Evaluation of Polymeric Materials IV

Granulating Agents for Compressed Tablets

By C. R. WILLIS, JR., GILBERT S. BANKER, and H. GEORGE DEKAY

Experimental granulations were produced using aqueous and alcoholic solutions of polymeric celluloses, vinyls, acrylamides, pyrrolidones, oxazolidinones, and ethylene oxide condensation products. Products were compared to control formulations granulated with starch paste. Dextroamphetamine sulfate was employed in a preliminary dialysis and dissolution study in the presence of the polymers shown to be of value. The experimental products exhibited gloss equal or superior to coated tablets in many instances, and no drug binding or inhibition of release occurred. The polymer-bound granulations displayed excellent flow properties, were easily compressed into tablets of various degrees of hardness, were generally more resistant to friabilation than the control; some of the polymers produced tablets which had equal or superior disintegration times compared to the control.

THE PHARMACEUTICAL elegance and ease of compression of tablets are related directly to the particulate material or granulation from which the tablets are compressed. Granulation quality, in turn, is dependent on the materials used, processing techniques, and equipment employed. Of these variables, the materials used—especially the binding agent employed—are fundamental to granulation particulate size uniformity, adequate hardness, and general quality.

Direct compression, facilitated by techniques such as induced die feeding and the availability of diluent granulation materials for admixture with drug, is a streamlined and substantially more economical method of tablet manufacture than the wet granulation approach. However, direct compression cannot completely replace wet granulation in the immediate future. Wet granulation may be required to produce uniform colored tablets, tablets containing potent drugs in low dosage levels with minimal intertablet variation, and special granulations such as those used in compression coating or pilule preparation.

Natural polymers, such as gums, have been used in the wet granulation operation as pilule or tablet granule binders, but few of the newer synthetic materials have thus far found application in this area. However, the synthetic polymeric materials do have a strong potential as binders based on their solubility characteristics, fibrous nature, long chain length, plasticity, compressibility, adhesive and binding abilities, as well as their ability to produce tablet surfaces of superior esthetic value (smoothness and gloss). This study of selected, nontoxic, commercially available, water-soluble polymers was initiated on the basis of these possible unique advantages of polymeric materials in this specialized area of application.

Received August 26, 1964, from the Industrial Pharmacy Research Laboratory, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Ind.
Accepted for publication October 22, 1964.
Presented to the Scientific Section, A.PH.A., New York City meeting, August 1964.
Abstracted from a thesis submitted by C. R. Willis, Jr., to the Graduate School, Purdue University, Lafayette, Ind., in partial fulfillment of Master of Science degree requirements.

EXPERIMENTAL

Granulating Agents.—Fifteen polymeric materials, including cellulosics, vinyls, acrylamides, pyrrolidones, oxazolidinones, and ethylene oxide condensation products, were selected for appraisal as tablet binding agents based on a survey of their physical properties and reported or probable nontoxicity. These materials (Table I) were incorporated in various concentrations in the granulations as aqueous and alcoholic (isopropanol) solutions and as dry mixtures with the diluents which were subsequently wet granulated. Each granulation was prepared using a base powder mixture composed of 53.2% magnesium trisilicate, 36.2% lactose, and 10.6% starch. This mixture was chosen, after experimentation with several diluent formulas, on the basis of its inherent resistance to binding agents. The control granulation was prepared by granulating the base powder mixture with 10% starch paste, prepared by adding a 1:1 starch in cold water suspension to the required volume of boiling distilled water. The paste then was stirred until cool.

Evaluation of the Experimental and Control Granulations.—Granulations were prepared by moistening the base powder mixture (300 or 500 Gm.) with polymeric granulating solutions or with the corresponding organic solvents, when the polymer was incorporated dry in the powder mixture, while mixing the wet mass for 15 to 20 minutes in a planary mixer.[1] The wet screening operation was conducted with an oscillating granulator[2] fitted with a 12-mesh screen. The wet screened granules were evaluated gravimetrically for moisture content, but not for organic solvent content, with a Cenco[3] moisture balance at 80°. All granulations were air-dried for 48 hours and were sized through a 16-mesh screen using the oscillating granulator.

The particle size distribution of each dried sized granulation was determined using a set of five 8-in. diameter nested A.S.T.M. classification screens

[1] Kitchen Aid, model K5-A, Hobart Mfg. Co., Troy, Ohio.
[2] Model 43A Stokes Machine Co., Philadelphia, Pa.
[3] Central Scientific Co., Chicago, Ill.

