choline, whereas other vascular beds are dilated. Results in this present investigation confirm that acetylcholine produces weak vasoconstriction in placental vessels—and sometimes even lacks this action.

Pretreatment of placental preparations with 5 mg. of iproniazid (only short cord placentas were tested) before the administration of the sympathomimetic amines, acetylcholine, or serotonin, did not produce an appreciable augmentation of perfusion pressure—except in the case of histamine—which at this time is inexplicable. However, increases in sympathomimetic amine activity would be expected since monoamine oxidase is one of the enzymes involved in the breakdown of the amines, and blockage of this placental enzyme sometimes can produce slight increased amine activity. In view of the results, it is possible that iproniazid is washed out too rapidly to tie up effectively the large quantity of monoamine oxidase present in the placenta. Also, it is possible that monoamine oxidase is so abundant that whatever quantity is blocked is still not sufficient to allow augmented responses to occur with these amines. These results are similar to studies conducted by Eliasson and Astrom (3), who showed that increased responses do not occur after administration of *l*-epinephrine or levarterenol to propamidine and *l*-isonicotinyl-2-isopropyl hydrazine (IIH) treated placental preparations.

Perfusion experiments attempted at lower pressures (under 50 mm. Hg), and consequently lower volume inflow but the same dose ranges, produced only slight changes in perfusion pressure with all the previously mentioned agents. Therefore, there appears to be a dependence upon volume inflow and perfusion pressure for the attainment of significant responses. Optimum results were recorded when the volume inflow rate was at least 70 ml. per minute, and the perfusion pressure was at least 60 mm. Hg, but preferably around 80 mm. Hg.

Although the results reported here are those occurring *in vitro*, the possibility of similar qualitative effects being manifested *in vivo* with the above drugs cannot be overlooked. With this in mind, it appears likely that the systemic release of excess quantities of sympathomimetic substances, serotonin, or even histamine in the pregnant state could, by directly constricting placental vessels, cause a decrease in the oxygenation of fetal blood flowing through such vessels—and hence contribute to fetal asphyxia.

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Properties of Fused Mannitol in Compressed Tablets

By JOSEPH L. KANIG

Among the carbohydrates used in compressed tablets, mannitol is the only one which possesses high heat stability. This substance melts at 167°, but does not decompose at temperatures up to 250°. Mannitol, alone and in combination with other carbohydrates, was fused and recrystallized or spray-congealed. Phase diagrams determined for these mixtures indicated that mannitol is eutectic with other carbohydrates. Selected drugs were soluble in the fused mixtures, and the crystallized or spray-congealed material obtained from these solutions possessed excellent flow and compression characteristics.

MANNITOL HAS BEEN used as a tablet diluent for more than a decade. This hexahydric alcohol, an isomer of sorbitol, is a white, odorless, crystalline powder and is the least hygroscopic of all known carbohydrate tablet diluents (1). It has a sweetness threshold of approximately the same value as glucose and a nutritive value of 2 cal. per gram (2).

In recent years, mannitol has been shown to exhibit a uniquely cooling and pleasant taste effect when used in formulations for tablets intended to be chewed or dissolved in the mouth. Several types of medicaments, including antacids, analgesics, multivitamins, and antihistamines are being marketed in the form of chewable tablets prepared in a mannitol base (3, 4). This diluent

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has also been suggested as a base in compression-coated and multilayer tablets (5).

The advantages exhibited by mannitol in such tablet formulations have been offset by its inherent shortcomings in that it has poor flow and compression characteristics. As a result, it generally requires the addition of a granulating-binding agent employed in a wet granulation procedure for producing compressible granules. The added binding agents generally tend to detract from the desired effects expected from mannitol, and the wet granulation process does not lend itself to the modern trend toward labor saving, automated techniques. Consequently, a need exists for enhancing the tableting characteristics of mannitol without detracting from its otherwise useful properties.

It was suggested (6) that spray-congealing fused mannitol might result in improved flow and compression properties. Mannitol is one of the few carbohydrates that possesses an exceptionally high heat stability. It has a melting point of 166.0 to 167.0°, but unlike other carbohydrates, it can be heated to 250° without decomposition. When fused, mannitol becomes a clear, colorless low-viscosity fluid which crystallizes very rapidly when the source of heat is removed. It is not susceptible to anhydrization under ordinary conditions during the fusion process. It has been demonstrated (7–9) that anhydrization of mannitol may be accomplished only under such drastic conditions as prolonged refluxing with concentrated hydrochloric acid.

