containing phenolic hydroxyl groups such as pyridoxine will be presented in a future report.

SUMMARY

Diazotized 4-amino-6-chloro-*m*-benzene disulfonamide has been found to couple with various estrogens containing a phenolic hydroxyl group to yield a stable red color in alkaline solution.

This reaction is the basis of a rapid, sensitive, and reproducible method for the determination of estrogens such as estradiol, ethinyl estradiol, estrone, and estradiol dipropionate.

Commonly encountered excipients such as lactose, starch, and sesame oil were found not to interfere in the determination of these estrogens.

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Effects of Adsorbents on Drug Absorption II

Effect of an Antidiarrhea Mixture on Promazine Absorption

By DONALD L. SORBY and GRACE LIU

An antidiarrhea mixture containing attapulgite and citrus pectin was studied for its potential effect on the absorption of promazine from the human gastrointestinal tract. Test conditions were established so that results would have maximum applicability to the clinical use situation. Drug and adsorbent were not equilibrated prior to administration. Under these conditions, the antidiarrhea mixture decreased the rate and extent of absorption of the test drug. An *in vitro* adsorption study established that the antidiarrhea mixture had a strong affinity for the test drug. Results are in general agreement with the previous report in this series.

A PREVIOUS report (1) showed that activated charcoal and activated attapulgite both altered the absorption of promazine from the gastrointestinal tract. Prior to administration to human subjects, a 50-mg. quantity of promazine was equilibrated with the particular adsorbent material. The resulting test doses contained 38.5 mg. of the total 50-mg. quantity of promazine adsorbed to activated attapulgite or 24.7 mg. bound to activated charcoal. Under these conditions, activated attapulgite slowed the rate of absorption; however, it had no significant effect on the total availability of the drug. Activated charcoal, on the other hand, appeared not to release any of the adsorbed drug while within the gastrointestinal tract and only promazine, which was free in solution in the test dose at the time of administration, was absorbed. *In vitro* studies of desorption rates from adsorbates demonstrated that promazine release was rapid from activated attapulgite and very slow from activated charcoal.

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Several pharmaceutical products containing adsorbent materials are intended to control diarrhea by exerting their action within the gastrointestinal tract. In this respect they are thought to adsorb certain toxic amines produced by putrefaction or as by-products of bacterial metabolism, and thus prevent their undesirable actions on the human body (2). The question arises concerning whether the presence of such adsorbent materials within the gastrointestinal tract might also interfere with absorption of amine-type drugs, many of which are known to be strongly adsorbed *in vitro* by the materials included in antidiarrhea preparations (2–6).

The observed effects of adsorbents on drug absorption (1) are applicable only to the situation where drug and adsorbent are equilibrated before administration to test subjects. The question concerning whether the same effects will be obtained if drug and adsorbent do not meet until both are within the confines of the gastrointestinal tract was left unanswered.

The purpose of this research was to determine whether the presence of an adsorbent antidiarrhea mixture within the gastrointestinal tract would interfere with the absorption of an amine-type drug. Promazine hydrochloride (50

mg.) was used as the test drug. The antidiarrhea mixture contained in each 30-ml. vol. activated attapulgite (3 Gm.), activated attapulgite, colloidal (0.9 Gm.), and citrus pectin, 0.3 Gm.[1]

EXPERIMENTAL

Determination of Adsorption Isotherm.—Adsorption of promazine by activated attapulgite was reported previously (1). The antidiarrhea mixture contained additional ingredients, however, and it was thus necessary to study the interaction between promazine and the specific product.

The antidiarrhea mixture was diluted with a quantity of distilled water equal to twice its own weight. While the resulting suspension was vigorously stirred, 20-ml. aliquots were pipeted into 50-ml. glass-stoppered test tubes.

Visking cellulose dialysis casings ($^{18}/_{32} \times 8$ in.) were pretreated by soaking in distilled water at 90° for 10 hr. The water was changed several times during this period. The inside of each casing was then flushed with distilled water and the casings were returned to a warm water soak for an additional half hour. Just prior to use, excess water was expressed, and a knot was tied in one end of each casing to form a small bag.

