wire, located centrally, 2 cm above the bottom of the beaker. Stirring was achieved with a 5-cm diameter, three-bladed, right-hand propeller, rotating clockwise at 100 ± 1 rpm 3.5 cm above the capsule.

Samples were taken at 5-min time intervals through membrane filters

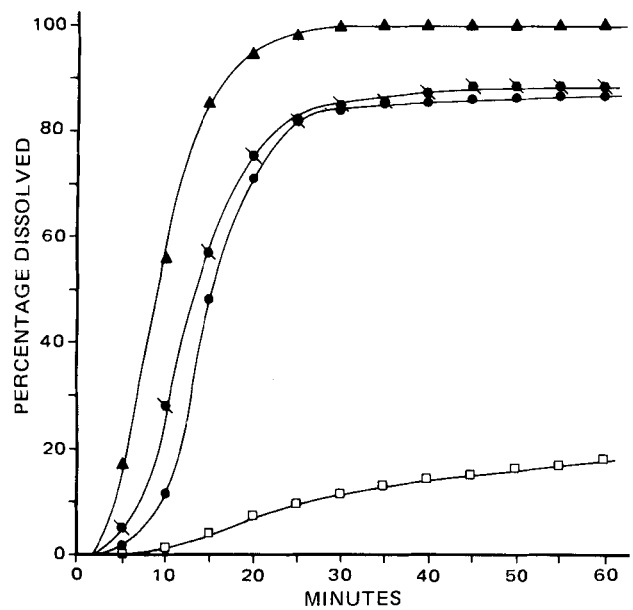

Figure 3—*Release from hard gelatin capsules of hexobarbital, untreated and treated with methylcellulose. Key:* □, *untreated; and* ●, ▲, *and* ◔, *treated for 4 min with 1, 3, and 5% binder solutions, respectively.*

[9] Snap-fit, Capsugel AG, Basel, Switzerland.
[10] Tevopharm, Schiedam, The Netherlands.

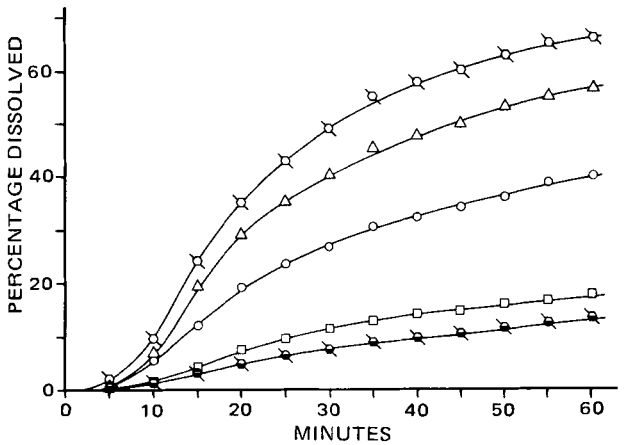

Figure 4—*Release from hard gelatin capsules of hexobarbital, untreated, treated, and mixed with hydroxyethylcellulose. Key:* □, *untreated;* ◔, *0.30% physical mix; and* ○, △, *and* ◔, *treated for 2 min with 1, 3, and 5% binder solutions, respectively.*

(0.8-μm pore diameter), diluted with pH 9.2 borate buffer to a buffer concentration of about 0.05 *M*, and analyzed spectrophotometrically[11] at 245 nm for hexobarbital. Corrections were applied for the samples removed. All release studies were based on six dissolution tests and were highly reproducible. Only average values are reported.

Intrinsic Dissolution Rates—Nondisintegrating disks, 13 mm in diameter, were prepared by compressing 500 mg of the powder at a load of 1500 kg for 5 min in a die and punch assembly. The die served as disk holder and allowed only one face of the disk to be exposed to the dissolution medium. The disk holder was attached to a shaft and was rotated at 100 ± 1 rpm in the center of a water-jacketed beaker containing 500 ml of ethanol maintained at 25°. Samples were taken at 10-min intervals, assayed for hexobarbital by dilution with a fivefold amount of 0.05 *M* borate buffer, and analyzed spectrophotometrically at 245 nm.

Wettability—The wettability of the different powders was characterized by contact angle determinations (13). For this purpose, compacts, 5 cm in diameter, were prepared by compressing about 5 g of the powder at 2000 kg in a die and punch assembly. The compacts were placed on a porous disk partly immersed in the test liquid to saturate the compact, but wetting of the compact surface was avoided (Fig. 1).