It was therefore of interest to investigate the possible advantages to be gained by utilizing fused mannitol as a means of altering its tableting characteristics. Concurrent with this approach was the equally interesting potential to be gained in exploring the ability of fused mannitol to function as a solvent or dispersant for other materials to produce solid-solid solutions or dispersions which might prove to be directly compressible into tablets.

PROCEDURES AND RESULTS

Fusion Apparatus.—Molten mannitol rapidly crystallizes into a hard mass if the temperature is permitted to drop only a few degrees below its melting point. Consequently, attempts to spray-congeal the hot liquid with the centrifugal wheel atomizer of a Nerco-Niro portable spray dryer resulted in rapid congealing within the feed-pipe and vaned-wheel of the atomizer. This clogged the mechanism and stopped the operation.

A specially designed apparatus was constructed to overcome this obstacle and to facilitate the incorporation of additional materials into the fused mannitol. A kitchen-type, electrically heated deep-fat fryer was converted into an apparatus which was used to fuse mannitol under controlled temperature and as a mixer and a feeder of the fused blends to the spray dryer. Figure 1 represents the apparatus and its essential components. An opening was drilled into the bottom of the electric pan (A), and this was fitted with an aluminum fitting (F) which served as the seat for a tapered Teflon needle valve attached to the bottom of a stainless steel threaded rod (E). The rod was positioned over the opening (F) with a stainless steel rod placed horizontally across the diameter of the pan and screwed into the walls on both sides (D). This rod also served to hold a thermometer (K) in position in the fused liquid. An electric overhead stirrer (G) was utilized to aid in the dispersion of materials added to the fused mixture.

A threaded nozzle was screwed into the aluminum fitting (F) and a $^1/_2$ in. I.D. Teflon tube was attached to the outlet nozzle. The tube was wrapped with a Nichrome heating element (H) which was controlled with a rheostat (J). The Teflon tube was utilized to connect the fusion apparatus with the feed-pipe of the atomizer in the spray dryer. It was necessary to use additional heating elements around the feed-pipe of the atomizer to prevent cold-spots and subsequent congealing of the fused mass within the atomizer.

The heating elements on the bottom of the pan (B) were rheostatically controlled, and the rheostat (C) was calibrated to correspond with centigrade units.

A heater was installed in the compressed air line which operates the atomizer of the Nerco-Niro spray dryer. This served to raise the temperature of the compressed air entering the atomizer so that the entire unit became hot by conduction; this was an additional safeguard against premature congealing within the atomizer.

All heating elements were turned on for about 30 minutes before each run. This was generally done while the solids in the fusion apparatus were being heated and fused.

Fused Mixtures.—Trial batches ranging in weight from several hundred grams to 2 kilos were fused and spray-congealed with the special apparatus and laboratory spray dryer. Mannitol, alone and in combination with other materials, was fused and spray-congealed after preliminary tests had indicated that the mixtures were miscible in the fused state and exhibited no signs of decomposition due to high heat. Subjective evidence of apparent decomposition among materials added to fused mannitol was noted by the production of an odor, change in color, or evolution of a gas.

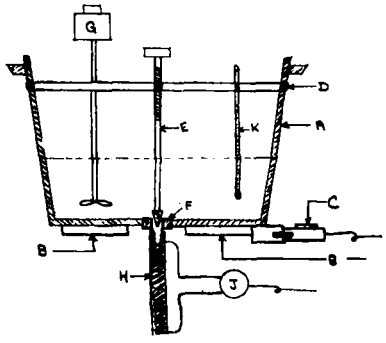

Fig. 1.—Fusion apparatus used in conjunction with Nerco-Niro portable spray dryer.

A number of randomly selected drugs and chemicals and inert materials were tested for their solubility or miscibility in fused mannitol. The screening procedure involved the addition of incremental quantities of the material under test to fused mannitol which was maintained at 175–180°. Observations were made after each addition to determine whether physical or chemical changes had taken place and whether the material being added was soluble in the fused mixture. Table I lists the materials which were thus tested. The drugs and chemicals which formed clear solutions in most proportions with fused mannitol and manifested no visible signs of decomposition were arbitrarily classified as being soluble without regard for the actual state of matter which resulted upon congealing. Additional tests and chemical analyses on these materials and other substances are being conducted to determine their stability in fused mannitol. The classification "insoluble-immiscible" is used to designate those mixtures which formed an insoluble dispersion of the solid in the fused mannitol or which melted into two immiscible liquid layers. Some materials, such as the metallic stearates and the celluloses, were not wetted by the fused mannitol and were not dispersible in the mixture.

Other materials which were tested and found to decompose readily included aspirin, *dl*-amphetamine sulfate, chlorobutanol, benzocaine, aminophylline, terpin hydrate, pyridium, pentabarbital sodium, and sulfaguanidine.