TABLE I.—EXPERIMENTAL POLYMERIC MATERIALS

Abbreviation	Polymer	Common Name	Mfr.
C	Carboxyvinyl polymer	Carbopol 934	B. F. Goodrich Chemical Co.
CN	Hydroxyalkylated starch derivative	Ceron N (4S)	Hercules Powder Co.
CS	Acrylic polymer	Carboset 511	B. F. Goodrich Chemical Co.
Cy270; 370	Modified acrylic polymer	Cyanamer A-270 Cyanamer A-370	American Cyanamid Co.
Cy26	Acrylamide copolymer	Cyanamer P-26	American Cyanamid Co.
Cy250	Polyacrylamide	Cyanamer P-250	American Cyanamid Co.
PVO	Polyvinyloxazolidinone	Devlex 130	Dow Chemical Co.
PVA	Polyvinyl alcohol	Elvanol 72-60	E. I. du Pont de Nemours Chemical Co.
G/A	Half-amide of Gantrez	Gantrez half-amide 5	General Aniline and Film Corp.
G119	Methylvinyl ether	Gantrez AN-119	General Aniline and Film Corp.
G139; G169	Maleic anhydride copolymer	Gantrez AN-139 Gantrez AN-169	
HPMC	Hydroxypropyl methyl cellulose derivative	Methocel HG-60	Dow Chemical Co.
M	Methylcellulose	Methocel U. S. P.	Dow Chemical Co.
PAM10; 50; 75; 100	Polyacrylamide	PAM-10; PAM-50; PAM-75; PAM-100	American Cyanamid Co.
PVP	Polyvinylpyrrolidone	PVP K-30	General Aniline and Film Corp.
P301; 205; 35	Ethylene oxide polymer	Polyox WSR-35; −205; −301	Carbide and Carbon Chemicals Co.

mounted on a Cenco Meinzer sieve shaker. The shaker was operated at low speed for 10 minutes, the shaking interval having been determined by consecutive analyses of several sample granulations.

Each granulation was subjected to friabilation using the laboratory granule friabilator described in Fig. 1. The samples, their particle size distributions previously determined, were tumbled for 30 minutes at 90 r.p.m. After tumbling, each granulation sample was reclassified and its resistance to friabilation computed. These computations were based on a modification of an A.S.T.M. test for the friability of coal (1, 2).

$$F\,\% = \frac{S - s}{S} \times 100 \qquad \text{(Eq. 1)}$$

The friability per cent ($F\%$) is the relative per cent difference in classification before and after friabilation. The sum of the products obtained when the percentage weight (based on the combined fraction weights) of granulation in each classification is multiplied by its sieve factor before friabilation is represented by S. The sieve factors are calculated by dividing the average opening (in inches) of two adjacent classification screens by the opening of the coarsest screen in the series—16 mesh in this case. The sum of the products obtained in the same manner after friabilation is represented by s.

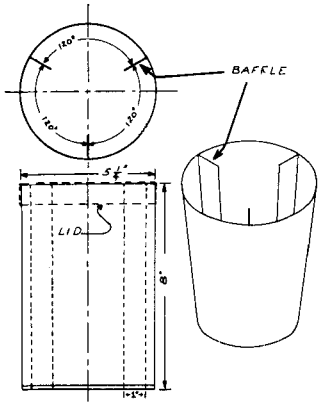

Fig. 1.—Laboratory granule friabilator.

In addition to the friability per cent ($F\%$), the fines index ($Fn.I.$), dust index ($D.I.$), and the friability index ($F.I.$) also were calculated. The fines index is the percentage of fine material (60 mesh or finer) contained in a granulation before friabilation, and the dust index is the percentage of fine material similarly determined following friabilation. The friability index is the difference between the fines and dust indices and presents an indication of the hardness and resistance to attrition of a particular granulation.

The bulk density of each granulation was determined using samples of the sized granulations subjected to additional drying at 105° for 20 hours. Fifty milliliters of each granulation was placed in a 50-ml. cylindrical graduate. The graduate then was tapped three times within 6 seconds, by dropping it a distance of 1 in. onto a piece of hard wood. After waiting 30 seconds, the volume occupied by the granulation was noted and the weight of the granulation sample divided by that volume. This method was not intended to produce a completely compacted volume but has been shown to produce consistent relative values (3, 4).

The thermal stability of the polymer-granulated products was tested under extreme oven drying conditions by subjecting the granulation samples to a temperature of 105° for 20 hours. At this time, the internal temperature of all the granulation samples had risen to at least 90°. The thermally treated and the air-dried granulation samples were observed for color changes.

The compressibility of each of the granulations was evaluated after adding a disintegrant (5% starch) and a lubricant (1% magnesium stearate), on a 16-station rotary tablet machine.[4] The tablet machine was operated at a speed of 450 tablets per minute, producing $^{7}/_{16}$-in. standard cup tablets.

[4] Model RB-2, F. J. Stokes Machine Co., Philadelphia, Pa.

