by charcoal appears to be mediated primarily by physical forces and probably occurs as a result of the tendency of the solute to accumulate at solution–solid interfaces. This tendency to accumulate at the solution–solid interface is similar to the demonstrated surface tension lowering effects of the phenothiazine derivatives.

Adsorption of phenothiazine derivatives by clay-type materials such as kaolin and talc is more complex in nature and is probably mediated through several different mechanisms simultaneously. Mechanisms based on simple electrostatic charge interactions cannot alone explain the process. Molecular size and interfacial properties of the solute do not appear to correlate with adsorption in systems containing kaolin or talc in simple aqueous media.

The results of this experiment show that adsorption of phenothiazine derivatives is dependent upon both hydrogen-ion and electrolyte concentration. Hydrogen-ion concentration is inversely related to the extent of adsorption. The effect of hydrogen-ion may be either to determine the amount of nonprotonated form which is present or to compete with the protonated form for adsorption sites. It is probable that adsorption of phenothiazine derivatives by talc and kaolin is subject to both of these effects. The presence of sodium chloride generally increases adsorption. This is probably due to effects on various physical properties of the solute which increase its tendency to accumulate at the solution–solid interface. The failure of sodium chloride to depress adsorption tends to discount simple ion-exchange as a major mechanism of adsorption.

The effects of pH and electrolyte concentration have important implications with respect to the effect of adsorbents in altering availability of promazine for absorption from the gastrointestinal tract.

The results of these experiments will be useful in further studies of the effect of adsorbents on drug availability. They should also be of use in interpretation of drug–adsorbent interactions in general.

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Inositol N.F.

New Excipient for Chewable Tablets

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An investigation of the suitability of inositol as a base for chewable tablets has been conducted by studying and comparing pertinent properties of inositol, mannitol, lactose, and a lactose–sucrose mixture (9:1). The amounts of moisture absorbed by the finely powdered materials, granulations made from these powders with the aid of selected binders, and tablets compressed from some of the granulations were determined (Karl Fischer method or difference in weight) before and after storage at selected relative humidities for specified periods of time. Tablets of similar weights and volumes were prepared from inositol as well as mannitol granulations and evaluated for hardness and dissolution times before and after aging and compared. Representative chewable tablets utilizing mannitol and inositol as bases were prepared for vitamins, antacids, and for acetylsalicylic acid and evaluated for compressability, hardness, dissolution, taste, and appearance. The experimental data indicate that inositol, due to its nonhygroscopic nature, chemical inertness, nontoxicity, physical stability, superior mouthfeel, and texture can be beneficially employed as the base for the formulation of chewable tablets.

ONE OF the recent modifications in tablet dosage forms has led to the development of the chewable tablet, a compressed dosage form, conveniently carried and self-administered, which can be chewed or sucked without the aid of external liquid (1, 2). Daoust and Lynch (1) state that the ideal chewable tablet must be nonhygroscopic and chemically stable, that it

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must disintegrate smoothly at a satisfactory rate, have a pleasant taste and mouthfeel, and leave no unpleasant aftertaste.

Since the excipient constitutes usually a large proportion of the substance of the tablet, the physical characteristics of the dosage form are necessarily influenced by those of the excipient, although not all to the same degree.

Extensive studies (1, 3) have been conducted on sugars and sugar alcohols in order to determine their suitability as bases for chewable tablets with the results indicating that mannitol possesses all the desirable characteristics of the "preferred excipient." No evaluation has been reported on the use of cyclic polyhydroxic alcohols for this purpose, although it was noted that inositol possesses many of the same desirable characteristics and properties (4–6). Inositol N.F. is an odorless, nonhygroscopic, chemically stable, sweet-tasting, white, crystalline material having a negative heat of solution (7) and is soluble to the extent of 1 Gm. in 5.7 ml. of water at 25°. This cyclic alcohol is widely distributed in nature being found in nearly all living cells investigated (8) and has demonstrated no toxicity.

With this information in mind and with the intent of possibly improving a well-accepted dosage form while, at the same time, extending the usefulness of an abundant natural product, a study was undertaken to determine the suitability of a cyclic polyhydroxic alcohol, inositol N.F., as a base for chewable tablets. The investigation included a comparison of some of the more pertinent properties of inositol, granulations of inositol, and tablets made from inositol with those corresponding properties of some accepted excipients.