As soon as saturation was achieved, the test solution was slowly

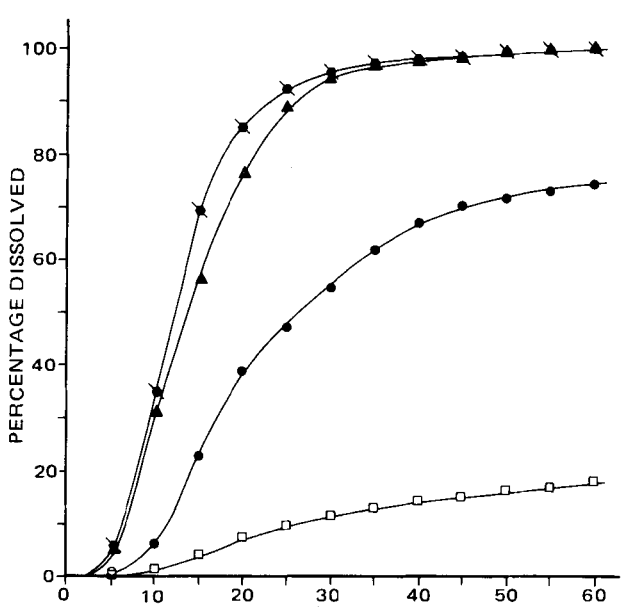

Figure 5—*Release from hard gelatin capsules of hexobarbital, untreated and treated with hydroxyethylcellulose. Key:* □, *untreated; and* ●, ▲, *and* ◔, *treated for 4 min with 1, 3, and 5% binder solutions, respectively.*

[11] Model 25, Beckman Instruments Co., Fullerton, Calif.

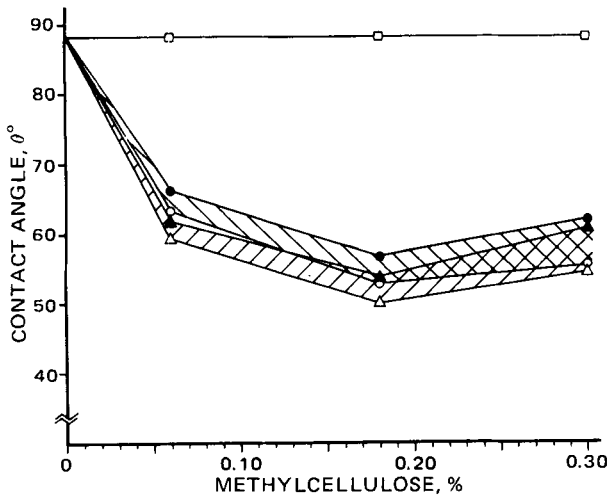

Figure 6—*Relation between percentage of methylcellulose and contact angle of hexobarbital, physically mixed or treated with the binder. Key: □, physical mix; ○ and ●, treated for 2 min; △ and ▲, treated for 4 min; ○ and △, with γ_{LV° = 72.4 dynes/cm; and ● and ▲, with γ_{LV° as given in Table II.*

dropped onto the compact surface; readings of the drop height were taken with a cathetometer[12] until additional drops caused no increase in height. The contact angle was then calculated from the appropriate equations as previously derived (14, 15), extended (16), and successfully adopted for pharmaceutical powders (13). All contact angle measurements were performed at least in duplicate. The reproducibility was better than 1° in each case.

Liquid and Solid Properties—Densities and surface tensions of the liquids and densities of the solids were determined by a balance[13], a tensiometer[14], and an air comparison pycnometer[15], respectively.

RESULTS AND DISCUSSION

Figure 2 shows the effect of the distribution of methylcellulose over the surface of the hexobarbital powder on the release profile of the drug from hard gelatin capsules. Significantly higher release rates were found for the treated hexobarbital than for the pure drug. The hexobarbital treated with 5% methylcellulose solution released the drug slower than when treated with 3% methylcellulose solution. This effect might be due to a large increase in the viscosity of the binder solution with an increasing methylcellulose concentration but also may be caused by thermal gelation

