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Hypoglycemic Activity of Oral Hypoglycemics with Increased Hydrophilicity

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Abstract □ The effect of increasing the hydrophilicity of acetohexamide and tolbutamide with hydroxypropyl methylcellulose and methylcellulose on drug dissolution and hypoglycemic activity in rats was examined. The dissolution rate of both drugs was increased according to the type and concentration of the polymer. The oral absorption of both drugs was improved, as indicated by potentiation of the reduction in blood glucose in rats. The efficiency of the polymer in increasing the dissolution rates of the drugs correlated with the hydrophilicity of the polymer.

Keyphrases □ Hypoglycemics—improved absorption through increased hydrophilicity □ Tolbutamide—improved absorption through increased hydrophilicity □ Acetohexamide—improved absorption through increased hydrophilicity □ Absorption—tolbutamide and acetohexamide, improved absorption through increased hydrophilicity

Certain oral hypoglycemics, *e.g.*, acetohexamide and tolbutamide, are poorly water soluble and have irregular dissolution rates (1–3). Coprecipitation with povidone and solid dispersion of tolbutamide in polyethylene glycols have been utilized to increase the dissolution rate (4, 5) and bioavailability (5, 6). Inclusion of acetohexamide in cyclodextrin enhanced its dissolution and hypoglycemic activity (3).

The increased hydrophilicity of drugs, *i.e.*, the conversion of the hydrophobic surface of the drug to a hydrophilic one through treatment with a film-forming water-soluble polymer, increased the dissolution of hexobarbital (7) and the bioavailability of phenytoin (8) and griseofulvin (9). The polymers used were methylcellulose, hydroxyethyl cellulose (7), and hydroxypropyl cellulose (9).

The objective of the present study was to investigate the

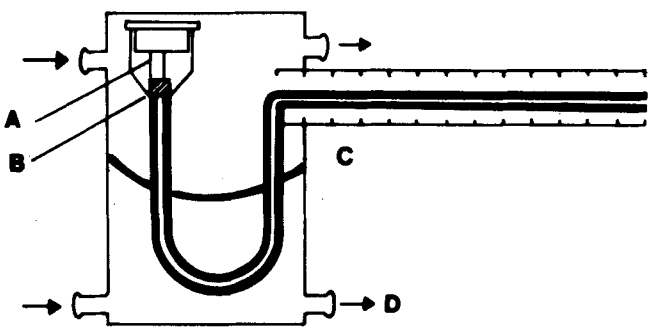

Figure 1—*Apparatus for measuring the uptake of dissolution fluid by drug disks. Key: A, disk stager; B, drug disk; C, graduated pipet; and D, water bath.*

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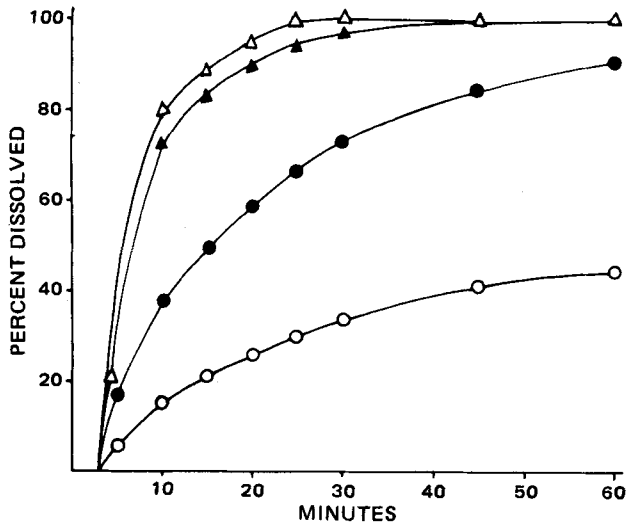

Figure 2—*Dissolution rate of tolbutamide untreated and treated with methylcellulose. Key:* ○, *untreated; and* ●, △, *and* ▲, *treated with 2.5, 5, and 10 ml of a 5% methylcellulose solution/20 g, respectively.*