A 10-ml. quantity of a solution containing either 10, 20, 30, 40, or 50 mg. of promazine hydrochloride in distilled water was pipeted into each dialysis bag, and a knot was tied to close the open end. Four bags were prepared for each concentration of promazine hydrochloride. Two of the four bags were placed into tubes containing the diluted antidiarrhea mixture. The remaining two bags were placed into tubes containing 20 ml. of distilled water. The tubes were stoppered and sealed with paraffin wax to prevent passage of water along the stoppers by capillary action. All tubes were placed in a rocker-shaker device totally immersed in a constant-temperature bath at 25.0°. Shaking proceeded for 5 days. Equilibrium was established by the end of this time period.

The dialysis bags were removed from the tubes and dried lightly with tissue. An appropriate aliquot of the solution inside the bag was removed, and the amount of promazine remaining in solution was determined by the method described previously (3). Control experiments showed that the antidiarrhea mixture contained no interfering materials at the levels of dilution used to assay for promazine. For systems containing only distilled water as the phase outside the dialysis bag, both external and internal solutions were assayed for promazine content.

The amount of material disappearing from solution in the systems containing no adsorbent was plotted *versus* the concentration of material remaining. This served as a calibration curve to provide a "dialysis cell adsorption value" for the samples containing adsorbent. The apparent amount of promazine adsorbed in systems containing the antidiarrhea mixture was calculated from the difference between the amount of promazine added initially and the amount present in solution at the end of the experiment minus the amount adsorbed by the dialysis cell.

Twenty-milliliter aliquots of the diluted suspension were pipeted into tared dishes, weighed, evaporated to dryness, and reweighed. From these data, it was possible to calculate the amount of water contributed to the dialysis system by the antidiarrhea mixture and also the weight of solids which it contained. This experiment also showed that there was a high degree of reproducibility in pipeting the diluted antidiarrhea mixture, even though there was some hold-back of material within the pipet.

The data obtained from the adsorption experiments were treated according to the Langmuir equation. Figure 1 shows the experimental values and the regression line calculated by the method of least squares. The constants for the Langmuir equation were calculated from the reciprocals of the slope and intercept values of the regression equation.

In Vivo Tests.—*In vivo* testing was conducted using an adult, male human, 31 years of age, weighing 80 Kg., and in apparent good

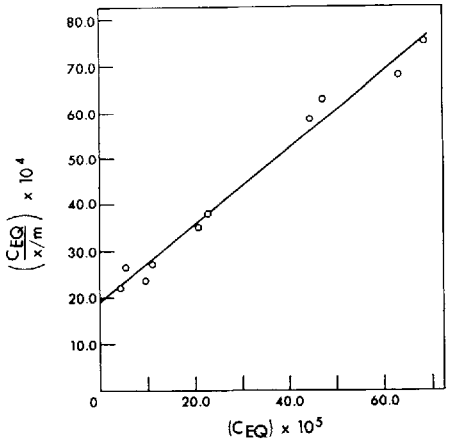

Fig. 1.—Langmuir isotherm for adsorption of promazine at 25.0° by the antidiarrhea mixture. C_{EQ} denotes the molar concentration of promazine in solution at equilibrium; x/m, the millimoles of promazine adsorbed per gram of solids in the antidiarrhea mixture.

[1] The antidiarrhea mixture was procured from a local source and was representative of the product as it appears in commerce.