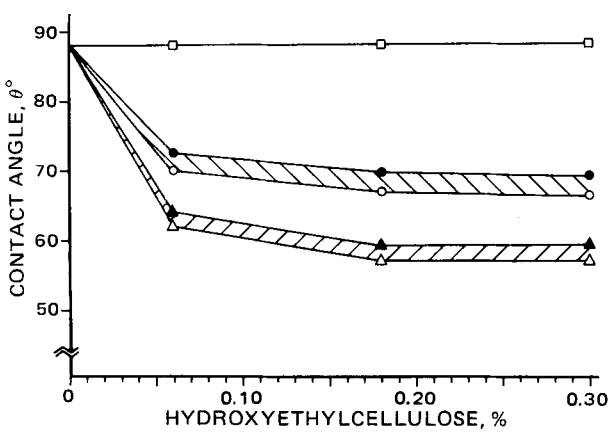

Figure 7—*Relation between percentage of hydroxyethylcellulose and contact angle of hexobarbital, physically mixed or treated with the binder. Key: □, physical mix; ○ and ●, treated for 2 min; △ and ▲, treated for 4 min; ○ and △, with γ_{LV° = 72.4 dynes/cm; and ● and ▲, with γ_{LV° as given in Table II.*

[12] Model 70000, Bouty, Paris, France.
[13] Mohr, G. Kern, Ebingen, West Germany.
[14] Du Noüy, 8600 EE Krüss, Hamburg, West Germany.
[15] Model 930, Beckman Instruments Ned. N.V., Amsterdam, The Netherlands.

Table I—Contact Angles of Cellulose Polymer Solutions on Hexobarbital Measured at 23°

Methylcellulose			Hydroxyethylcellulose		
Concentration, %	γ_{LV°, dynes/cm	θ, degrees	Concentration, %	γ_{LV°, dynes/cm	θ, degrees
0	72.4	88	0	72.4	88
1	45.6	76	1	62.7	87
3	44.6	76	3	62.5	86
5	44.6	76	5	62.3	86

of the methylcellulose at temperatures near 37° during dissolution (17).

The physical mixes exhibited release rates of the same order of magnitude as the pure drug and even showed a slight decrease in rate with an increasing amount of binder. These results indicate that the degree of distribution of a hydrophilic binder over the surface of a hydrophobic drug affects the release rate from capsules. This conclusion is supported by the results shown in Fig. 3. In this study, the hexobarbital powder was intensively mixed with the binder solutions for 8 × 0.5 min instead of 4 × 0.5 min. Comparison of Figs. 2 and 3 shows increased release rates for the drug treated for the longer period.

Distribution of hydroxyethylcellulose over the surface of the hexobarbital powder and blending of the dry binder with the drug resulted in the release rates from capsules shown in Figs. 4 and 5. The data show slightly lower release rates for the physical mixtures than for the pure drug. The release rate increased, over the range studied, with increasing concentrations of hydroxyethylcellulose and with an increasing degree of distribution.

To characterize the wettability of the pure drug by the binder solutions, contact angle measurements were made. Table I presents the contact angles between hexobarbital and solutions of different concentrations of methylcellulose or hydroxyethylcellulose. The results show a decrease in the contact angle from 88° for distilled water to 76° for solutions containing 1–5% methylcellulose. Almost no difference in contact angle was found over a concentration range of 0–5% for solutions of hydroxyethylcellulose. These results imply that neither binder solution would spread spontaneously on hexobarbital since both contact angles were high.

The input of energy from the mixer can, however, promote spreading of the liquid. The success of this operation depends first on factors affecting the spreading such as mixer efficiency, contact angle, and viscosity and second on whether the film is stable when formed and does not "dewet" from the surface (18). This latter factor may be a complex function of the contact angle and the viscosity of the liquid. These arguments are to some extent borne out by the finding that hydroxyethylcellulose, which exhibited higher contact angles and higher surface tensions than the methylcellulose, required greater mixing times to achieve equivalent effects.

To elucidate the mechanism of the change in release rate from capsules, the wettability of pure drug, treated drug, and physical mixtures of drug and binder was determined by contact angle measurement (Figs. 6 and 7). Both the pure drug and the physical mixtures exhibited contact angles of 88°. High-speed mixing of hexobarbital with methylcellulose or hydroxyethylcellulose solutions resulted in decreased contact angles. The contact angles given were calculated on the basis of the surface tension of distilled water and of the solution in the pores of the compact when the maximum amount of binder was dissolved completely from the drug surface (Table II).