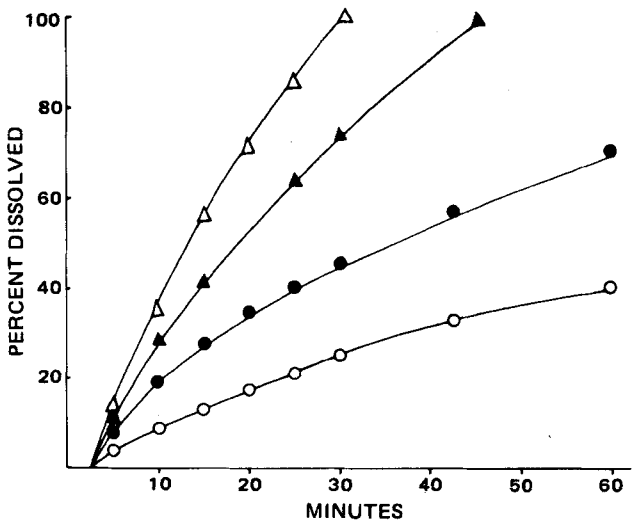

Figure 4—*Dissolution rate of acetohexamide untreated and treated with methylcellulose. Key:* ○, *untreated; and* ●, △, *and* ▲, *treated with 2.5, 5, and 10 ml of a 5% solution of methylcellulose/20 g, respectively.*

effects of increasing the hydrophilicity of acetohexamide (I) and tolbutamide (II) on their dissolution and oral absorption in rats. The polymers selected for increasing the hydrophilicity were hydroxypropyl methylcellulose (III) and methylcellulose (IV). The uptake of dissolution fluid by the treated and the untreated drug was measured.

EXPERIMENTAL

Materials—Acetohexamide[1] (mean particle size 6 μm), tolbutamide[2] (mean particle size 7 μm), hydroxypropyl methylcellulose[3], and methylcellulose[4] were used.

Treatment of Powders—The dispersion of III and IV onto the surface of I and II was carried out in a small high-speed mixer[5]. The drug (20 g) was placed in the mixer with 2.5, 5, or 10 ml of a 5% aqueous solution of the polymer. Mixing was continued for 45 min and then stopped to allow removal of material adhering to the walls with a spatula. This process was repeated three times.

The resultant mass was dried *in vacuo* at 50° for 24 hr and screened through a No. 20 mesh screen. The powder then was manually filled into No. 9 capsules[5], each containing a quantity equivalent to 100 mg of the drug.

Dissolution Testing—The dissolution of the capsules was tested according to USP XIX (10) using the USP dissolution apparatus[5]. The dissolution medium consisted of 900 ml of the medium specified in the monograph for each drug [containing 0.01% (w/v) polysorbate 80[6]]. Samples (5 ml) were withdrawn at 10, 15, 20, 25, 30, 45, and 60 min and filtered through a membrane filter[7] (0.5-μm diameter), and their absorbances[8] were measured at 245 and 226 nm for I and II, respectively. Correction of the analysis was carried out by subtracting the absorbance, if any, due to the polymer solution to obtain the actual drug concentration. Each study was based on three dissolution tests, and the average values are reported.