TABLE II.—MOISTURE CONTENTS OF WET AND AIR-DRIED GRANULATIONS[a]

Granulation	Wet	Dried	Granulation	Wet	Dried	Granulation	Wet	Dried
Control	36.5	6.6	PVA-W1	42.4	7.4	PAM50-W1	43.5	7.3
C-W1[b]	42.4	7.0	PVA-W3	42.5	12.2	PAM50-W3	41.7	7.2
C-W10	48.4	9.2	PVA-W5	41.7	8.8	PAM50-W5	41.5	6.8
C-A10	500[c]	9.4	G/A-W1	40.7	6.9	PAM75-W1	43.6	11.6
CN-W1	39.0	6.6	G/A-W3	41.0	7.0	PAM75-W3	41.4	9.0
CN-W3	39.1	6.2	G/A-W5	39.8	7.4	PAM75-W5	41.5	8.6
CN-W5	38.8	6.7	G119-W1	41.4	7.6	PAM100-W1	42.5	10.4
CS-W1	41.4	7.0	G119-W3	39.5	8.2	PAM100-W3	40.9	8.0
CS-W3	40.0	7.2	G119-W5	39.0	8.5	PAM100-W5	40.8	8.8
CS-W5	39.7	7.3	G139-W1	40.3	7.6	PVP-W1	35.4	8.6
CS-W10	38.5	6.7	G139-W3	40.8	8.2	PVP-W3	34.0	6.6
CS-W20	37.9	7.0	G139-W5	40.6	9.0	PVP-W5	35.4	7.0
Cy270-W10	41.2	7.6	G169-W1	41.4	7.6	PVP-A1	380.0[c]	5.8
Cy370-W1	37.0	6.6	G169-W3	41.0	8.7	PVP-A3	355.0[c]	6.0
Cy370-W3	41.6	7.3	G169-W5	39.8	8.4	PVP-A5	325.0[c]	6.0
Cy370-W5	41.6	7.4	HPMC-W1	40.8	6.2	P35-W1	41.3	6.6
Cy26-W1	41.5	7.0	HPMC-W3	39.5	7.0	P35-W3	39.1	6.6
Cy26-W3	40.5	7.0	HPMC-W5	38.8	7.4	P35-W5	38.8	6.6
Cy26-W5	39.8	7.0	HPMC-AW4[d]	210.0[c]	8.2	P205-W1	42.3	7.2
Cy250-W1	42.6	7.8	M-W1	42.2	7.1	P205-W3	41.4	6.8
Cy250-W3	40.5	7.0	M-W3	41.9	6.7	P205-W5	39.5	7.0
Cy250-W5	38.8	7.2	PAM10-W1	40.0	6.7	P301-W1/2	44.4	6.6
PVO-W1	42.2	7.0	PAM10-W5	33.0	6.8	P301-W1	41.8	6.8
PVO-W3	38.9	7.5	PAM10-W10	38.5	6.6	P301-W5	40.8	6.0
PVO-W5	37.9	7.2						

[a] All values given as per cent loss of moisture by weight upon drying at 80°C. in the moisture balance. [b] W, aqueous solution; A, alcoholic solution. Numbers following these letters denote concentration of solutions. [c] Wet moisture contents of granulations containing organic solvents were not determined; values shown represent the volume of solution used. [d] Solvent system was composed of 20% isopropanol and 80% water; concentration of polymer was 4%.

TABLE III.—FRIABILITY CHARACTERISTICS OF THE EXPERIMENTAL GRANULATIONS

Granulation	*F* %	*Fn. I.*	*D. I.*	Granulation	*F* %	*Fn. I.*	*D. I.*	Granulation	*F* %	*Fn. I.*	*D. I.*
Control	2.8	22	24	PVA-W1	30.9	24	51	PAM50-W1	27.0	31	49
C-W1	27.6	26	45	PVA-W3	20.7	39	57	PAM50-W3	25.6	30	42
C-W10	1.5	21	23	PVA-W5	15.8	23	36	PAM50-W5	16.7	28	39
C-A10	15.4	46	56	G/A-W1	20.8	35	60	PAM75-W1	19.7	34	48
CN-W1	29.8	30	50	G/A-W3	35.0	23	51	PAM75-W3	17.5	19	32
CN-W3	17.3	31	42	G/A-W5	7.3	27	32	PAM75-W5	17.0	20	33
CN-W5	14.9	29	39	G119-W1	23.7	27	44	PAM100-W1	21.1	31	45
CS-W1	28.0	41	67	G119-W3	20.8	19	35	PAM100-W3	19.4	22	35
CS-W3	52.5	48	86	G119-W5	14.2	23	33	PAM100-W5	16.2	25	37
CS-W5	49.3	52	85	G139-W1	25.9	24	44	PVP-W1	38.1	36	62
CS-W10	51.1	48	85	G139-W3	22.3	20	38	PVP-W3	13.3	25	32
CS-W20	46.3	41	74	G139-W5	22.1	35	52	PVP-W5	9.5	27	33
Cy270-W10	17.7	24	37	G169-W1	34.1	49	72	PVP-A1	8.5	96	100
Cy370-W1	9.0	18	23	G169-W3	23.8	42	59	PVP-A3	47.2	58	83
Cy370-W3	16.9	21	33	G169-W5	11.7	34	43	PVP-A5	53.1	29	67
Cy370-W5	16.9	21	32	HPMC-W1	36.0	43	68	P35-W1	34.9	44	66
Cy26-W1	22.3	23	38	HPMC-W3	26.9	38	58	P35-W3	30.2	79	94
Cy26-W3	15.6	20	31	HPMC-W5	16.5	34	45	P35-W5	39.5	52	77
Cy26-W5	13.3	20	29	HPMC-AW4	21.6	21	37	P205-W1	43.2	43	73
Cy250-W1	25.1	23	43	M-W1	32.4	32	55	P205-W3	38.8	45	69
Cy250-W3	15.4	18	30	M-W3	20.8	22	39	P205-W5	26.5	80	93
Cy250-W5	5.0	19	22	PAM10-W1	23.3	42	54	P301-W1/2	34.5	46	67
PVO-W1	30.3	45	66	PAM10-W5	17.0	34	46	P301-W1	44.5	49	81
PVO-W3	31.0	34	56	PAM10-W10	26.2	26	45	P301-W5	32.2	69	87
PVO-W5	33.4	24	51								