EXPERIMENTAL

Materials.—The mannitol N.F. and inositol N.F. were obtained in powdered form from Mann Research Laboratories and the lactose U.S.P. was purchased from City Chemical Corp. Other materials used included sucrose U.S.P., gelatin U.S.P., potato starch,[1] acacia U.S.P., methylcellulose U.S.P. (1500 cps.), alcohol U.S.P., magnesium stearate U.S.P., magnesium trisilicate U.S.P., aluminum hydroxide,[1] aspirin U.S.P., liquid glucose U.S.P., and sodium saccharin N.F. The vitamins used in the preparation of the multivitamin tablets were U.S.P. grade as obtained from Mann Research Laboratories.

Preparation of Powders.—The finely powdered mannitol, inositol, and lactose were passed through a 60 mesh screen in preparation for the moisture absorption studies and prior to the preparation of the various granulations.

[1] Obtained from J. T. Baker Chemical Co., Phillipsburg, N. J.

Preparation of Granulations.—Four series of granulations were prepared using mannitol, inositol, lactose, and lactose–sucrose (9:1) as bases according to the following formula: base, 993 Gm.; sodium saccharin, 7 Gm.; binder solution, as required.

Five granulations were prepared from each of the four bases utilizing purified water, 10% acacia solution, 10% gelatin solution, 10% starch paste, and diluted alcohol U.S.P. as the binder solutions. The volumes of granulating solutions required for the granulation of 500 Gm. of each base are shown in Table I.

The dry and previously mixed materials were moistened with the binder solutions and kneaded by hand until masses were formed. The wetted masses were then passed through an Erweka F.G.S. granulator fitted with a screen having 1.5 mm. openings (approximately 14 mesh). The resulting wet granules were dried in a Glatt TR-2 fluidized bed dryer at 40° with a gate opening of 2.5 for a period of 30 min. for the mannitol and inositol granulations, and for 50 min. for those granulations containing lactose and the lactose–sucrose mixture. The increased drying times for the lactose and lactose–sucrose granulations were necessary in order to reduce the moisture content to an acceptable level as determined by the Karl Fischer method. The moisture content of each of the dried granulations expressed as averages of triplicate determinations is shown in Table I. After drying, the granules were passed through a No. 18 screen and stored in airtight containers for future use.

Additional series of granulations were prepared both from mannitol and from inositol, but using the No. 14 sieve as the final size in order to obtain larger granules. Similar granulations were prepared with 2% liquid glucose added as an additional binder solution. These granulations also were reserved for further study.

Compression of Granulations.—Portions (1000 Gm.) of each of the prepared granulations were mixed with portions (10 Gm.) of magnesium stearate as lubricant with the aid of an Erweka cube mixer. The granulations were then compressed into tablets on a Colton model 204 four-station rotary press equipped with a model 205 induced die feeder and 0.5 in. flat-faced, beveled-edged punches. The representative weight, hardness, thickness, and dissolution times of the resulting tablets are shown in Table II. The dissolution times were determined with the aid of a U.S.P. apparatus and taken at the time when all of the tablet passed through the screen of the apparatus.

Hygroscopicity Studies.—*Powdered Materials.*—Accurately weighed samples (approximately 100 mg. each) of the powdered inositol, the powdered mannitol, and the powdered lactose were placed in open wide-mouth glass vials and stored for 96 hr. in relative humidities of approximately 65 and 100%. Previous experiments indicated that similar samples of the inositol reached maximum moisture concentration in less than 72 hr. The controlled humidity chambers were prepared using desiccators containing saturated solutions of suitable salts (9) and maintaining the temperature at 24° ± 2° with relative humidities of approximately 10, 51, 65, 84, 95, and 100% being produced.

The moisture contents of the powdered materials

TABLE I.—PROPERTIES OF SOME GRANULATIONS PREPARED WITH DIFFERENT BINDERS AND BASES

Binder	Base	Vol. of Binder Soln. Used, ml./500 Gm.	% Moisture After Drying	Hardness of Granules	Percentage Fines[c]
Acacia, 10% soln.	Inositol	110	3.3[a]	Hard	20.0
	Mannitol	125	3.7[a]	Hard	20.0
	Lactose	107	7.4[b]	Hard	12.5
	Lactose + sucrose (9:1)	80	7.7[b]	Hard	13.0
Gelatin, 10% soln.	Inositol	105	3.6[a]	Hard	13.1
	Mannitol	112	3.5[a]	Hard	17.1
	Lactose	100	6.4[b]	Hard	15.1
	Lactose + sucrose (9:1)	74	6.6[b]	Hard	13.0
Starch, 10% soln.	Inositol	130	2.3[a]	Fairly hard	13.0
	Mannitol	140	3.1[a]	Fairly hard	20.0
	Lactose	100	6.2[b]	Hard	17.0
	Lactose + sucrose (9:1)	75	7.9[b]	Hard	15.5
Diluted alcohol U.S.P.	Inositol	155	3.0[a]	Soft	28.0
	Mannitol	170	2.1[a]	Very soft	38.0
	Lactose	125	6.4[b]	Soft	21.3
	Lactose + sucrose (9:1)	86	5.7[b]	Fairly hard	23.0
Water	Inositol	140	2.5[a]	Very soft	32.0
	Mannitol	155	3.0[a]	Very soft	41.0
	Lactose	112	8.2[b]	Soft	49.0
	Lactose + sucrose (9:1)	63	7.4[b]	Fairly hard	38.0