TABLE I.—CUMULATIVE PROMAZINE EQUIVALENTS PRESENT IN TOTAL URINE SAMPLES AT THE END OF VARIOUS TIME INTERVALS FOLLOWING ADMINISTRATION OF TEST DOSAGE FORMS[a]

Time After Administration of Test Dose, hr.	Mean Promazine Equivalents Excreted — Test Dosage Form			
	Solution,[b] 25 mg.	Solution,[c] 37.5 mg.	Solution,[c] 50 mg.	Antidiarrhea[c] Mixture
1	83 ± 92[d]	96 ± 105[d]	121 ±78[d]	36 ± 61[d]
2	311 ± 167	478 ● 141	739 ± 265	159 ± 138
3	634 ± 311	1004 ± 180	1393 ± 303	333 ± 216
4	910 ± 443	1463 ± 191	1929 ± 411	561 ± 266
5	1114 ± 455	1764 ± 242	2233 ± 428	804 ± 324
6	1252 ± 518	1962 ± 311	2495 ± 480	1074 ± 389
8	1451 ± 590	2301 ± 392	2920 ± 496	1580 ± 355
10	1623 ± 678	2585 ± 492	3238 ± 452	2042 ± 453
12	1751 ± 792	2791 ± 567	3495 ± 434	2395 ± 596
15	1948 ± 882	3024 ± 640	3798 ± 437	2732 ± 754
18	2091 ± 931	3204 ± 700	4068 ± 448	2992 ± 884
24	2303 ± 955	3491 ± 793	4429 ± 589	3368 ± 1030
30	2411 ± 1032	3491 ± 793	4720 ± 747	3619 ± 1084
36	2445 ± 1137	3549 ± 774	4906 ± 721	3730 ± 1098

[a] For a definition of the promazine equivalent, see under *Analysis of Urine Samples*. [b] Mean of four experiments. [c] Mean of five experiments. [d] Plus-minus values represent the 95% confidence intervals about means.

health. The subject had participated in previous experiments (1) where he was designated as subject *A*.

The subject was assigned the various test doses in a random order determined through use of a table of random numbers. At least 1 week elapsed between administration of consecutive test doses. During the course of the study, there was no appreciable change in the amount of background material in the urine which was sensitive to the assay procedure. Thus, the 1-week delay between tests appeared to be adequate to avoid carryover effects between consecutive doses.

On the day prior to each experiment, the subject collected three separate urine samples to serve as blanks in the assay. Upon arising the morning of the test day, the subject voided his bladder, consumed 4 fl. oz. of water and, after waiting 0.5 hr., collected a urine sample also to be used as a blank in the assay. The subject immediately consumed the test preparation, rinsing the bottle with a small portion of water to insure complete transfer of the test dose. Urine samples were collected over the time intervals shown in Table I. No further food or drink was consumed for at least 1 hr. Consumption of food and water was *ad libitum* for the remainder of the test period. Immediately after collection, the volume of each urine sample was measured and recorded. An aliquot of the sample was frozen for assay at a later time. At the conclusion of each experiment, the frozen samples were returned to the laboratory, and after reaching room temperature they were assayed for their content of promazine excretion products.

When the experiment involved measurement of the effects of the antidiarrhea mixture, the subject consumed 1 fl. oz. of the undiluted preparation at bedtime the night before the test. Upon arising the next morning, the subject consumed an additional 1 fl. oz. of the antidiarrhea mixture. Finally, 0.5 hr. later, he took another 0.5 fl. oz. A solution containing 50 mg. of promazine hydrochloride in 45 ml. of distilled water was immediately consumed. Experiments were also carried out to measure excretion characteristics following doses of 25 mg., 37.5 mg., and 50 mg. of promazine hydrochloride in distilled water and with no antidiarrhea mixture present in the gastrointestinal tract. Data obtained from the various experiments are shown in Table I.

Analysis of Urine Samples.—Urine samples were analyzed by a procedure similar to the method used before (1). It was found previously that the yellow-colored urine pigments cause some interference with the assay procedure. This interference introduces a systematic but variable error into each assay since the intensity of the yellow color varies from sample to sample. The assay procedure was further modified in this experiment to better correct for this interference in order to obtain higher precision.

A relationship exists between the transmittance at 420 mμ of urine samples containing no promazine and the intensity of color developed at 515 mμ in these same samples when assayed by the method for determining promazine content of the urine. The assay procedure was thus modified in the following fashion. Four urine blanks were collected prior to each experiment. The transmittance of all samples, as well as urine blanks, was determined at 420 mμ before assay for promazine content.[2] The samples and blanks

[2] Per cent transmittance at 420 mμ was measured on the diluted urine sample immediately prior to passing it through the ion-exchange column.