As seen from Fig. 7, distribution of 3 ml of 3% methylcellulose over 50 g of hexobarbital powder, corresponding with a weight percentage of 0.18, decreased the contact angle of the drug from 88° to mean values of about 55 and 52° when treated for 4 × 0.5 and 8 × 0.5 min, respectively. Distribution of 3 ml of 5% methylcellulose over the drug resulted in contact

Table II—Surface Tensions of the Solutions in the Pores of the Compacts When the Binder Has Been Completely Dissolved from the Drug Surface

Weight Concentration of Binder on Drug, %[a]	Surface Tension, dynes/cm	
	Methylcellulose	Hydroxyethylcellulose
0	72.4	72.4
0.06	62.4	64.4
0.18	55.4	62.8
0.30	48.6	62.7

[a] Values of 0.06, 0.18, and 0.30% correspond with treatment of 50 g of hexobarbital with 3 ml of 1, 3, and 5% of a binder solution, respectively.

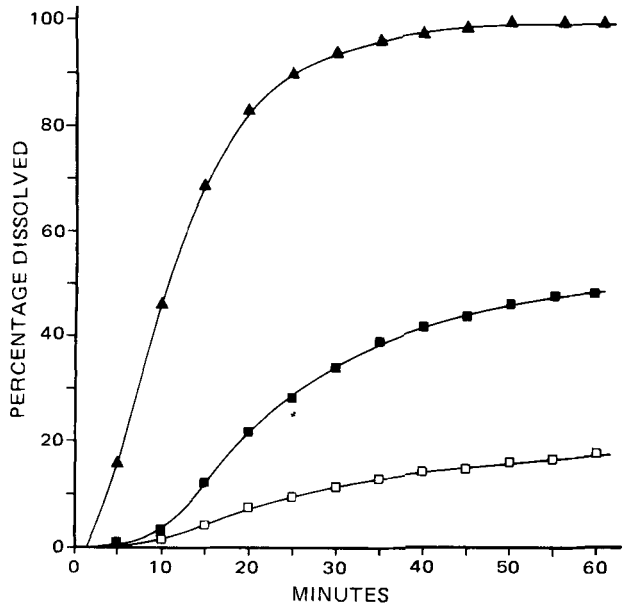

Figure 8—*Release from hard gelatin capsules of pure hexobarbital and hexobarbital treated for 4 min with 3% methylcellulose. Key: □, untreated drug in distilled water, ■, untreated drug in 0.14% methylcellulose; and ▲, treated drug in 0.14% methylcellulose.*

angles of 59 and 58°, respectively. The slight increase in the contact angle found when the concentration of the methylcellulose solution was increased from 3 to 5% was possibly due to the increased viscosity of the binder solution.

Figure 7 shows the change in the contact angle when the drug was treated with hydroxyethylcellulose. The decrease in the contact angle was smaller, compared with a methylcellulose treatment, whereas the difference in contact angles between the powders treated for 4 × 0.5 and 8 × 0.5 min was more pronounced. This result was expected since the hydroxyethylcellulose solution exhibited higher surface tensions and higher contact angles on the drug than the corresponding methylcellulose solutions.

To prove that the increased penetration rates, resulting in increased release rates, were caused primarily by the decreased contact angle of the treated powder and not, or at most to a small extent, to dissolved binder in the pores of the capsule, release rates were measured from capsules filled with pure or treated hexobarbital immersed in water or binder solutions. The concentration of the binder solution was equal to the maximum concentration of binder in the pores of the capsule if all binder had been dissolved from the surface of the treated drug (0.14%). As seen from Fig. 8, the release rate increased when the pure drug was immersed in the methylcellulose solution. The slight decrease in rate observed for the hydroxyethylcellulose solution (Fig. 9) may have been due to a slight increase in solution viscosity. A dramatic increase in release rate was found when the drug had been treated with the binder and immersed in the appropriate binder solution.

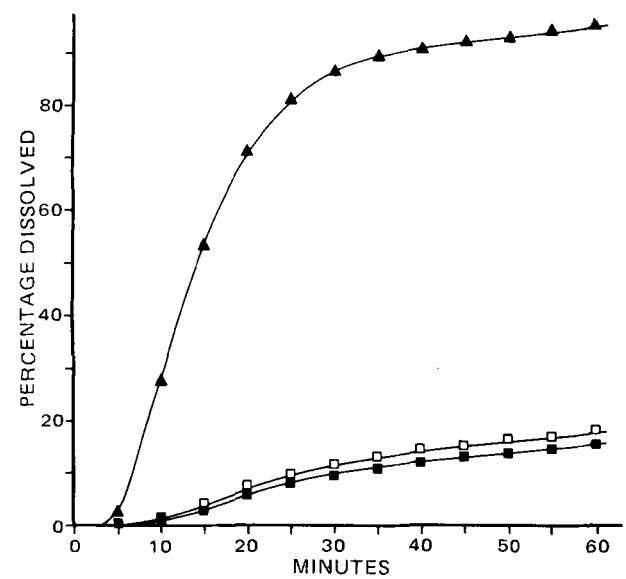

Figure 9—*Release from hard gelatin capsules of pure hexobarbital and hexobarbital treated for 4 min with 3% hydroxyethylcellulose. Key: □, untreated drug in distilled water; ■, untreated drug in 0.14% hydroxyethylcellulose; and ▲, treated drug in 0.14% hydroxyethylcellulose.*