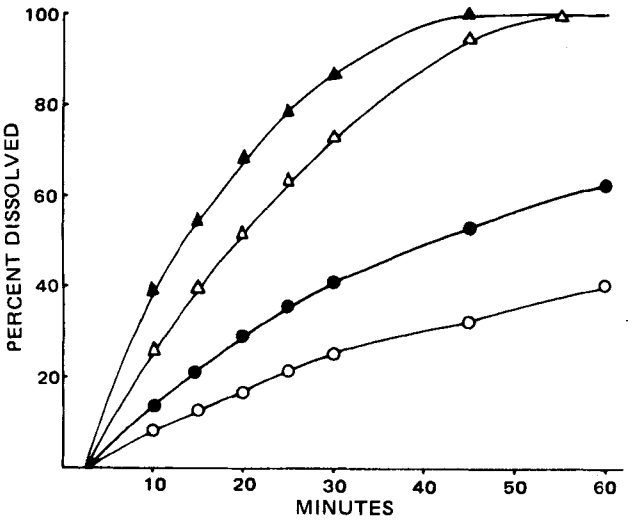

Figure 3—*Dissolution rate of tolbutamide untreated and treated with hydroxypropyl methylcellulose. Key:* ○, *untreated; and* ●, △, *and* ▲, *treated with 2.5, 5, and 10 ml of a 5% solution of hydroxypropyl methylcellulose/20 g, respectively.*

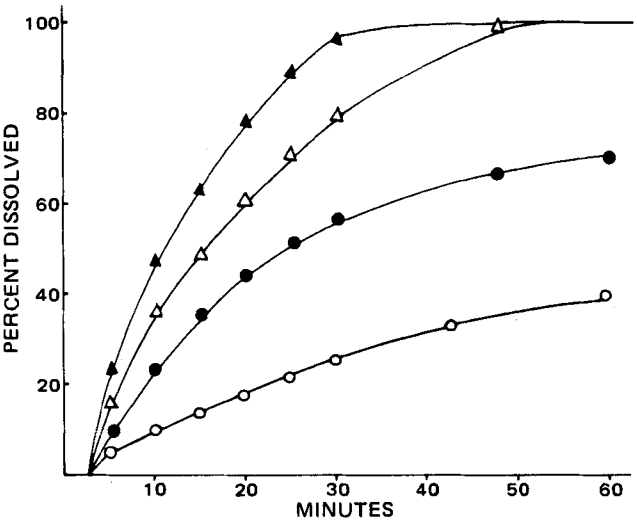

Figure 5—*Dissolution rate of acetohexamide untreated and treated with hydroxypropyl methylcellulose. Key:* ○, *untreated; and* ●, △, *and* ▲, *treated with 2.5, 5, and 10 ml of hydroxypropyl methylcellulose/20 g, respectively.*

[1] Eli Lilly, Indianapolis, Ind.
[2] Industriale Handelmaeatscharani, Amsterdam, The Netherlands.
[3] Al-Arabia Factory for Pharmaceuticals, Ameria, Cairo, Egypt.
[4] BDH, Poole, England.
[5] Erweka-Haeusenstamn, Kr, Offenbach, Main, West Germany.
[6] Koch-Light Laboratories, Bucks, England.
[7] Millipore Corp., Bedford, Mass.
[8] Varian Techtron UV–visible model 635.