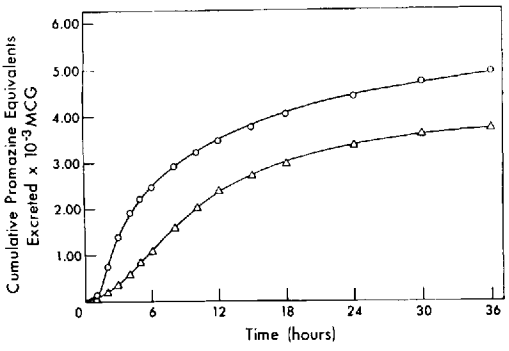

Fig. 2.—Cumulative amounts of promazine equivalents excreted in the urine following administration of promazine hydrochloride (50 mg.) in simple aqueous solution. Key: O, promazine administered alone; △, promazine administered immediately following antidiarrhea mixture. Points on each curve represent means from five separate experiments.

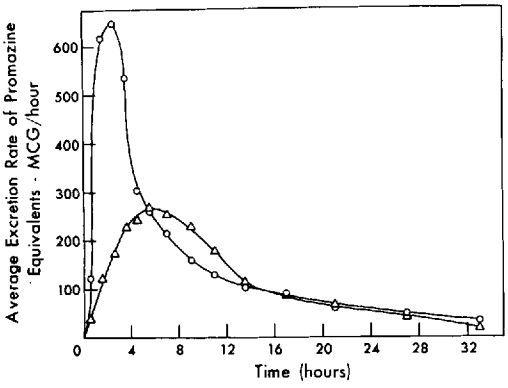

Fig. 3.—Average urinary excretion rate of promazine equivalents following administration of promazine hydrochloride (50 mg.) in simple aqueous solution. Key: O, promazine administered alone; △, promazine administered immediately following antidiarrhea mixture. Points on each curve represent means from five separate experiments.

were then assayed as described previously (1) for their apparent content of promazine excretion products. A blank correction curve was prepared by plotting the per cent transmittance at 420 mμ against per cent transmittance at 515 mμ after assay for each of the urine blanks. A blank correction was made for each test sample by comparing its per cent transmittance at 420 mμ with the correction curve. The probable color intensity at 515 mμ contributed by blank was therefore obtained for each test sample.

As discussed previously (1), due to the nonspecific nature of the assay procedure, it is necessary to express the results of assays on the basis of promazine equivalents. A promazine equivalent is defined as representing the amount of promazine hydrochloride which, if carried through the assay procedure, would give the same color intensity at 515 mμ as the urine sample in question. The excretion products in urine samples were quantitated by comparing their per cent transmittance at 515 mμ to a standard curve prepared by assaying known amounts of promazine hydrochloride dissolved in distilled water. The promazine equivalent representing the blank for a particular sample was subtracted from the assay value to obtain the actual amount of excretion product.

Treatment of Excretion Data.—Methods for treating urinary excretion data were described previously (1). Cumulative amounts of promazine equivalents excreted up to the end of each time interval and the average excretion rates during each time period were calculated. Statistical comparisons of data were made by a t test for independent sample means. Two-tail t values were used in assessing the level of significance of all data. The results of the various calculations are presented in Figs. 2, 3, and 4 and in Tables I and II.