[a] Drying time, 30 min.; Glatt TR-2 dryer; temp., 40°; gate opening, 2.5. [b] Drying time, 50 min.; Glatt TR-2 dryer; temp., 40°; gate opening, 2.5. [c] Amount of material passing through a No. 40 sieve.

TABLE II.—SOME PHYSICAL PROPERTIES OF TABLETS[a] PREPARED FROM GRANULATIONS OF INOSITOL OR MANNITOL

Binder, 10% Soln.	Base	Tablet, Wt., Gm. ± S.D.	Thickness, mm. ± S.D.	Dissolution Time, min. ± S.D.	Hardness of Tablets (Kg. Stokes) Initial	Aged 2 Mo.	Aged 6 Mo.
Acacia	Inositol	0.620 ± 0.013	3.77 ± 0.02	26.6 ± 1.0	5.0	6.8	13.5
	Mannitol	0.623 ± 0.010	3.76 ± 0.01	30.0 ± 1.6	5.0	8.0	11.0
Gelatin	Inositol	0.555 ± 0.018	3.88 ± 0.07	36.6 ± 2.0	6.5	9.2	13.5
	Mannitol	0.557 ± 0.017	3.89 ± 0.01	40.6 ± 2.0	7.5	10.4	13.0
Starch	Inositol	0.590 ± 0.017	3.70 ± 0.07	41.6 ± 2.0	2.5	7.6	11.0
	Mannitol	0.583 ± 0.024	3.75 ± 0.06	46.1 ± 1.0	3.0	4.0	6.5

[a] Compressed using 0.5 in. beveled edge punches (flat-faced).

TABLE III.—MOISTURE CONTENT (%) IN POWDERS[a] AFTER STORAGE[b] AT SELECTED RELATIVE HUMIDITIES

Base	Relative Humidity 65%	100%
Inositol	1.00	2.93
Mannitol	0.99	2.66
Lactose	5.16	5.13

[a] Sample size approximately 100 mg. of finely divided material. [b] Stored for 96 hr. at 24° ± 2°.

so treated were determined by the Karl Fischer method (10) with the aid of a Lab Industries aquametry apparatus. The results, averages of triplicate determinations, are shown in Table III.

Granulations.—Each of the granulations was analyzed for moisture content when freshly prepared (Table I) and after storage for 96 hr. in the controlled humidity chambers (Table IV). The moisture contents of powders and granulations were determined by the Karl Fischer method with minor modifications. A measured portion of anhydrous methanol (60 ml.) was titrated to the Karl Fischer end point, after which 10 ml. of this solution was removed and retained in a pipet. The sample for analysis was then washed with this 10 ml. of solution through a funnel into the receiver of the aquametry apparatus. The mixture was stirred magnetically for 2 min., after which it was titrated to a Karl Fischer end point which remained stable for 30 sec.

Tablets.—The extent of moisture absorption or desorption by tablets was determined by the differences in weights observed before and after storage for 20 days in the controlled humidity chambers.

The tablets of mannitol and inositol prepared using selected binder solutions were accurately weighed, stored for 20 days in the previously described controlled humidity chambers, then reweighed. The percentage by weight of moisture absorbed or desorbed was calculated from the change in weight of the tablets. The results are shown in Table V.

Preparation of Representative Tablets.—Three different types of tablets, antacid, multivitamin, and aspirin tablets, were prepared using inositol and mannitol as bases. The formula (11) for the antacid tablets was modified by the use of gelatin solution as the binder and the omission of the disintegrator. In one batch of the antacid tablets inositol was used in place of mannitol; batches of both types of tablets were prepared, compared, and evaluated. The results are shown in Table VI.

Aspirin tablets were prepared according to a published formula (12) modified by the use of 10% gelatin solution as the binder and the omission of a

disintegrator. Batches of tablets were prepared with both inositol and mannitol as bases and were compared and evaluated. The results are shown in Table VI.