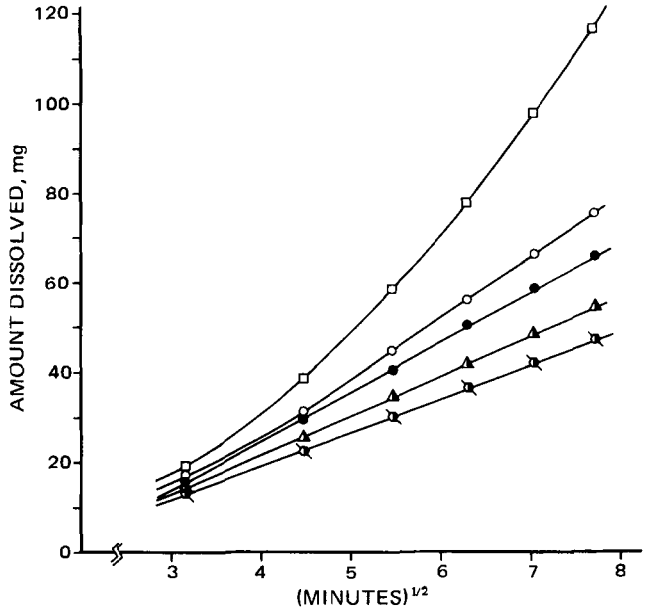

Figure 10—*Dissolution in alcohol from rotating disks of hexobarbital, untreated and treated with hydroxyethylcellulose, as a function of the square root of time. Key: □, untreated; ○ and ●, treated with a 1% binder solution for 2 and 4 min, respectively; ▲, treated with a 3% binder solution for 2 and 4 min, respectively; and ◔, treated with a 5% binder solution for 2 and 4 min, respectively.*

To demonstrate the degree of binder distribution over the drug, the intrinsic dissolution rates of the untreated and treated drugs were measured in ethanol to prevent binder dissolution.

The dissolution rates measured are presented in Fig. 10 as the amount dissolved *versus* the square root of time. The hexobarbital dissolution rates were significantly inhibited on treatment in a high-speed mixer with small amounts of hydroxyethylcellulose solutions. The dissolution rate decreased with increasing mixing times and increasing binder concentrations. A matrix of hydroxyethylcellulose was left when the drug leached out (Fig. 11). The existence of a matrix of hydroxyethylcellulose is consistent with the linear plots obtained when the amount of drug released was plotted as a function of the square root of time (Fig. 10).

The release rate of a strongly hydrophobic drug like hexobarbital from capsules thus can be increased considerably by rendering the hydrophobic surface of the drug hydrophilic. The release rate of a hydrophobic drug from a capsule, however, also can be increased by decreasing the surface tension of the dissolution medium (7). Figure 12 shows the release profiles of pure hexobarbital from capsules immersed in distilled water with varying concentrations of polysorbate 80[16]. As expected, increased release rates were obtained with decreasing surface tensions of the dissolution medium.

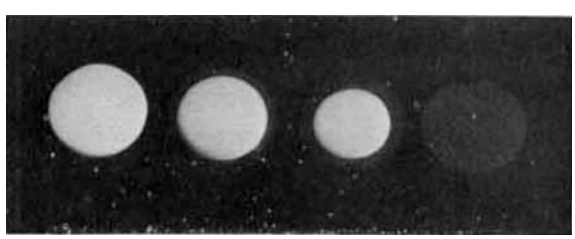

Figure 11—*Photograph of a partly leached matrix of hydroxyethylcellulose.*

[16] Tween 80, Atlas Chemie, Essen, West Germany.