The weight and pressure settings were maintained as nearly constant as possible while yielding satisfactory tablets throughout the compression of the control and all of the experimental granulations. This procedure permitted the evaluation of the polymer containing granulations according to the flow and compression characteristics, based on the resultant variations in tablet weight and hardness for granulations of approximately equivalent particle size distribution and friability characteristics (Table V).

Evaluation of Experimental Tablets.—Tablets made from the control and all experimental granulations were evaluated visually for their general appearance, color, sheen, and defects.

Disintegration rate studies were performed by the official method (5), except that the disks were not used (6). The disintegration tests were performed in both distilled water and simulated gastric juice (7). Samples were selected at random and in quantities corresponding to the square root of the batch size. The maximum and average disintegration times were noted for each sample evaluated.

Tablet hardness was evaluated using a Dillon[5] prototype hardness tester which employs a direct force maximum register gauge. Square-root samples were subjected to the test, and the average hardness was calculated.

[5] W. C. Dillon and Co., Van Nuys, Calif.

TABLE IV.—MOISTURE CONTENT AND BULK DENSITY OF THE OVEN-DRIED GRANULATIONS[a]

Granulation	%H_2O	ρ_b	Granulation	%H_2O	ρ_b	Granulation	%H_2O	ρ_b
Control	6.0	0.54	PVA-W1	3.8	0.41	PAM50-W1	4.9	0.46
C-W1	5.0	0.46	PVA-W3	3.5	0.35	PAM50-W3	5.5	0.44
C-W10	6.9	0.50	PVA-W5	2.9	0.35	PAM50-W5	4.4	0.42
C-A10	5.3	0.31	G/A-W1	1.1	0.43	PAM75-W1	5.8	0.48
CN-W1	3.7	0.58	G/A-W3	1.3	0.43	PAM75-W3	6.7	0.46
CN-W3	4.1	0.58	G/A-W5	0.5	0.59	PAM75-W5	4.9	0.43
CN-W5	3.7	0.57	G119-W1	2.6	0.54	PAM100-W1	6.4	0.46
CS-W1	0.9	0.57	G119-W3	3.3	0.50	PAM100-W3	3.9	0.45
CS-W3	1.2	0.49	G119-W5	3.5	0.54	PAM100-W5	5.2	0.42
CS-W5	1.1	0.50	G139-W1	4.0	0.45	PVP-W1	6.0	0.50
CS-W10	1.9	0.47	G139-W3	3.9	0.44	PVP-W3	5.9	0.60
CS-W20	1.2	0.49	G139-W5	3.7	0.43	PVP-W5	5.0	0.62
Cy270-W10	3.5	0.50	G169-W1	3.6	0.42	PVP-A1	5.0	0.63
Cy370-W1	5.4	0.57	G169-W3	4.0	0.42	PVP-A3	4.5	0.47
Cy370-W3	2.4	0.47	G169-W5	4.5	0.44	PVP-A5	4.9	0.44
Cy370-W5	2.4	0.52	HPMC-W1	4.4	0.55	P35-W1	3.9	0.54
Cy26-W1	3.5	0.54	HPMC-W3	5.2	0.47	P35-W3	5.1	0.48
Cy26-W3	3.6	0.44	HPMC-W5	5.5	0.46	P35-W5	4.5	0.49
Cy26-W5	2.8	0.46	HPMC-AW4	5.9	0.46	P205-W1	4.3	0.49
Cy250-W1	4.2	0.46	M-W1	1.0	0.45	P205-W3	5.1	0.55
Cy250-W3	4.2	0.44	M-W3	1.9	0.44	P205-W5	4.6	0.50
Cy250-W5	3.6	0.53	PAM10-W1	2.6	0.60	P301-W$^1/_2$	4.2	0.52
PVO-W1	0.05	0.59	PAM10-W5	5.6	0.55	P301-W1	4.7	0.47
PVO-W3	0.8	0.49	PAM10-W10	4.0	0.47	P301-W5	3.9	0.54
PVO-W5	1.0	0.47						

[a] Bulk densities and moisture contents shown are for granulations dried at 105° C. for 20 hours.