Two batches of multivitamin tablets were prepared with mannitol as the base in one and with inositol as the base in the other. The published formula (11) was modified through use of 10% gelatin solution as the binder and the omission of the disintegrator. The prepared tablets were compared and evaluated with the results being shown in Table VI.

DISCUSSION AND RESULTS

In order to limit the maximum particle size and minimum specific surfaces for the powders examined for their hygroscopic nature, the materials were passed through a 60-mesh sieve. This procedure was considered advisable to ensure more uniform and complete moisture absorption by the powdered materials. In order to reduce the time required for maximum absorption of moisture the weights of the samples exposed at the various relative humidities were limited to approximately 100 mg. each, which were spread in thin layers.

The results of the experiment, as shown in Table III, indicate that for the range of relative humidities studied, the hygroscopic nature of inositol is very similar to that of mannitol, the hygroscopicity of both being much less than that of lactose.

A comparison of the physical properties of the various granulations (Table I) shows that the inositol granulations required less binder solution than did the mannitol granulations and that both of these required significantly more binder solution than did the others tested. The hardness of the granules and the percentages of fines in the granulations indicated that a strong binding material must be used to make satisfactory granulations from

TABLE IV.—MOISTURE CONTENT OF GRANULATIONS AFTER STORAGE FOR 96 hr. AT SELECTED RELATIVE HUMIDITIES (% ± S.D.)

Binder, 10% Soln.	Base	Relative Humidity 10%	51%	65%	84%	95%	100%
Acacia	Inositol	1.51 ± 0.17	1.64 ± 0.17	1.70 ± 0.21	2.16 ± 0.25	3.83 ± 0.30	10.10 ± 0.29
	Mannitol	1.83 ± 0.19	2.00 ± 0.16	3.75 ± 0.20	3.85 ± 0.32	5.03 ± 0.16	11.40 ± 0.47
	Lactose	9.68 ± 0.37	9.96 ± 0.19	10.30 ± 0.10	11.30 ± 0.10	12.20 ± 0.36	13.20 ± 0.20
	Lactose + sucrose (9:1)	8.20 ± 0.40	9.20 ± 0.25	9.40 ± 0.30	9.61 ± 0.36	11.80 ± 0.23	X[a]
Gelatin	Inositol	2.61 ± 0.38	3.80 ± 0.26	4.02 ± 0.40	4.08 ± 0.19	4.09 ± 0.28	13.20 ± 0.42
	Mannitol	2.17 ± 0.10	3.73 ± 0.36	5.03 ± 0.28	5.20 ± 0.36	8.31 ± 0.22	16.51 ± 0.19
	Lactose	7.90 ± 0.31	8.20 ± 0.24	8.30 ± 0.15	9.20 ± 0.23	11.20 ± 0.17	13.00 ± 0.29
	Lactose + sucrose (9:1)	8.30 ± 0.22	8.98 ± 0.38	10.40 ± 0.32	11.20 ± 0.33	12.80 ± 0.32	X[a]
Starch	Inositol	2.75 ± 0.10	3.84 ± 0.30	5.80 ± 0.36	5.87 ± 0.36	5.89 ± 0.33	12.50 ± 0.10
	Mannitol	2.60 ± 0.10	5.91 ± 0.60	6.10 ± 0.44	7.22 ± 0.37	7.35 ± 0.33	16.50 ± 0.11
	Lactose	7.98 ± 0.28	8.14 ± 0.34	8.15 ± 0.35	8.64 ± 0.29	11.90 ± 0.44	17.18 ± 0.42
	Lactose + sucrose 9:1	8.00 ± 0.28	8.06 ± 0.23	8.47 ± 0.37	9.68 ± 0.22	13.62 ± 0.31	X[a]

[a] X, liquifaction.

TABLE V.—GAIN OR LOSS OF MOISTURE OF TABLETS AFTER STORAGE[a] AT SELECTED RELATIVE HUMIDITIES EXPRESSED AS PER CENT OF WEIGHT OF FRESHLY PREPARED TABLET

Binder, 10% Soln.	Base	Relative Humidity 10%	51%	65%	84%	95%
Acacia	Inositol	(0.18)[b]	0.30	0.95	1.56	2.90
	Mannitol	(0.23)	0.16	0.70	1.50	2.50
Gelatin	Inositol	(0.10)	0.25	1.05	2.00	3.27
	Mannitol	(0.40)	0.23	1.00	1.60	3.30
Starch	Inositol	(0.10)	0.13	0.60	1.19	1.60
	Mannitol	(0.13)	0.13	0.61	0.90	1.70

[a] Equals 20 days at 24° ± 2°. [b] = Values in parentheses signify loss in weight.