DISCUSSION

Adsorption of promazine by the contents of the antidiarrhea mixture appears to conform to the Langmuir equation (Fig. 1). The equation for the regression line shown in Fig. 1 is

$$\frac{C_{EQ}}{x/m} = 8.31\ C_{EQ} + 1.90 \times 10^{-3}$$

where C_{EQ} is the concentration of promazine

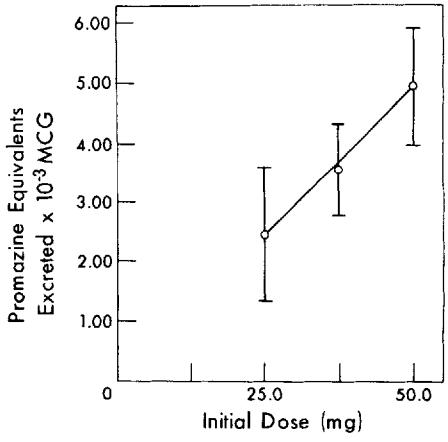

Fig. 4.—Relationship between initial dose of promazine hydrochloride and cumulative promazine equivalents excreted in the urine after 36 hr. Points represent means of five separate experiments for the 50.0 and 37.5 mg. doses and four separate experiments for the 25.0-mg. dose. Bars denote 95% confidence intervals about means. Differences between means are significant at the $P = 0.05$ level by the t test.

TABLE II.—RESULTS OF STATISTICAL COMPARISONS OF EXCRETION DATA FOR PROMAZINE, 50 mg., IN SOLUTION ADMINISTERED WITH AND WITHOUT ANTIDIARRHEA MIXTURE

Time After Administration of Test Dose, hr.	Comparison of Cumulative Amount Excreted[a]	Midpoint Time of Collection Period, hr.	Comparison of Average Excretion Rate[b]
1	$0.05/P/.025$	$^1/_2$	$0.05/P/0.025$
2	$0.001/P$	$1^1/_2$	$0.001/P$
3	$0.001/P$	$2^1/_2$	$0.001/P$
4	$0.001/P$	$3^1/_2$	$0.005/P/0.001$
5	$0.001/P$	$4^1/_2$	$0.30/P/0.25$
6	$0.001/P$	$5^1/_2$	$0.90/P/0.80$
8	$0.001/P$	7	$0.50/P/0.40$
10	$0.001/P$	9	$0.20/P/0.10$[c]
12	$0.005/P/0.001$	11	$0.25/P/0.20$[c]
15	$0.005/P/0.001$	$13^1/_2$	$0.70/P/0.60$
18	$0.02/P/0.01$	$16^1/_2$	$P/0.90$
24	$0.05/P/0.025$	21	$0.90/P/0.80$
30	$0.05/P/0.025$	27	$0.70/P/0.60$
36	$0.05/P/0.025$	33	$0.50/P/0.40$

[a] These comparisons pertain to plots shown in Fig. 2. [b] These comparisons pertain to plots shown in Fig. 3. [c] The variance ratio of these comparisons exceeded the critical value at the $P = 0.05$ level.

remaining in solution at equilibrium, and x/m is the amount of promazine adsorbed per unit weight of adsorbent, *i.e.*, the specific adsorption. The reciprocal of the slope yields a Langmuir adsorption constant which predicts the maximum amount of promazine which can be adsorbed. At that point, the surfaces of all adsorbing materials in the preparation supposedly are saturated with the adsorbed substance. The value of this constant is 0.120 mmole/Gm. of solids in the antidiarrhea mixture.[3] This amount corresponds to 38.5 mg. of promazine adsorbed per gram of solids. While the extent of adsorption is not always directly proportional to the total adsorbent in a system (7), it appears that the usual 1-fl. oz. dose of the antidiarrhea mixture would be capable of adsorbing nearly all of a 50-mg. dose of promazine hydrochloride. It should be pointed out that the degree of dilution by gastric fluids and by water in the test dose, as well as the effects of the various gastrointestinal contents, could make the adsorption characteristics quite different in the *in vivo* situation. These *in vitro* data do show, however, a high potential for adsorption of promazine by the antidiarrhea mixture. The quantity of antidiarrhea mixture consumed by the test subject would be more than adequate to adsorb all of the test dose under conditions similar to the *in vitro* experiment.