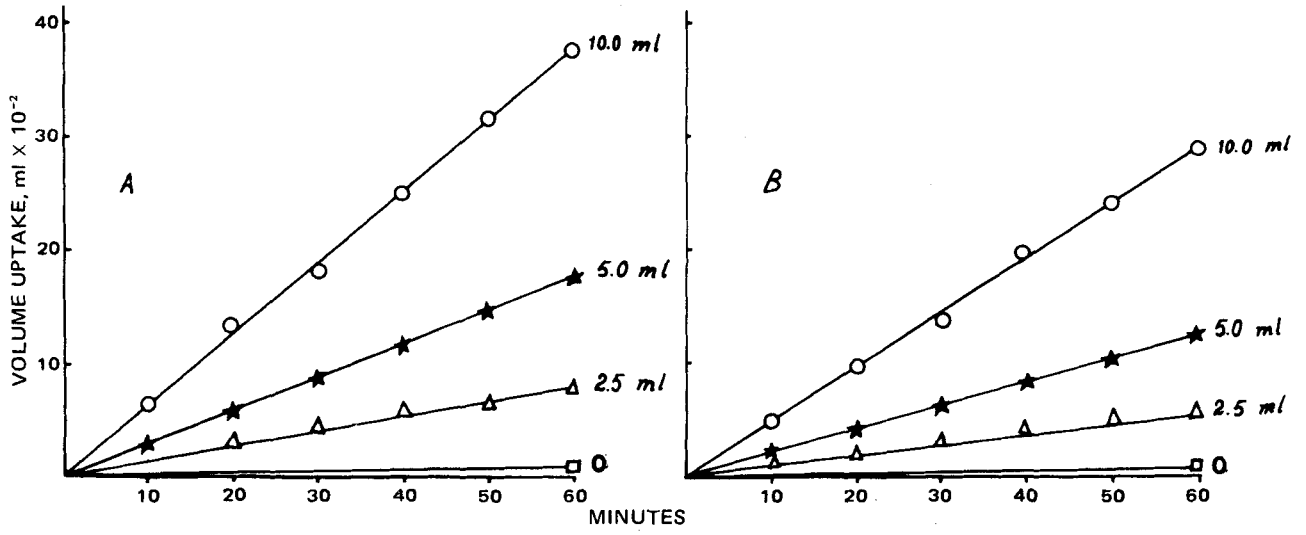

Figure 6—*Uptake of dissolution fluid by untreated and treated tolbutamide disks. Key: A, treated with methylcellulose; and B, treated with hydroxypropyl methylcellulose. The volumes shown were used for each 20 g of drug.*

Disk Preparation—The powders were compressed with a tablet machine[5] to produce disks of 200 mg, having a hardness of ~4 kg on a tablet hardness tester[5].

Liquid Penetration—The unidimensional penetration of the medium used for dissolution of II through disks of treated and untreated drug was carried out using the proposed apparatus (Fig. 1). The disk was fixed in position as shown. The medium used for dissolution was allowed to fill the whole capillary and just to touch the lower surface of the disk.

The movement of the liquid surface in the capillary was observed for 1 hr, and the change during each time interval was converted to volume in milliliters. The experiment was repeated with six disks of each batch. The average cumulative volume of liquid taken up by the disks was compared. The accuracy and reproducibility of the proposed technique were obtained by comparing the coefficient of variation for each batch tested.

Hypoglycemic Activity—The effect of orally administered acetohexamide and tolbutamide and their treated powders on the blood glucose concentration of adult male albino rats was studied. Male albino rats, 150–200 g, were fasted 24 hr before the experiment but were allowed free access to water. They were divided into six groups of 18 rats each. One group was given a suspension of II in water (1%) at a dose of 200 mg/kg. A second group was given an equal dose of II treated with a 5% solution of IV (2.5 ml/20 g). A third group was given the same dose of II treated with a solution of III (2.5 ml/20 g). The remaining three groups of rats were given treated and untreated forms of I in a similar schedule.

Each group was divided into six subgroups of three rats each. One group was sacrificed at each time interval (0.5, 1, 2, 3, 4, and 5 hr), and ~3 ml of the blood was collected from each animal. The blood samples were centrifuged at 3500 rpm for 20 min, and 0.5 ml of serum for each sample was analyzed for its glucose content[9] (11). Three animals were used as controls to determine the blood glucose level at time zero. The mean blood glucose levels of each subgroup were compared, and the differences were tested for significance using the Student *t* test.

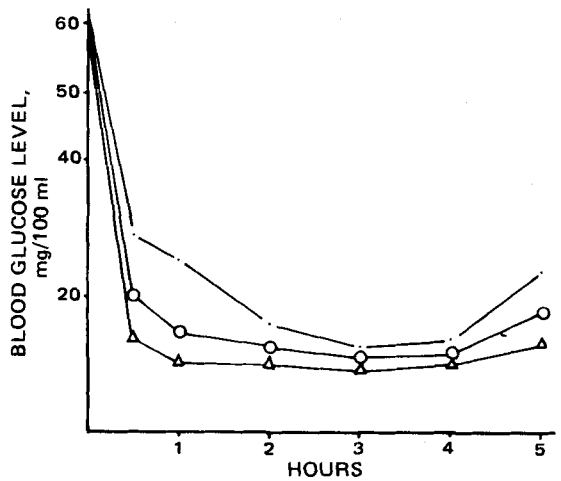

Figure 7—*Changes in blood glucose levels of rats after oral administration of untreated and treated tolbutamide. Key: ·, untreated; and ○ and △, treated with 5% hydroxypropyl methylcellulose and methylcellulose (2.5 ml/20 g), respectively.*