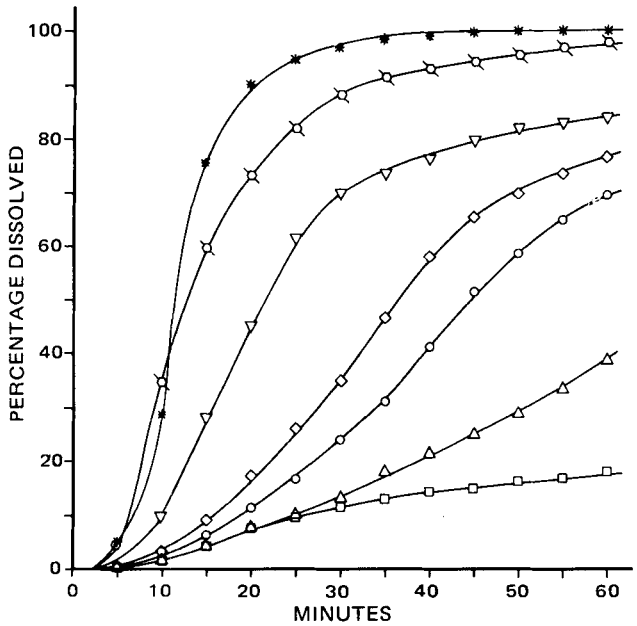

Figure 12—*Release profiles of pure and methylcellulose-treated hexobarbital from hard gelatin capsules in water with varying concentrations of polysorbate 80 at 37°. Key: open symbols, untreated drug; □, 0% polysorbate 80 (γ_{LV}° = 70.1 dynes/cm); △, 0.01% (45.4 dynes/cm); ○, 0.05% (42.7 dynes/cm); ◇, 0.1% (41.4 dynes/cm); ▽, 0.2% (39.3 dynes/cm); ◺, 0.5% (37.7 dynes/cm); and ✱, 0.18% binder-treated drug in solutions with 0–0.5% polysorbate 80.*

According to Finholt and Solvang (19), the surface tension of human gastric juice is nearly independent of pH and secretion rate, having a value between 35 and 50 dynes/cm. Therefore, a mean surface tension of human gastric juice of 43 dynes/cm would require a concentration of 0.05% polysorbate 80. To compare the release rates of pure and treated drug, the release profiles from capsules of hexobarbital, treated as described with a 3% methylcellulose solution and immersed in dissolution media of varying surface tension, are incorporated in Fig. 12. The results show the release rate of the treated drug to be independent of the surface tension of the dissolution medium. Because of the aforementioned differences in the surface tension of human gastric juice, the realization of a release rate from capsules that is independent of the surface tension of the medium is of practical importance, especially where absorption is dissolution rate limited.

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Kinetics of Aggregation of Human Platelets

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Abstract □ A study of the aggregation kinetics of human platelets using an electronic counting device is reported. The experimental data were analyzed quantitatively by a physical model, which assumed that the initial disappearance rate of single platelets *versus* time fitted a second-order type of aggregation with respect to platelet number. The mechanism of aggregation was surface barrier controlled. Thus, the aggregation rate constants in different adenosine diphosphate concentrations (1.5–9.0 μg) were 10–100 times greater than the rate constant (6.6325×10^{-12} cm^3/sec) for a diffusion-controlled process as calculated from Smoluchowski's model. Also, the stability constant values, which were equal to unity in a fast diffusion-controlled mechanism, were smaller in the surface-barrier-controlled process and ranged from 0.00741 to 0.0467. The extent of aggregation was indicated by the calculation of a sticking probability constant as determined by the barrier. Adenosine diphosphate induced a rapid aggregating effect. Prostaglandin E_1 produced the most drastic deaggregating effect as compared to dinoprostone (prostaglandin E_2) and dinoprost (prostaglandin $F_{2\alpha}$). Aspirin completely blocked the aggregating effect of arachidonic acid.

Keyphrases □ Aggregation, platelet—kinetic study, effect of adenosine diphosphate, various prostaglandins, and arachidonic acid □ Kinetics—human platelet aggregation, effect of adenosine diphosphate, various prostaglandins, and arachidonic acid □ Adenosine diphosphate—effect on human platelet aggregation with and without various prostaglandins, kinetic study □ Prostaglandins, various—effect on human platelet aggregation with and without adenosine diphosphate, kinetic study □ Arachidonic acid—effect on human platelet aggregation with and without aspirin, kinetic study

The origin, morphology, chemical composition, lifespan, and role of some endogenous substances on blood coagulation and platelet aggregation have been reported (1–13). Nevertheless, very few quantitative and mechanistic studies have been conducted on human platelet aggregation. The present study was an attempt to develop exper-