TABLE V.—REPRODUCIBILITY OF GRANULATION CHARACTERISTICS

Granulation[a]	% Mesh Classification[b] (<16)	(16–20)	(20–40)	(40–60)	(>60)	Moisture Content, %	Bulk Density
Control	2.33	19.31	40.78	15.47	22.11	6.0	0.54
C-W10	0.23	19.85	46.44	12.02	21.46	6.9	0.50
C-W10-2	2.65	21.01	42.07	15.22	19.05	3.5	0.63
Cy370-W1	0.09	15.56	51.93	14.13	18.29	5.4	0.57
Cy370-W1-2	0.06	12.56	46.08	13.88	27.42	2.2	0.58
Cy370-W3	0.02	9.75	52.37	16.55	21.31	2.4	0.47
Cy370-W3-2	0.09	16.03	46.42	12.54	24.92	2.7	0.63
Cy370-W5	0.14	13.93	50.85	14.25	20.83	2.4	0.52
Cy370-W5-2	0.19	15.63	47.25	13.66	23.27	2.3	0.60
Cy26-W5	0.16	14.98	51.56	12.98	20.32	2.8	0.46
Cy26-W5-2	0.18	9.92	40.04	15.56	34.29	2.0	0.61
Cy250-W5	0.22	13.85	52.06	14.57	19.30	3.6	0.53
Cy250-W5-2	0.13	16.55	43.49	13.75	26.07	1.1	0.57
G/A-W5	0.15	11.68	47.88	13.79	26.50	0.5	0.59
G/A-W5-2	0.57	9.47	36.22	15.63	38.08	1.7	0.56
PVP-W5	0.09	11.00	47.13	15.08	26.70	5.0	0.62
PVP-W5-2	0.10	12.98	47.19	18.85	20.88	1.3	0.57

[a] The -2 batches of each series denote the second 2-Kg. batches. [b] Based on the combined fraction weights.

Weight variation studies were performed using another square root sample of each granulation. The average tablet weight and the standard deviation were calculated then for each sample.

Tablets not capped or broken were subjected to friabilation in the laboratory granule friabilator. A sample of 130 Gm. of tablets was weighed after the adherent powder had been removed with compressed air and was placed in the apparatus, which was then rotated for 10 minutes at 90 r.p.m. After again removing the adherent powder, the sample was weighed again, and the percentage loss of weight was calculated.

Polymer-Drug Binding.—Polymer-drug binding between a typical primary amine drug salt, dextroamphetamine sulfate U.S.P., and the best of the polymeric binding agents in the investigation was studied. A dialysis procedure was employed to evaluate polymer-drug association or binding in aqueous solution. Using a membrane of No. 30 NoJax[6] casing, 20 ml. of each selected polymer solution was dialyzed without drug for 144 hours. The sac containing the 20 ml. of polymer solution was contained in a 3-oz. round powder jar containing 70 ml. of simulated gastric juice without pepsin (the actual capacity of these jars is 110 ml.). The sealed jar was rotated at 40 r.p.m. in a water bath maintained at 37 ± 1° during the dialysis procedure. Ten-milliliter samples were extracted from the ambient fluid and placed on tared watch glasses. These samples were dried for 12 hours at 50°, then for 4 hours at 105°. The residue weights were compared with those resulting from the simulated gastric juice to determine how much, if any, of the polymer had dialyzed.

The equilibrium time for dextroamphetamine sulfate was determined by a similar dialysis procedure using standard aqueous solutions of the drug. A standard assay curve was constructed according to the method of Royal (8). The standard curve

[6] NoJax Casing, size 30, Visking Co., Chicago, Ill.