Melting Point–Composition Relationships.—To obtain additional information on the physical characteristics of several of the fused mixtures, phase diagrams were obtained with mixtures of mannitol and other sugars and with mannitol and several active ingredients.

TABLE I.—SOLUBILITY/MISCIBILITY OF RANDOMLY SELECTED DRUGS AND CHEMICALS WITH FUSED MANNITOL

Soluble	Insoluble-Immiscible
Amobarbital	Aluminum hydroxide
Barbital	Beeswax
Chlorpheniramine maleate	Butylaminobenzoate
Diphenhydramine HCl	Caffeine
Dulcitol	Hydrogenated castor oil[a]
Erythritol	Cetyl alcohol
Galactose	5,5-Diphenylhydantoin
Lactose	Glyceryl distearate
p-Hydroxy acetanilide	Glyceryl monostearate
Phenobarbital	Hydroxy propyl sucrose
Phenobarbital sodium	Magnesium stearate
Phenylephrine HCl	Magnesium trisilicate
Procaine HCl	Microcrystalline waxes
Sucrose	Phenolphthalein
Sulfacetamide	Polyethylene glycol 400
Sulfanilamide	Polyethylene glycol 4000
	Polyvinyl alcohol
	Prednisolone
	Prednisolone acetate
	Sodium carboxymethylcellulose
	Spermaceti
	Stearic acid
	Stearyl alcohol
	Sterotex[b]
	Succinylsulfathiazole
	Sulfamerazine

[a] Marketed as Castorwax by the Baker Castor Oil Co.
[b] Marketed by Capital City Products Co., Columbus, Ohio.

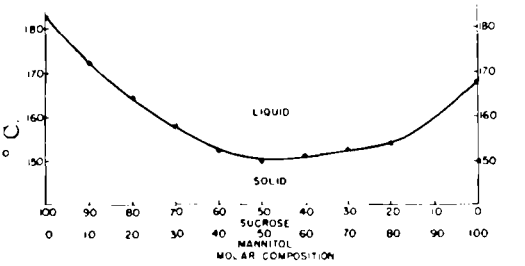

Fig. 2.—Mannitol-sucrose phase diagram

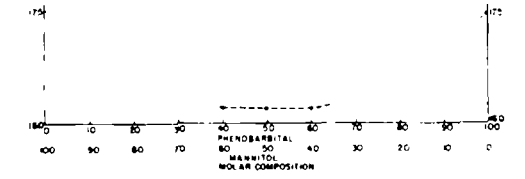

Fig. 3.—Phase diagram of fused mixtures of mannitol and phenobarbital.

A number of binary mixtures of mannitol and other materials were prepared with accurately weighed quantities ranging in overall composition from 100 molar parts of one to 100 molar parts of the other. Each mixture was fused in an oil bath at a temperature approximately 5° higher than the melting point of the component in the mixture which had the highest melting point. The fused mass was stirred, transferred to a watch glass, and allowed to crystallize. A portion was then ground to a fine powder in a small glass mortar, and the melting point of the powder was then obtained.

Phase diagrams were plotted on binary systems of mannitol with other carbohydrates such as sucrose, lactose, dulcitol, erythritol, and galactose. Three physiologically active materials were chosen from the list of soluble drugs, and binary mixtures of mannitol with diphenhydramine hydrochloride, with phenobarbital, and with sulfanilamide were prepared and phase diagrams obtained.

All blends of carbohydrates and mannitol resulted in eutectic mixtures. Figure 2 is illustrative of the phase diagrams obtained with the carbohydrates listed above. In each instance the mixture permitted melting of the carbohydrate involved at a point below its own melting point and thus prevented decomposition. Mannitol-sucrose binary systems manifested the lowest melting point at an equimolar composition. This mixture made possible a 32° decrease in the melting point of sucrose.

Figures 3 and 4 indicate the eutexias formed between mannitol and phenobarbital and mannitol and sulfanilamide. These curves are similar to the mannitol-carbohydrate curves, and all of them indicate solid state miscibility. Just as two liquids may dissolve in each other to form a liquid solution, so one solid may dissolve in another to form a solid solution. These solutions are homogeneous and may vary in composition within wide limits. This uniformity of distribution differentiates a solid solution from a mixture of solids, for in the latter instance each constituent preserves its own characteristic crystal structure. This is borne out by the existence of a minimum in the melting point curve (10).