RESULTS AND DISCUSSION

Figures 2–5 show the effect of treating the surfaces of I and II with III and IV on their dissolution from hard gelatin capsules. The treated powders exhibited faster dissolution than the nontreated drugs. Powders treated with III showed a smaller increase in dissolution than those treated with IV. The effect on the dissolution of the drugs tested increased with increasing amounts of IV from 2.5 to 5 ml/20 g. A further increase in the amount of the polymer solution to 10 ml/20 g produced a mild decrease in the dissolution. At 30 min, the average percent amounts of II dissolved were 29.8, 77.1, 99.8, and 95.5 from untreated powder and powders treated with 2.5, 5, and 10 ml of IV solution/20 g, respectively. Therefore, 5 ml of a 5% solution of IV/20 g of tolbutamide apparently is sufficient to achieve optimal hydrophilicity.

On the other hand, in the presence of III, the dissolution of II continued

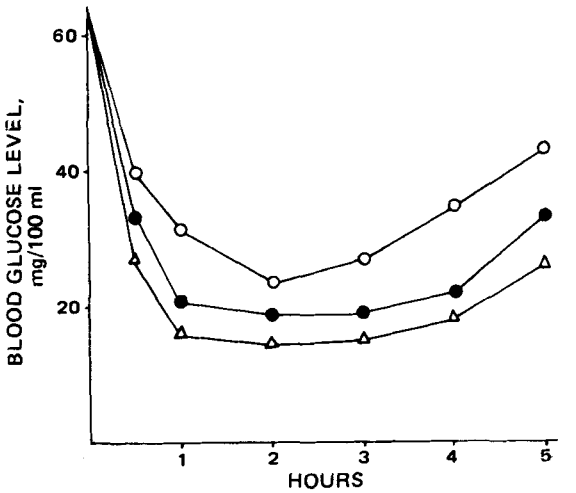

Figure 8—*Changes in blood glucose levels in rats after oral administration of untreated and treated acetohexamide. Key: ○, untreated; and ● and △, treated with 5% hydroxypropyl methylcellulose and methylcellulose (2.5 ml/20 g), respectively.*

[9] Automated analyzer, Boehringer, Mannheim, West Germany.

Table I—Uptake of Dissolution Fluid by Tolbutamide Disks Prepared Using Treated Drug

Milliliters of Polymer Solution per 20 g of Tolbutamide	Disks Prepared from Powder Treated with *Methylcellulose*		Disks Prepared from Powder Treated with *Hydroxypropyl* Methylcellulose	
	Volume Uptake, ml × 10^{-2}	*CV*, %	Volume Uptake, ml × 10^{-2}	*CV*, %
2.5	7.5	1.25	5.5	1.32
5	17.4	1.12	12.6	1.22
10	42.5	1.23	26.8	1.31

to increase with increasing polymer concentrations within the range tested. At 30 min, the average percent amounts of II dissolved were 29.8, 72.3, 95.2, and 99.5 from untreated powder and powders treated with 2.5, 5, and 10 ml of a solution of III/20 g, respectively. The same findings were obtained with I. At 30 min, the average percent amounts of I dissolved were 22.5, 51.5, 76.3, and 96.1 from untreated powder and powders treated with 2.5, 5, and 10 ml of a solution of IV/20 g, respectively. The corresponding average percent dissolved values observed with powders treated with 2.5, 5, and 10 ml of a solution of III were 42.3, 70.2, and 95.3, respectively.