TABLE VI.—PROPERTIES OF CONTROL AND POLYMER-GRANULATED TABLETS

Granulation	General Appearance	Sheen	Defects	Av. Hardness	Av. Wt.	S. D. of Wt.
Control	Good	Good	None	30+	872	8.2
Control-2[a]	Good	Good	None	6.0	606	7.8
C-W1	Poor	Poor	Capping	4.4	733	20.4
C-W10	Good	Fair	None	22.9	885	5.4
C-A10	Good	Poor	Soft	2.8	517	10.6
CN-W1	Poor	Poor	Capping	7.8	749	40.0
CN-W3	Fair	Poor	Capping	8.8	745	24.8
CN-W5	Fair	Poor	Capping	12.2	789	41.7
CS-W1	Poor	Poor	Fissuring	1.5	703	23.7
CS-W3	Poor	Poor	Fissuring	5.6	771	30.5
CS-W5	Poor	Poor	Fissuring	4.8	768	36.1
CS-W10	Poor	Poor	Fissuring	4.5	773	32.8
CS-W20	Poor	Poor	Fissuring	6.2	763	52.3
Cy270-W10	Fair	Poor	Capping	8.5	760	15.0
Cy370-W1	Good	Fair	None	26.1	886	4.6
Cy370-W3	Good	Good	None	30+	920	3.9
Cy370-W5	Good	Good	None	30+	892	3.3
Cy26-W1	Fair	Poor	Capping	6.6	721	49.1
Cy26-W3	Good	Good	Capping	13.7	732	11.1
Cy26-W5	Good	Good	None	30+	851	13.2
Cy250-W1	Fair	Poor	Capping	9.7	781	24.3
Cy250-W3	Fair	Poor	Capping	7.5	675	12.8
Cy250-W5	Good	Fair	None	30+	859	3.9
PVO-W1	Fair	Poor	Capping	2.1	720	30.4
PVO-W3	Fair	Poor	Capping	10.8	779	18.1
PVO-W5	Good	Fair	Capping	13.9	759	15.0
PVA-W1	Fair	Poor	Capping	5.7	665	15.8
PVA-W3	Fair	Poor	Capping	3.9	553	16.9
PVA-W5	Fair	Poor	Capping	10.7	610	32.3
G/A-W1	Poor	Poor	Capping	4.2	693	25.6
G/A-W3	Fair	Poor	Capping	5.9	730	17.2
G/A-W5	Good	Good	None	30+	836	4.1
G119-W1	Fair	Good	Capping	15.5	757	27.1
G119-W3	Fair	Good	Capping	14.4	751	14.0
G119-W5	Good	Good	Capping	23.7	769	27.6
G139-W1	Poor	Poor	Capping	5.7	703	39.4
G139-W3	Fair	Fair	Capping	13.9	691	27.5
G139-W5	Good	Good	None	14.2	662	9.8
G169-W1	Fair	Poor	Capping	8.3	671	21.3
G169-W3	Fair	Poor	Capping	9.5	686	25.1
G169-W5	Fair	Poor	Capping	17.1	685	10.4
HPMC-W1	Poor	Poor	Capping	7.4	742	19.0
HPMC-W3	Poor	Poor	Capping	5.7	681	25.2
HPMC-W5	Fair	Poor	Capping	7.6	674	21.1
HPMC-AW4	Good	Fair	Capping	6.9	665	16.7
M-W1	Fair	Poor	Capping	8.5	700	19.1
M-W3	Fair	Poor	Capping	6.8	729	21.3
PAM10-W1	Poor	Fair	Capping	10.1	725	26.8
PAM10-W5	Poor	Fair	Capping	10.1	802	22.6
PAM10-W10	Poor	Fair	Capping	11.2	689	12.9
PAM50-W1	Fair	Fair	Capping	8.2	694	30.1
PAM50-W3	Fair	Fair	Capping	6.6	659	21.0
PAM50-W5	Good	Good	Capping	9.6	659	9.7
PAM75-W1	Fair	Poor	Capping	11.0	729	14.1
PAM75-W3	Good	Poor	Capping	8.2	682	16.5
PAM75-W5	Good	Fair	None	7.8	658	6.9
PAM100-W1	Good	Fair	Capping	7.8	695	10.5
PAM100-W3	Good	Good	None	9.1	696	5.7
PAM100-W5	Good	Good	None	10.7	686	8.7
PVP-W1	Fair	Poor	Capping	2.6	733	20.9
PVP-W3	Good	Fair	Capping	8.3	799	13.3
PVP-W5	Good	Good	None	28.2	916	5.6
PVP-A1	Fair	Poor	Fissuring	2.2	746	66.4
PVP-A3	Fair	Poor	Capping	3.4	733	59.9
PVP-A5	Fair	Poor	Capping	5.1	749	25.7
P35-W1	Poor	Poor	Capping	2.6	706	40.4
P35-W3	Poor	Poor	Capping	2.9	659	33.6
P35-W5	Poor	Poor	Capping	3.5	682	30.4
P205-W1	Poor	Poor	Capping	4.3	683	43.4
P205-W3	Poor	Poor	Capping	3.4	679	34.6
P205-W5	Poor	Poor	Capping	3.2	664	41.5
P301-W1/2	Poor	Poor	Fissuring	3.0	699	45.8
P301-W1	Poor	Poor	Fissuring	2.1	710	20.0
P301-W5	Poor	Poor	Capping	1.5	675	36.1

[a] This control was compressed in a manner the same as the experimental formulations, using the same pressure and weight settings. The harder control was compressed separately and required additional pressure to achieve the result shown above.

having been established and the equilibrium time for the drug determined, polymer solutions were placed inside the sac along with the drug, and the dialysis procedure was repeated to determine which of the polymers, if any, retarded drug dialysis and equilibrium across the membrane.

The drug-polymer combination was also investigated in solid form to determine whether any slowly soluble films were being formed around the solid particles upon rewetting the polymers. A 4:1 mixture of magnesium trisilicate and dextroamphetamine sulfate was wetted with each of the aqueous polymer solutions until a thick paste was formed. These pastes were then dried for 4 hours at 105° and sized into 16-mesh granules. A weighed sample of each of the granulations was then placed in a dialysis sac, and the equilibrium time for the drug was established again. An identical sample, which had been massed with 10% starch paste, was processed and assayed in the same manner as a control procedure.