When two pure components react to form a new

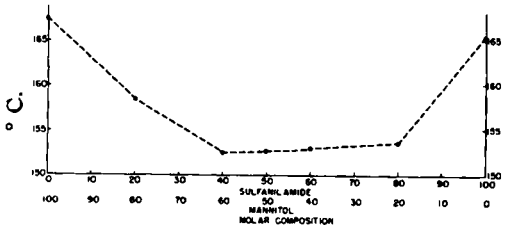

Fig. 4.—Phase diagram of fused mixtures of mannitol and sulfanilamide.

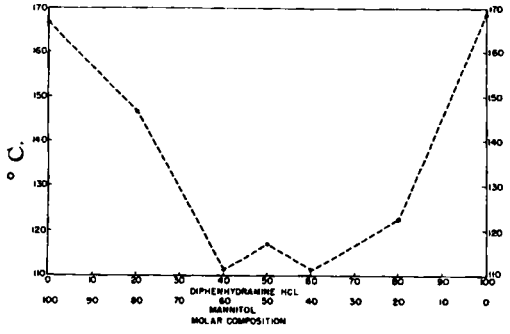

Fig. 5.—Phase diagram of fused mixtures of diphenhydramine hydrochloride and mannitol.

compound stable up to its melting point, the phase diagram takes on the typical appearance shown in the curve for the mannitol-diphenhydramine hydrochloride system (Fig. 5). The maximum observed at equimolar composition is indicative of 1:1 compound formation (10).

Tableting Characteristics.—To determine the tableting characteristics of fused mannitol, alone and in combination with other inert and active components, the following mixtures were prepared in 2-kilo batches and spray congealed.[1]

(*a*) Mannitol (100)
(*b*) Mannitol (95) + sucrose (5)
(*c*) Mannitol (50) + sucrose (50)
(*d*) Mannitol (50) + sucrose (40) + lactose (10)
(*e*) Mannitol (50) + lactose (50)
(*f*) Mannitol (80) + phenobarbital (20)
(*g*) Mannitol (80) + sulfanilamide (20)
(*h*) Mannitol (80) + diphenhydramine HCl (20)

No consideration was given to the usual dosages of the active ingredients in mixtures (*f*), (*g*), and (*h*). The ratios of drug to mannitol was selected only as a basis for comparison of the tableting characteristics of the resulting solid solutions.

Each of these mixtures was carefully fused in the fusion apparatus and spray-congealed. Additional batches of the same mixtures were prepared by fusion but were permitted to congeal in stainless steel vessels. These crystallized masses were removed and passed through a No. 20-mesh screen in a Stoke's oscillating granulator. This latter procedure was conducted so that a comparison could be made between granular material obtained in this manner and that obtained by spray-congealing.

Both single punch and rotary tablet machines (F. J. Stoke's model F and model B-2) were employed in the compression studies. Tablets weighing 0.5 Gm. each were compressed with $^{13}/_{32}$ in. S.C. or F.F. punches.

Flow Properties.—Fused mannitol and its mixtures, processed by either spray-congealing or screening, possessed excellent flow characteristics. All of the batches employed in this study presented no problem by flowing smoothly from the hoppers of the tablet compression machines, in the feed frames, and into the dies. Flow properties were decidedly superior to powdered mannitol, especially in the feed frames and in the dies. Uniform filling of the dies was evidenced by tablet weight deviations within U.S.P. limits.

Compressibility Factors.—In all cases it was found that, although the materials had excellent flow properties and required no glidant, they all needed a lubricant to assist in the removal of the compressed tablets from the dies. Calcium or magnesium stearate, 1 to 2%, blended into each batch before comrpression, was sufficient for this purpose.

A difference in lubricant requirements was observed between batches prepared by spray-congealing and identical mixtures processed by screening.

Tablets prepared from the screened materials exhibited a high degree of resistance to ejection from the dies. This difficulty was overcome by the further addition of 1% of talc to the lubricated mixture. This difference between the screened and spray-congealed material may be attributed to the shape of the particles. Microscopic examination of spray-congealed particles revealed them to be spherical in shape while those prepared by screening were irregular and angular. It is conceivable that the smooth, regular spheres are capable of producing tablets with edges that offer decreased frictional resistance during ejection.

Fused mannitol and the various mixtures prepared by either spray-congealing or screening possessed excellent tableting properties. Other than the lubrication problem previously cited, no additional difficulties were encountered in compressing tablets over a wide range of pressures. There was no evidence of capping, laminating, sticking, or other physical deterrents to the production of suitable compressed tablets. The surfaces of the tablets were hard and smooth with no indications of dusting or friability.