Increased dissolution of I and II by III and IV was attributed to the increased hydrophilicity of the drug particles, in accordance with the observation of Lerk *et al.* (7). However, the increase in the dissolution of I and II produced by treatment with IV seemed to decrease slightly after a certain point. This result was not observed with III in the concentration range studied and might be due to possible thermal gelation of IV at temperatures near 37° during dissolution (12).

Figure 6 shows the uptake of dissolution fluid by treated and untreated tolbutamide. Table I lists the mean cumulative volumes of fluid taken up by the untreated disks along with the coefficient of variation. The mean coefficient of variation was 1.24 ± 0.0725 (*SD*), which indicates the excellent reproducibility and accuracy of the method. It is obvious that the extent of fluid uptake by the treated powders was greater than that of the untreated powder. Also, the fluid uptake by disks of II was increased proportionally by increasing the amount of polymer used. Disks treated with IV showed a higher fluid uptake than did those treated with III. The average cumulative volumes of fluid taken up by disks of II and those prepared from powders treated with 2.5, 5, and 10 ml of a solution of IV/20 g were 0.9×10^{-2}, 9.1×10^{-2}, 17.5×10^{-2}, and 37.5×10^{-2} ml after 60 min. The corresponding average values obtained from disks treated with 2.5, 5, and 10 ml of a solution of III/20 g were 6.5×10^{-2}, 14.2×10^{-2}, and 29.9×10^{-2} ml. Therefore, it seems that the effects produced by III and IV on the dissolution of I and II clearly are correlated to the hydrophilic nature of the polymer, as measured by their water-absorbing ability.

The mean blood glucose concentration of 24-hr fasted rats was 62.53 mg/ml, and this amount was significantly higher than that of all of the treated groups ($p < 0.02$). Figure 7 shows the effect of I, untreated and treated with a 5% solution of III or IV (2.5 ml/20 g), on the blood glucose concentration of rats. The blood glucose concentration (milligrams per 100 ml) observed at 2 hr in rats given II treated with III was 64.2 compared to 88.3% in rats given the untreated drug. The blood glucose concentration observed at the same time in animals given II treated with IV was 74.5% compared to 52.3% in rats given the untreated drug. The reduction in the blood glucose level was greater with the treated drug than with the untreated drug and seemed more pronounced when the drug was treated with IV.

The difference between the average blood glucose concentration obtained from rats given I treated with III or IV and that obtained from rats given untreated drug was significant ($p < 0.05$) at all time intervals. Insignificant differences were calculated between the blood glucose concentrations for animals given II treated with III or IV, except at 1 and 2 hr, where a significant difference ($p < 0.05$) was observed. Figure 8 shows the effect of treated and untreated powders of I on the blood glucose concentration of rats. The mean blood glucose concentration observed at 2 hr in rats given I treated with III and IV was 82.5%; it was only 62.3% for animals given the untreated drug. Again, the differences were significant ($p < 0.05$) at all time intervals. The data show that I treated with IV exhibited a higher hypoglycemic effect than that treated with III. No significant differences were observed between values of the blood glucose concentration for rats treated with III or IV, except after 1 and 2 hr, where significant differences ($p < 0.05$) were calculated.

The increase in the dissolution of I and II after treatment with III and IV was reflected by increased drug absorption, as indicated by the greater reduction in glucose levels. Moreover, IV, which achieved higher hydrophilicity, induced better drug absorption.

Increasing hydrophilicity of the drugs by methylcellulose or hydroxypropyl methylcellulose seems better than coprecipitation with povidone or solid dispersion in polyethylene glycols. In the latter two techniques, the quantity of the polymer required to enhance the dissolution and bioavailability of tolbutamide was too high (about equal to the dose). By increasing the hydrophilicity, only a minute quantity of the polymer is required to enhance the dissolution and bioavailability of drugs.

The method of increasing the dissolution characteristics of poorly soluble drugs by increasing the hydrophilicity using a highly hydrophilic polymer may be widely applicable to other drugs.

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