varying periods of disintegration testing, and microscopically examined for soluble dye migration through the coat layer. Calcium sulfate dihydrate, due to its water absorbant character, drew test fluid into the coating resulting in coat failure. Lactose, though completely soluble, did not have the water-sorptive character of calcium sulfate, and was a satisfactory coat diluent in this study. Microscopic examinations of tablet cross sections also indicated that enteric compression coatings were produced when the matrix of partially coated granules is bound by the intergranular enteric bonding agent forming an impervious coat as illustrated in Fig. 5.

The greater off-centering found with the lactose cores in all of the compression-coated tablets, regardless of coat formulation (Table VII), is probably related to the greater expansion of the lactose cores during recovery which accentuates the core dislocation (9). Experiments by Kaplan and Wolff (10) have shown that calcium sulfate dihydrate is more compressible than lactose under the same conditions.

Of the 4 carboxyl-containing polymers evaluated in this study, 3 were subject to slow swelling or coat erosion in gastric fluid *in vitro*. The principle of enteric disintegration of PVM/MA 169, PVAc-C-H, and PVAc-C-L formulations appeared to be slow solubility at lower simulated gastric pH values and faster rates of solubility at higher simulated intestinal pH values. Bauer and Masucci (11) found that the disintegration of CAP coatings in intestinal contents of pH 6.9 is the result of the hydrolytic action of intestinal esterases. In this experiment pancreatin was found to have no influence on the disintegration of tablets compression coated with CAP in intestinal fluids of pH 6.9 and 7.5. This probably is due to the modification of the enteric properties of the polymer by the plasticizer, triacetin.

PVM/MA 169, which most quickly swelled *in vitro* was observed to fail in 1 subject *in vivo* as an enteric coating. A partially esterified derivative of the polymer (12, 13) with a slower dissolution rate would probably produce a more satisfactory enteric coating.

CONCLUSIONS

A method has been developed for the incorporation of slowly soluble polymer materials in a diluent by simple mixing and standard granulation procedures to produce enteric compression coatings. The granulations thus produced with each of 4 polymer materials when mixed with an intergranular enteric bonding agent, magnesium stearate, and an effective granule binder, polyvinylpyrrolidone, and compression coated at an optimum hardness range was found to be enteric by *in vitro* disintegration tests. The formulation factors, physical and tablet properties of the formulations, were investigated for their effect on *in vitro* enteric properties. *In vivo* evaluation using an X-ray technique and human volunteers indicated that 3 of the polymer systems studied were enteric and that the reported simplified method of polymer incorporation to produce enteric compression coatings is feasible.

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Evaluation of Amylose as a Dry Binder for Direct Compression

By K. C. KWAN* and GEORGE MILOSOVICH†

Because of the economies of direct compression, there exists a need for good dry binders which will effect compression of drugs at relatively low filler-to-drug ratios. This paper reports an evaluation of amylose for this purpose. The results on compression effects, physical properties, stability, and drug availability show that this material has the characteristics desired of the ideal binder.

THE DEVELOPMENT of forced-feed mechanisms for tableting presses and relatively free flowing tablet excipients has stimulated interest in commercial tableting by direct compression (1). The objective of direct compression is to produce pharmaceutically elegant tablets with a minimum of processing time and cost. Since many drugs cannot be compressed directly, 1 or more agents must be added to impart suitable compression properties. Unfortunately, many of these addi-

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TABLE I.—PROPERTIES OF AMYLOSE-BASED TABLETS

Drug	Amylose, % of Total	Other Additives	Disintegration[a]	Hardness[b]	Friability[c]	Wt. Variation,[d] Gm.
Aspirin	20	...	160 ± 47	4.8 ± 1.2	0.4	0.234 ± 0.004
Sodium PAS	55	5% Talc	>1800	5.9 ± 1.6	0.2	0.238 ± 0.004
Ascorbic acid	55	5% Talc	74 ± 36	5.7 ± 1.8	0.3	0.232 ± 0.006
Sulfathiazole	59	1% Stearic acid	43 ± 6	5.7 ± 1.6	0.3	0.220 ± 0.008
Sodium phenobarbital	62	3% Stearic acid	969 ± 336	4.1 ± 1.4	0.5	0.210 ± 0.004
Phenacetin	80	...	148 ± 22	4.3 ± 1.2	0.6	0.209 ± 0.004

[a] U.S.P. test without disks, sec. ± 2 S.E., 12 tablets. [b] Pfizer, Kg. ±2 S.E., 20 tablets. [c] Roche Friabulator, % on 6 Gm. of tablets. [d] Mean ±2 S.E., 20 tablets.

tives are either too costly or react with the active ingredients to decrease stability. Also, the ratio of these fillers to the drug necessary to effect compression may preclude use with higher dosage drugs.