RESULTS AND DISCUSSION

Granulation Characteristics.—The moisture contents of the granulations were determined after wet screening and again after drying at room temperature (Table II). The wet moisture content was usually between 39 and 42%.

The dried sized granulations were evaluated for particle size distribution, friabilation, and reclassification of particle size distribution. Table III shows the results of these determinations according to the values of the various calculated indices. A good granulation might be denoted by a *F*% of less than 10, accompanied by a *Fn.I.* of 30 or less, and a relatively small *D.I.*, not more than 15% greater than the *Fn.I.* As shown in Table III, granulation C-W10 has the characteristics of an ideal tablet granulation.

Nearly all the granulations dried under the extreme drying conditions of 105° for 20 hours showed changes in color from their original white to beige or tan, except for the controls, the Carbopol granulations, and to a lesser extent, the PVP–isopropanol granulations.

The bulk densities of most of the granulations seemed to have little bearing on the quality of the granulation. These values (Table IV) appeared to be more or less dependent on the corresponding moisture contents.

Reproducibility of Granulation Characteristics.—An evaluation of the data presented in Table III led to the selection of eight granulations for further investigation. These eight granulations were reproduced in 2-Kg. batches. Table V shows the particle size distributions of the original and replicated granulations before friabilation and the corresponding moisture contents and bulk densities. The variation in moisture content between the original and the replicated batches resulted from the fact that the former were air-dried, while the latter were dried under the more extreme oven drying conditions.

Evaluation of the Experimental Tablets.—Tablets made from the various polymer-bound granulations were evaluated visually for general appearance, sheen, and notable defects. This evaluation appears in Table VI along with the average hardness, average tablet weight, and standard deviation of

TABLE VII.—AVERAGE AND MAXIMUM DISINTEGRATION TIMES OF THE TABLETS

Granulation	In Distilled Water		In Simulated Gastric Juice	
	Av. in min.	Max.	Av. in min.	Max.
Hard control	8.6	15.0	13.1	19.0
Soft control	1.0	1.5	0.8	1.2
C-W10	39.4	60.0	23.3	60 +
C-A10	9.3	11.6	7.9	12.2
Cy370-W1	20.1	30.0	22.2	33.0
Cy370-W3	28.8	34.0	27.7	32.0
Cy370-W5	25.0	27.5	26.8	41.7
Cy26-W5	45.9	59.9	50.0	60 +
Cy250-W5	60 +	60 +	60 +	60 +
PVO-W5	0.69	0.92	0.58	0.68
PVA-W5	60 +	60 +	60 +	60 +
G/A-W5	5.0	8.5	3.9	6.3
PAM50-W5	60 +	60 +	60 +	60 +
PAM75-W5	60 +	60 +	60 +	60 +
PAM100-W3	60 +	60 +	60 +	60 +
PAM100-W5	60 +	60 +	60 +	60 +
PVP-W5	2.3	3.7	2.9	5.3

TABLE VIII.—FRIABILITY CHARACTERISTICS OF CONTROL AND EXPERIMENTAL TABLETS

Granulation	Initial Wt.	Final Wt.	% Loss
Hard control	130.8	129.3	0.8
Soft control	130.6	126.4	3.2
C-W10	130.5	130.2	0.2
Cy370-W1	130.4	129.9	0.4
Cy370-W3	130.7	130.6	0.1
Cy370-W5	130.3	130.2	0.1
Cy26-W5	130.3	129.7	0.5
Cy250-W5	130.0	129.7	0.2
G/A-W5	131.0	130.7	0.2
PVP-W5	130.4	128.7	1.3

tablet weight. These values of the polymer-granulated tablets may be compared with the control formulation, as shown in the table. Since the machine settings were maintained constant as far as possible, the tablet weight and hardness may be taken as an indication of the flow characteristics of the granulation. As was expected, the granulations judged of superior quality produced tablets of greater hardness and greater weight and with less weight variation than other experimental granulations exhibiting less favorable friabilation and particle size distribution characteristics. It was also noted that tablets could be produced at widely varying hardnesses using the polymer-granulated formulations. While control tablets were produced at a hardness of 6 Kg., weighing 606 mg., experimental granulations of superior quality could be compressed at hardnesses ranging from this value to more than 30 Kg., with little variation in tablet weight.

The disintegration times of 15 of the experimental tablet formulations and the corresponding values for the two control formulations denoted in Table VI are shown in Table VII. The second control formulation was prepared to investigate the effect of soluble tablet ingredients on the maximum and average disintegration times.

The results of the friabilation of the control and the experimental tablet formulations are depicted in Table VIII. A comparison of the values in Table VI with those corresponding values shown in Table VIII illustrates a superior resistance to mechanical shock in every instance. It may be assumed that

TABLE IX.—DIALYSIS OF POLYMER-DRUG SOLUTIONS

Polymer	Drug Concn., *M*
Carbopol 934	0.00642
Cyanamer A-370	0.00667
Cyanamer P-26	0.00643
Cyanamer P-250	0.00657
Gantrez half-amide	0.00648
Polyvinylpyrrolidone	0.00642

tablets of lesser hardness would also exhibit acceptable resistance to mechanical shock, since this was shown to be true in the case of the control formulation friabilated at two different hardnesses.