Data presented in Tables I and II and in Figs. 2 and 3 amply demonstrate the fact that the antidiarrhea mixture interferes with absorption of the test drug from the human gastrointestinal tract. Both the absorption rate and the over-all extent of absorption, as judged by urinary excretion data, are modified when the antidiarrhea mixture is present. The delay in the time of peak urinary excretion rate (Fig. 3) suggests that, for a period of time, the apparent absorption rate constant for promazine is altered. Such an effect was also seen previously (1) when promazine pre-equilibrated with activated attapulgite was administered to test subjects. These results differ from those obtained previously in that the total amount of drug absorbed is also significantly decreased. This may be seen in both Figs. 2 and 3. Judged by the 36-hr. cumulative excretion, the relative availability of promazine was 76% after administration with the antidiarrhea mixture. The same value can also be arrived at independently by comparing the 36-hr. cumulative excretion after the antidiarrhea mixture to Fig. 4. This amount of excretion product would be obtained from an initial dose of 38 mg. of promazine hydrochloride in solution, again 76% of the actual dose.

Data shown in Fig. 4 add proof to the validity of test methods employed here and previously (1) for studying the effects of adsorbents on the absorption of the model amine. While the assay method is indeed nonspecific and will determine only a portion of total drug metabolites excreted (1, 8), Fig. 4 shows that a direct relationship exists between the initial dose of promazine and the amount of excretion product collected over a 36-hr. period. While not presented here, similar plots of data for other collection periods are also linearly related to initial dose. Differences between the three doses with respect to the mean cumulative excretion products at each collection period were significant in every case at the $P = 0.05$ level as well. It is thus established that the differences between excretion curves found both here and previously (1) reflect differences in the amount of test drug absorbed.

[3] No attempt was made to distinguish between adsorbing and nonadsorbing solids in the antidiarrhea mixture. It is likely that only a portion of the total solids present after evaporating the mixture to dryness possess adsorbent power.

The decision to perform the experiments in replicate with one subject rather than by using a test panel of different subjects was based on several factors. Between subjects variability with respect to elimination of the test drug is quite high (1). This reduces the sensitivity of the experiment with respect to its ability to detect adsorbent effects. Replicate experiments in one individual should be subject to less variability. The data show that even with one subject, variability is high but it is not so great as was obtained previously (1). Data in the literature (9–12) point out the importance of urine flow rate and urine pH to the excretion rate of various amines. It was not considered to be desirable to attempt to control urine pH since this would involve administration of materials which might alter the local environment within the gastrointestinal tract at the time of administering the test dose. It was thought that by using a single test subject, patterns of diet and fluid intake would be less varied and would result in a more constant influence of urine pH and flow rate on promazine excretion. The difficulty of securing cooperation of test subjects in an experiment where many samples are collected and several tests are to be performed was another factor behind use of a single test subject. Others have also employed a single test subject in cases where precise and careful subject cooperation was required (13).

Of course it may be argued that the responses of one individual cannot be extrapolated to the general population of subjects. This would certainly be true in many cases and indeed one must proceed with caution in interpreting the results of this experiment. In this case, however, the human subject is used to provide a suitable environment to study uptake and release of the test drug from the adsorbent material. A more precise estimation of these effects may be obtained where the data are not subject to the additional variables arising from differences in the way individuals metabolize and excrete the drug once it is absorbed. In a sense the human subject provides an experimental instrument which no *in vitro* apparatus can be made sufficiently refined to do, *viz.*, to provide a system containing all of the variables usually met within the human gastrointestinal tract. It is also necessary to study the adsorption phenomenon where it is subject to the influence of the dynamic situation which is provided by constant removal of drug from solution in the gut through absorption. Obviously, there will be quantitative differences in the magnitude of adsorbent effects between different individuals. Between subject differences with respect to gastric and intestinal pH, gastrointestinal motility, ionic content of the gastrointestinal fluids, presence of food, the adsorbent dose, and even the disease state may all alter the magnitude of the adsorbent effect in a given individual. It is considered, however, that the results of this experiment amply demonstrate the potential effect of an adsorbent on drug absorption. In showing that this potential exists, the results should be applicable to the general population of subjects.