The amylose used in this study[1] is unusual in that it can be tableted directly into pharmaceutically acceptable tablets. It is free-flowing, self-lubricating, and self-disintegrating so that it, by itself, functions as the filler, lubricant, and disintegrant. Since amylose is composed of large molecular weight polymers of glucose attached through 1–4 linkages, it has a minimum of reducing groups; thus, it should have very little, if any, reactivity with drug molecules. It does, however, require about 10–12% moisture for optimum compression and may be unsuitable for use with drugs subject to hydrolytic decomposition.

It was the purpose of this investigation to evaluate this amylose for its potential usefulness in direct compression applications.

EXPERIMENTAL

Six drugs known to be difficult to compress directly were selected for this study. Sulfathiazole, sodium *p*-aminosalicylate, ascorbic acid, sodium phenobarbital, phenacetin, and aspirin either do not form tablets of adequate hardness when compressed directly or form tablets with poor weight variation. Each of these materials, received from their respective suppliers as U.S.P. or N.F. grade, was mixed with an equal amount of amylose for 5 min. in a twin shell blender (Paterson-Kelly model LB2630). The resulting mixes then were tableted on a Colton 216 using $^5/_{16}$-in. standard concave punches and the standard feed frame. All tablets were prepared at maximum pressure obtainable with this press. Appropriate changes in the 1:1 formula were then made to establish the minimum amylose-to-drug ratio necessary for suitable tablets. The resulting tablets were tested for disintegration, hardness, friability, and weight variation.

To assess the possibility of classification and bridging in these powder mixes, weight variation and drug content were determined on samples removed periodically during tableting of a full hopper (2.0 Kg.) of mix. Aspirin, 200-mesh powder and 40-mesh crystals, and ascorbic acid, 200-mesh powder and 40/80-mesh crystals, were chosen to represent the range in particle sizes and amylose-to-drug ratio used in this investigation.

[1] Nepol amylose, pharmaceutical grade, a development product of the A. E. Staley Manufacturing Co., Decatur, Ill.

TABLE II.—WEIGHT AND DRUG CONTENT VARIATION

Sample Time, min.	Wt., Gm.	Drug, %
Ascorbic Acid Powder		
0–1	0.229 ± 0.006	40.4
16–17	0.232 ± 0.004	40.2
24–25	0.233 ± 0.005	40.3
32–33	0.233 ± 0.006	40.6
Ascorbic Acid Crystal		
0–1	0.254 ± 0.008	42.3
8–9	0.253 ± 0.007	41.7
16–17	0.253 ± 0.006	41.6
24–25	0.251 ± 0.008	42.5
Aspirin Powder		
0–1	0.232 ± 0.004	78.9
16–17	0.240 ± 0.004	77.8
32–33	0.239 ± 0.003	78.0
40–41	0.238 ± 0.003	79.5
Aspirin Crystal		
0–1	0.246 ± 0.007	78.1
12–13	0.252 ± 0.006	78.0
28–29	0.248 ± 0.007	78.1
36–37	0.242 ± 0.010	78.1

TABLE III.—RELATIVE STABILITY OF AMYLOSE AND COMMERCIAL ASCORBIC ACID TABLETS

Temp., °C.	$T_{.90}$ Values, Days — 75% R.H. Amylose	75% R.H. Control	45% R.H. Amylose	45% R.H. Control
55	37	20	6	6
45	15	15	5	5
37	43	43	16	16

Aspirin and ascorbic acid tablets were chosen also to test the effect of amylose on chemical stability. These and commercially available tablets were powdered using a mortar and pestle and were stored in loosely capped vials at 3 elevated temperatures and 2 relative humidities. The sample vials were arranged randomly in each desiccator and were withdrawn in a random manner to eliminate possible bias due to variation in storage conditions. Periodic assays were conducted using the U.S.P. method for acetylsalicylic acid tablets (2) and the method of Barakat *et al.* (3) for ascorbic acid.