Taste Properties.—Tablets made with fused mannitol were found to have a moderate grittiness which is not found in tablets prepared with mannitol N.F. In addition, the "cooling" effect was noticeably reduced. Sweetness and flavoring efficiency were unimpaired by the fusion process. It was observed, however, that fused mixtures of mannitol and other carbohydrates more closely approximated the taste properties of unfused mannitol.

Dry Binder Qualities.—In view of the excellent tableting properties of the fused carbohydrate mixtures it was decided to study the dry binding applica-

Table II.—Strong-Cobb Hardness Values of Fused Mannitol Tablets

Pressure, p.s.i.	Fused Mannitol	
	No. 20 mesh	Spray-congealed
1000	6	...[a]
2000	14	6
3000	22	9
4000	...	12

[1] Numbers in parentheses indicate parts by weight.

[a] A tablet was not formed at this pressure.

tions of these materials. Dried aluminum hydroxide gel U.S.P. was selected as an example of a powdered material which cannot be compressed directly. Blends containing 25 and 50% by weight of the aluminum compound were prepared with fused mannitol, mannitol and sucrose (50:50), and mannitol and lactose (50:50) in a Twin Shell blender. Magnesium stearate (1%) was included as a lubricant. These blends continued to exhibit the excellent flow and compression characteristics which had been observed with the vehicles alone. Tablets weighing 0.5 Gm. prepared on a model F compression machine gave Strong-Cobb hardness tester values of up to 10–11 with no signs of capping. The tablets were satisfactory in all other respects.

Comparison of Fused Spray-Congealed and Screened Mannitol.—To compare the relative compressibility of the two physical states of mannitol obtained by either spray-congealing or screening, a Carver laboratory hydraulic press was employed. This press was modified to operate a specially constructed rig containing a set of 13/32 in. F.F. punches and a die. Accurately weighed 500-mg. portions of the different batches of mannitol were compressed at pressure levels of 1000, 2000, 3000, and 4000 p.s.i. Tablets produced at each level were tested for hardness. It was determined that the spray-congealed mannitol produced softer tablets at corresponding pressure levels than did the 20-mesh screened material (Table II).

SUMMARY AND CONCLUSIONS

The unusual heat stability of mannitol has led to the development of several new applications which possess a high degree of potential. Foremost among these is the discovery that fused mannitol, which is recrystallized and processed by either spray-congealing or screening, possesses exceptionally good tableting characteristics.

The liquid state of mannitol has been shown capable of dissolving or dispersing a number of pharmaceutical adjuvant or physiologically active drugs. Phase diagrams of several of these combinations have indicated that solid-solid solutions are obtained. In at least one instance (mannitol-diphenhydramine HCl) the phase diagram indicates the probable formation of a new compound. New compounds formed in this manner may conceivably possess different physical, chemical, and physiological properties.

In view of present day considerations of the effect of particle size on the biological availability of drugs, these solid-solid solutions or microcrystalline dispersions offer a unique opportunity of making available an extremely fine state of subdivision of active ingredients in tablet form. Moreover, these solid solutions, capable of being directly compressed into tablets, obviate the necessity for blending procedures and assure complete uniformity of dosage.

Additional investigations are under consideration which will explore more thoroughly the nature of the interaction involved in the solid-solid solution in fused mannitol and will quantify the extent of solubilities of various chemicals and drugs.

Fused mannitol has also been utilized to produce eutectic mixtures with other less costly carbohydrates, such as sucrose and lactose. These mixtures have also been found to possess excellent flow and compression properties when used either as solvents for active principles or when admixed with them as a dry tablet binder.

Fused mixtures of mannitol with other sugars advance the possibility of large-scale production of an inexpensive, efficient vehicle for the direct compression of tablets.

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4′,5,6,7-Oxygenated Flavones and Flavanones

By MASON G. STOUT, HANS REICH, and MAX N. HUFFMAN

The preparation of 4′-hydroxy-5,6,7-trimethoxyflavanone, 6-hydroxy-4′,5,7-trimethoxyflavanone, and the corresponding flavones is described as well as a new synthesis of 4′,6-dihydroxy-5,7-dimethoxyflavone. The results of the biological tests of these and other closely related bioflavonoids in our general endocrine screening assay are tabulated.

For biological experiments, the 4′,5,6,7-substituted flavanones X, XII, XIV, and XV and the corresponding flavones XVI, XVIII, XX, and XXII were required. Compounds X and XVI had been prepared previously (1) from the acetophenone derivative II and anisaldehyde *via* the chalcone IV, and the flavanone XV had been obtained from the acetophenone derivative I by condensation with *p*-hydroxybenzaldehyde (2). This flavanone was later used as starting material for the preparation of the flavone XXII

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