TABLE VI.—SOME PHYSICAL PROPERTIES OF REPRESENTATIVE TABLETS

Type	Base	Wt., Gm. ± S.D.	Thickness, mm. ± S.D.	Dissolution Time, min. ± S.D.	Hardness, Kg. Stokes Initial	Hardness, Kg. Stokes Aged 2 Mo.
Antacid	Inositol	0.680 ± 0.025	4.22 ± 0.02	45.0 ± 1.6	6.0	6.5
	Mannitol	0.687 ± 0.036	4.67 ± 0.01	52.0 ± 1.7	6.0	7.5
Aspirin	Inositol	0.791 ± 0.032	4.72 ± 0.02	61.0 ± 0.7	6.0	6.0
	Mannitol	0.788 ± 0.041	4.88 ± 0.02	65.0 ± 1.3	7.0	7.5
Multivitamin	Inositol	0.341 ± 0.011	4.03 ± 0.01	15.0 ± 0.2	1.5	1.0
	Mannitol	0.336 ± 0.017	4.20 ± 0.01	22.0 ± 0.3	2.0	1.5

inositol and mannitol. The data of Table I also reveal that the inositol and mannitol granulations are dried more easily and thoroughly than the others examined.

The studies of the absorption of moisture were conducted on those granulations prepared with stronger binding solutions with the results (Table IV) showing that the inositol granulations generally absorbed less moisture than did those others tested. The inositol and mannitol granulations both showed little tendency to absorb moisture even at 95% relative humidity, with the inositol granulations demonstrating significantly less absorption of moisture at all the higher relative humidities. It should be noted that both of these granulations showed a sharp increase in moisture content and that the lactose–sucrose (9:1) granulation liquified at 100% relative humidity. This demonstrated that low degree of hygroscopicity can be expected to enhance the stability of solid dosage forms prepared from the inositol granulations.

The compression of the inositol and mannitol granulations into tablets was accompanied by considerable capping. Attempts to modify the granulations by decreasing the percentage of fines and by increasing the granulation size to 14 mesh produced no significant improvement in compressibility. Although the compression characteristics of both granulations were greatly improved by the addition of 2% liquid glucose as an auxiliary binder, the tablets prepared by these granulations were not studied because of the known and undesirable hygroscopic nature of liquid glucose. Suitable tablets were prepared from the original granulation (18 mesh) but with reduced hardness as measured by a Stokes hardness tester.

The hardness of these tablets increased considerably on aging, as indicated in Table II. The dissolution times of the prepared tablets show that those prepared from the inositol granulations dissolved in a shorter period of time than did those prepared from the mannitol granulations. This quality, although not too important in "chewable tablets," does deserve mention.

The period of time that the tablets prepared with inositol and mannitol as excipients were stored at controlled relative humidities was limited by mold growth to 20 days. The behavior of the tablets in respect to moisture absorption compares very closely, with each series demonstrating almost identical absorption as shown in Table V.

The problem of capping did not occur during the compression of representative tablets in which the bases, inositol and mannitol, were diluted with the therapeutically active substances. Excellent antacid and aspirin tablets were easily prepared having smooth, glossy surfaces and having equally elegant appearances, but the multivitamin tablets could not be compressed to a hardness above 2.0 Kg. When special granulations using methylcellulose and alcohol as binders were prepared and compressed, the maximum hardness achieved was 2.5 Kg. as measured by the Stokes hardness tester. All of the vitamin tablets had sufficient surface hardness such that chipping, powdering, and breaking did not occur.

The dissolution times of these representative tablets prepared with inositol as the base were consistently less than the corresponding tablets prepared with the mannitol.

One of the important qualities of mannitol which contributes to its utility as a base for chewable tablets is the ability to mask the unpleasant tastes of some drugs. It was noted that inositol possesses this same characteristic as reported by randomly selected and untrained subjects. In addition, inositol has a mouthfeel as comparably pleasant and cool as that described for mannitol.

CONCLUSIONS

1. Inositol N.F. possesses those properties described as characteristic of the ideal excipient for chewable and other compressed tablets.
2. Granulations prepared from inositol N.F. generally absorbed less moisture from varied environmental conditions than did granulations prepared from mannitol N.F. and other excipients.
3. Tablets prepared from inositol granulations compare favorably with those prepared from mannitol granulations in respect to appearance, taste, dissolution times, low degree of moisture absorption, and hardness.
4. The results of the study indicate that further evaluation of tablets prepared from granulations of inositol N.F. in order to determine stability, drug release characteristics, and drug availability is warranted.
5. In view of the results of this study, inositol N.F. should be seriously considered as an excipient for chewable and other compressed tablets.

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