To estimate the effect of aging on physical properties, tablets of each drug were stored in tightly capped amber bottles at 55° for 24 days, and their respective hardness, friability, disintegration time, and appearance were re-evaluated.

TABLE IV.—EFFECT OF AGING AT 55°C. FOR 24 DAYS ON PHYSICAL PROPERTIES

Drug	Hardness, Kg. ± 2 S.E. Before	Hardness, Kg. ± 2 S.E. After	Disintegration Time, sec. ± 2 S.E. Before	Disintegration Time, sec. ± 2 S.E. After	Friability, % Before	Friability, % After	Appearance after Storage
Aspirin	4.8 ± 1.2	7.2 ± 1.6	160 ± 47	32 ± 30	0.4	0.4	Needle crystals of salicylic acid on cap and neck of bottle
Ascorbic acid	5.7 ± 1.8	4.8 ± 1.8	74 ± 36	52 ± 26	0.3	0.5	Discolored
Sulfathiazole	5.7 ± 1.6	6.3 ± 1.6	43 ± 6	220 ± 132	0.3	0.4	No visible change
Sodium phenobarbital	4.1 ± 1.4	2.8 ± 1.2	969 ± 336	861 ± 56	0.5	1.0	Discolored
Phenacetin	3.4 ± 0.5	4.3 ± 1.4	333 ± 53	422 ± 80	0.6	0.8	No visible change

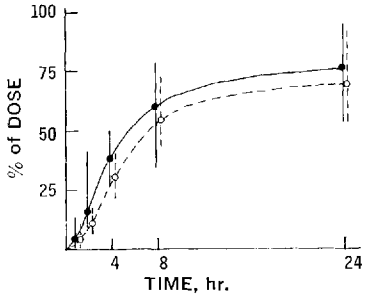

Fig. 1.—Cumulative urinary excretion of salicylates following ingestion of amylose and commercial aspirin tablets. Key: —●—, average of 8 subjects, amylose tablets; --○--, average of 8 subjects, commercial tablets; vertical lines, ranges of individual values obtained.

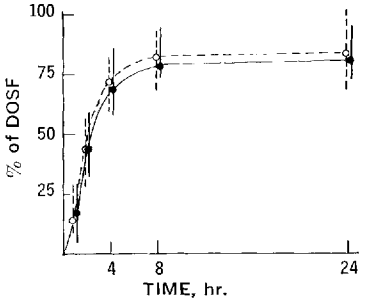

Fig. 2.—Cumulative urinary excretion of aromatic amines following ingestion of amylose and commercial sodium *p*-aminosalicylate tablets. Key: —●—, average of 8 subjects, amylose tablets; --○--, average of subjects, commercial tablets; vertical lines, ranges of individual values obtained.

Aspirin and sodium *p*-aminosalicylate tablets were chosen for investigation of drug release from amylose-based tablets. These tablets represented the 2 extremes in the *in vitro* disintegration test. Eight apparently healthy males were used in a crossover experiment, and urinary excretion data were obtained following controlled ingestion of test and commercially available control tablets. Prior to breakfast, each subject voided completely and was given 240 ml. of water. One hour later the subjects voided and were given their respective doses with an additional 240 ml. of water. They were then allowed to eat regular meals commencing 1 hr. after dosing. Urine samples were collected at 0, 1, 2, 4, 8, and 24 hr. for assay. Aspirin was determined on the basis of total salicylate content using Trinder's reagent, and sodium *p*-aminosalicylate by the method of Way *et al.* (4) for aromatic amines.

RESULTS

Amylose to Drug Ratios.—Table I gives the results obtained with the 6 test drugs. Acceptable tablets were obtained with each drug, although the proportion of amylose required varied from 20% for aspirin to 80% for phenacetin. The physical properties would be considered statisfactory for pharmaceutical application except for the relatively poor disintegration of sodium *p*-aminosalicylate. This was attributed to the basicity of this compound which may be sufficient to dissolve amylose to form a viscous gummy coating at the tablet surface retarding further penetration of water. From these results it appears that amylose can be used to effect successful direct compression of even the most difficult materials. It is expected that the amount of amylose required will depend on the inherent compression characteristics of a drug and that minimum amounts of amylose will suffice for drugs approaching aspirin in compression properties.