Characteristics of the Drug-Polymer Combination.—The aqueous polymer solutions exhibited a wide range of viscosities according to polymer concentration in solution and molecular weight of the material. These viscosities and the molecular weights influenced the dialysis of the various polymer solutions. As little as 0.4% of polymer (PVP-W5) to as much as 35% (Cy370-W5) was shown to pass through the membrane during dialysis; but in most cases the polymer did not traverse the membrane in a significant amount.

Standard solutions of dextroamphetamine sulfate in simulated gastric juice (without pepsin) were dialyzed until equilibrium occurred. This period was determined to be from 12 to 16 hours for the rotating samples, according to the results of assays performed using a Beckman DU spectrophotometer.[8]

Table IX shows the molar concentration of dextroamphetamine sulfate found outside the dialysis sac after 16 hours. Originally, all the drug was in solution with 5% aqueous solutions of the six polymers. The calculated equilibrium concentration for the drug was 0.00652 *M*. Table IX indicates that according to equilibrium dialysis there was no significant binding or interaction between the polymers and the dextroamphetamine sulfate in aqueous solution.

Another dialysis study performed to detect the formation of slowly soluble films upon rewetting the polymers yielded the same result. The polymer-wetted pastes, after being dried and broken into granules, yielded a concentration of drug the same as the control formulations. In this case, the equilibrium time was taken again as 16 hours, and this was found sufficient even for the equilibration of the drug from the solid particles placed in the sac.

DISCUSSION

Many synthetic polymers are soluble in both organic and aqueous solvent systems. This permits the use of the synthetic polymers in anhydrous organic solvent systems to wet granulate drugs which are water labile, without causing hydrolytic drug decomposition and, based on polymer water solubility or dispersibility, without necessarily increasing tablet disintegration times. On the other hand, natural polymers, while being water soluble, are as a class, insoluble in organic solvents and are precipitated by the addition of miscible organic solvents to aqueous colloidal gum–polymer systems.

Care should be taken in selecting anhydrous organic solvent systems as carrier solvents for the polymeric tablet granulating and binding agent, especially in full scale production applications. Such solvents should be nonexplosive, have a low order of topical and inhalation toxicity, and preferably be nonflammable. A mixed organic solvent system of a nonflammable but generally toxic halogenated hydrocarbon solvent, with a flammable but generally nonexplosive and nontoxic alcohol plus an ester or ketone to provide added polymer solvency, will come closest to producing an ideal solvent in this application. By adjusting the proportion of components in the mixed solvent, a polymer solvent system with minimal toxicity and a safe flash point may be found frequently.

The toxicities of the polymeric materials also must be considered. All of the polymers mentioned in this study are described as nontoxic in general. Some are used presently in pharmaceutical applications, though none are now approved as direct food additives.

The synthetic polymers are more expensive than the natural gums; but as viscosity imparting agents and binders, the synthetic polymers are more efficient based on their higher molecular weights. The cost of synthetic polymers as binding and granulating agents for tablets may consequently be no greater or only slightly greater than that of the natural gums.

SUMMARY

Experimental granulations were produced using aqueous and alcoholic solutions of selected, commercially available, water-soluble nontoxic polymeric materials. The granulations were evaluated for particle size distribution, friability characteristics, moisture content, and density. Those granulations expected to produce satisfactory tablets were compressed, and the finished tablets were evaluated. As a result of this investigation, the following conclusions may be drawn.

1. Many polymeric materials apparently have pronounced tablet binding abilities, are easily applied, and are effective in small concentrations.

2. Granulations shown to be of superior quality as a result of the analysis of particle size distribution and friability data produced the better tablets in every case.

3. Tablet gloss frequently may match that of film-coated, sugar-coated, or polished tablets with the use of polymeric binding or granulating agents.

4. Disintegration rates and physical stability of tablets made from polymer-bound granulations may be improved and controlled by varying the tablet hardness. A wide variation in tablet hardness is made possible by the use of these tablet binders.

5. Flow characteristics of the granulations made using polymeric materials as binding agents are in some cases superior to those manufactured with conventional binders.

REFERENCES

(1) *ASTM Bull.*, **8**, 1045(1958).
(2) *Ibid.*, **8**, 1050(1958).
(3) Butler, A. Q., and Ramsey, J. C., Jr., DRUG STANDARDS, **20**, 217(1952).
(4) Martin, A. N., "Physical Pharmacy," Lea and Febiger, Philadelphia, Pa., 1960, pp. 574–595.
(5) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 934.
(6) O'Brien, J. L., Pacenti, D., and Duescher, H. O., DRUG STANDARDS, **23**, 126(1955).
(7) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 1072.
(8) Royal, J., DRUG STANDARDS, **26**, 41(1958).

[8] Beckman Instruments, Inc., Fullerton, Calif.