SUMMARY

It is apparent, on the basis of evidence presented, that the presence of the antidiarrhea mixture within the gastrointestinal tract is sufficient to retard absorption of the model amine drug. While availability was retarded in this case, the results still compare qualitatively with those obtained previously (1) for attapulgite-promazine adsorbates. Considering the overwhelming excess of adsorbent present, and its affinity for the drug *in vitro*, the degree of interference with absorption is more remarkable for the fact that it does not occur to a greater extent rather than for the fact that it does occur. It has already been shown *in vitro* (1) that desorption is facilitated in acidic media. It was also found for other clay-type adsorbents (14) that acidic media retard adsorption of various phenothiazine derivatives. In the gastrointestinal tract, therefore, the affinity between drug and the antidiarrhea mixture may be considerably less than found *in vitro*.

The results of this study have important clinical implications. While it has not been established whether adsorbent effects determined here and previously (1) are applicable to other amine-type drugs, it is probably true that effects would be similar for amines of similar basicity and adsorbability *in vivo*. If this is the case, a potential exists for interference with the absorption of many drugs when the gastrointestinal tract is "loaded" with an antidiarrhea mixture. In view of the somewhat questionable merits of these preparations as adjuncts to controlling diarrhea (15), their use in a given situation should be carefully weighed against potential harmful effects on the absorption of certain more therapeutically important drugs which the subject might be taking concurrently.

Further studies now in progress should provide more information concerning the general applicability of these results to other amine-type drugs. Also in progress are studies aimed at establishing correlations between *in vitro* adsorption studies and *in vivo* effects of adsorbents on drug absorption.

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Technical Articles

Microcrystalline Cellulose in Tableting

By GEORGE E. REIER* and RALPH F. SHANGRAW

The development of microcrystalline cellulose has made available to the pharmaceutical industry an extremely valuable tableting agent. It was found that tablets of plain microcrystalline cellulose will tend to soften and swell when exposed to humid conditions, but the effect is reversed upon the removal of increased humidities. Elevated temperatures have no effect on these tablets. Microcrystalline cellulose tablets will disintegrate very slowly in solvents of a relatively low polarity. It is postulated that tablets of this material are a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. Tablet disintegration is merely the breaking of the intercrystallite bonds by the disintegrating medium. No significant separation of components was found during the compression of a microcrystalline cellulose-containing formulation. The release of amphetamine sulfate and sodium phenobarbital from tablets containing microcrystalline cellulose is excellent. Determinations after 10 weeks at various environments indicate that no release problems exist. When the cellulosic compound was used as a dry binder–disintegrator in the direct compression of formulations of ephedrine hydrochloride, quinine sulfate, and a low melting steroid, tablets of outstanding quality were produced.

THE SUCCESSFUL application of direct compression as a tableting procedure is dependent upon the development of suitable materials which in themselves are both highly fluid and cohesive. Spray-dried lactose exhibits these characteristics and has enjoyed considerable success as a tableting agent in direct compression. However, it has the disadvantage of browning under certain conditions (1–3) and there is a limiting hardness to tablets produced from spray-dried lactose which, if exceeded, results in capping. This pressure sensitivity occurs at lower tablet hardnesses than usually encountered with granulations of conventional lactose.

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Another material which possesses the required properties for direct compression is microcrystalline cellulose.[1] This material is not a derivative of the parent compound, nor is it merely purified cellulose (4, 5).

A preliminary report pointed up the ability of microcrystalline cellulose to form extremely hard tablets that are not friable and yet possess unusually short disintegration times (6). The preparation and stability of glyceryl trinitrate tablets produced by direct compression of the drug in a microcrystalline cellulose matrix have been described (7). A comparison of the effect of water vapor pressure on the moisture sorption and stability characteristics of aspirin and ascorbic acid tablets containing various fillers including microcrystalline cellulose has been published (8). Microcrystalline cellulose has been included in

[1] Marketed as Avicel by the American Viscose Corp., Marcus Hook, Pa.