Weight and Drug Content in Extended Operation.—The data obtained from tablets made during extended operation in which the pressure and fill settings were held constant are given in Table II. The constancy of tablet weight and drug content during the time required to empty the hopper is a strong indication that classification was not prevalent for these mixes. Since these mixes represent wide ranges in both particle size and amylose-to-drug ratio, it is expected that classification will not be a problem with most amylose–drug mixes.

Stability.—Considering that amylose contains 10–12% water and can absorb considerably more at high humidity, it was expected that amylose would accelerate the hydrolytic degradation of aspirin. The results of this study showed, however, that even at 75% R.H. and 55°, amylose-based aspirin was equivalent in stability to the control. Since there was much more water in the amylose system, it appears that this water was bound tightly and not free for reaction.

The ascorbic acid powders exhibited considerably more decomposition than was evidenced with aspirin. Table III gives the $T_{.90}$ values for the various storage conditions. It is known that ascorbic acid degradation is very complex and no attempt is made to interpret these results. The important consideration is that there was no significant difference in

stability between amylose and the commercial control.

The results of accelerated aging on amylose-based tablets are shown in Table IV. It can be seen that physical stability was relatively good, even in cases where chemical decomposition was marked. Although changes in hardness, disintegration, and friability occurred, they were still well within the limits for acceptable tablets. Data on sodium *p*-aminosalicylate tablets are not included since this compound degraded to such an extent that the tablets were destroyed under the conditions of this test.

Drug Availability.—The results of the availability experiments are shown graphically in Figs. 1 and 2, where the mean and range of cumulative urinary excretion are plotted for each time period. It can be seen that even for the sodium *p*-aminosalicylate tablets showing poor *in vitro* disintegration the availability is essentially the same as for the control. Apparently the viscous surface film which retarded *in vitro* disintegration was mechanically eroded in the gastrointestinal tract.

CONCLUSIONS

It appears, from the results of this investigation, that amylose merits serious consideration for use as a direct compression tablet binder. In the form used in this study it can effect compression of problem drugs at relatively low concentration and yields tablets possessing the characteristics desired for pharmaceutical use. Although each drug formulation is unique and must be thoroughly tested, there is every indication from these results that successful application can be obtained. It should be pointed out that these results relate only to this particular amylose and may not extrapolate to other amyloses or amylose derivatives.

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Notes

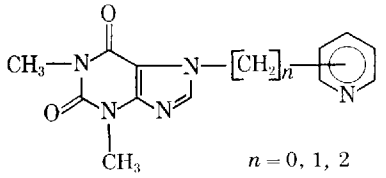
New Drugs in Xanthine Derivatives XXVI. Pyridylthioethyl Derivatives of Theobromine and Theophylline, and Products of Their Oxidation

By M. ECKSTEIN and J. SULKO

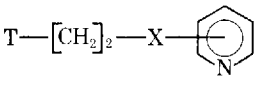
The synthesis of new 1- or 7-pyridylthioethyldimethylxanthines and their oxidation products (sulfoxides, *N*-oxides, and sulfones) are described.

SEVERAL, among previously synthesized theophylline (1) and theobromine (2) derivatives containing in the side-chain —S, —SO, —SO_2 groups, displayed interesting pharmacodynamic properties (3, 4). Compounds of the alkylthioether type are more hypotensive and less toxic than aminophylline. Water-soluble arylalkylsulfoxide derivatives appear to be active diuretics and their therapeutic index more favorable than aminophylline. The authors were interested in the synthesis of new sulfur derivatives of dimethylxanthines containing pyridyl rest in the side-chain. Among 7-substituted theophyllines, only a few compounds with a pyridine ring of type A are known.

Jucker *et al.* (5) patented 7-(pyridyl-4′)-theophylline (A, $n = 0$), and 7-(picolyl-3′ and 4′)-theophylline



A



B

T = 7-Theophyllinyl, resp. 1-theobrominyl rest.
X = —S, —SO, —SO_2

(A, $n = 1$) as the reaction products of sodium theophylline with 4-chloropyridine or picolyl chlorides, respectively. 7-β-(2′ and 4′-Pyridylethyl)-theophyllines were obtained in the reactions of pyridylethylation.

In this paper the synthesis of compounds of type B is described in which pyridine is coupled with the

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