Polyethylene Glycol as a Binder for Tablets

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Abstract □ Polyethylene glycol 6000 was evaluated as a binder for the direct compression of 11 tablet formulations. Six formulations compressed quite well, and the resulting tablets were satisfactory in all respects. To evaluate stability, actual shelflife studies were considered more appropriate than the accelerated studies. After a shelflife of 3 years, five of the six formulations were stable. The ascorbic acid formulation was stable for up to 18 months.

Keyphrases □ Polyethylene glycol—as binder for direct compression of tablets, various drugs, stability evaluated □ Tablets—various drugs, polyethylene glycol as binder for direct compression, stability evaluated □ Stability—tablets of various drugs using polyethylene glycol as binder □ Binders—polyethylene glycol in direct compression of tablets, various drugs, stability evaluated □ Dosage forms—tablets, various drugs, polyethylene glycol as binder for direct compression, stability evaluated

Most therapeutic agents lack compression and flow characteristics required for direct compression and must be processed prior to tableting. The most widely used method of tablet preparation is wet granulation (1). This process is obviously unsuitable for heat- and solvent-labile substances. In such cases, the precompression or slugging method is applicable (1). At present, one promising alternative to granulation is direct compression. It offers several advantages, *e.g.*, ease, economy, and increased product stability and dissolution.

BACKGROUND

Few drugs possess a crystalline structure suitable (1) for direct compression. For tablets where the drug constitutes a major portion of the total weight, direct compression should not be used. Direct compression is feasible when the drug makes up only a small percentage of the total tablet. The drug is formulated with a suitable agent like pregranulated calcium phosphate (1), a mixture of sucrose powder and invert sugar[1] (1), spray-dried mannitol (1), spray-dried lactose USP[2] (2), a special form of dextrose[3] (2), lactose USP (beadlets[4]) (3), dextrose corn syrup solids[5] (3), directly compressible starch[6] (4), and microcrystalline cellulose[7] (5).

The discoloration on standing that occurs with directly compressible sugars and the moisture absorption and poor flow properties of microcrystalline cellulose and directly compressible starch are their main drawbacks.

Recently, polyethylene glycols or polyglycols, which have the basic formula of $HO(CH_2CH_2O)_nH$, have become very useful and versatile in pharmaceutical formulation due to their chemical stability, physiological inertness, and water solubility. The lower molecular weight liquids are useful solvents; the higher molecular weight solids, having a waxy appearance and various melting ranges, are ideally suited to preparing ointment and suppository bases (6).

Polyethylene glycol 6000 has been used to prepare solid dispersions of poorly water-soluble or water-insoluble drugs such as griseofulvin (7), hydrocortisone acetate (8), methyltestosterone (8), prednisolone acetate (8), and digitoxin (8) to increase dissolution, absorption, and total availability. Five poorly water-soluble liquids (9), benzonatate, clofibrate, methyl salicylate, benzyl benzoate, and *dl*-alpha-tocopheryl acetate, were converted into convenient solid dosage forms by dispersing them in polyethylene glycol 6000 as a carrier by the melting method. Solid polyethylene glycols[8] of higher molecular weights are potentially strong binders and have been used as wet granulating agents (10) and coating materials (11). Acid-neutralizing rates of the conventional antacids can be tailored by incorporation of polyethylene glycol 6000 (12).

This study was initiated to investigate the use of polyethylene glycol 6000 as a tablet binder for direct compression. When the bulk of the tablet consists of the potent drug, the process is highly economical in restricting the size and weight of the tablet to the minimum without impairing pharmaceutical elegance, hardness, weight uniformity, friability, disintegration, and dissolution.

EXPERIMENTAL

Materials and Equipment—Polyethylene glycol 6000[9] in the form of flakes, mp 60–63°, was used.

The tablets were compressed on a rotary tableting machine[10], using punches and dies ranging from 8.5 to 13.5 mm.

Tablet hardness was determined on a hardness tester[11], and disintegration times[12] were measured by the BP method using distilled water at room temperature. The tablet disintegration unit[12], using No. 50 mesh sieves for the baskets, was employed to study the dissolution patterns.

An air oven with a thermostatic control (±5°) was used to heat the formulations after pulverization through a comminuting mill[13]. The active ingredients, excipients, and magnesium stearate in the formulations complied with USP requirements. Phenprobamate[14] and glucuronolactone[15] were tested according to the specifications of their manufacturers, and clefamide[16] was tested according to the BPC.

Methods—The active ingredient with the required excipients was uniformly mixed with 8–17% of polyethylene glycol 6000. The mixture was passed through the pulverizer using a No. 20 mesh sieve. The powdered mixture was heated at 80–85° in an air oven for 3 hr. Then the heated mass was cooled and screened through a No. 12 mesh sieve by hand and blended with magnesium stearate, if necessary. For sulfisomidine tablets, a mixture of sulfisomidine and polyethylene glycol 6000 was pulverized, heated, cooled, passed through a No. 12 mesh sieve by hand, and then mixed with the excipients. About 5000 tablets were compressed at a rate of 300 tablets/min after correct adjustments of weight and pressure. The first 500 and the last 500 tablets were rejected. Eleven formulations of the tablets were evaluated.

The compressed tablets were evaluated for weight variation, hardness, content uniformity, disintegration time, and 50% dissolution time. A 2-ml aliquot of the 1 liter of dissolution medium (distilled water) was sampled every 5 min with a filter pipet for 30 min. The withdrawn samples were assayed for the active ingredients, and percent dissolved–time plots were drawn. The time for 50% dissolution of the active ingredient was determined from the respective plot. Friabilities for fresh samples were determined in a Roche-type friabilator. The tablets of each type were weighed, subjected to rotation for 20 min at 25 rpm, and then reweighed after careful dusting. The percentage of weight loss was then calculated.

Each sample was packed in 100-ml amber glass bottles having child-proof seals and subjected to a shelflife study for 3 years. Every year the samples were examined for physical appearance, hardness, disintegration time, and 50% dissolution time. Active ingredients in the formulations at the time of preparation and at the end of 3 years were determined by the official methods.

RESULTS AND DISCUSSION

Out of the 11 formulations evaluated, five formulations failed to give satisfactory tablets. The 250-mg iodochlorhydroxyquin tablets and the

[1] Dry-Tab, Nulomoline Division, Sucrest Corp., New York, NY 10005.
[2] Foremost Dairies Inc., Appleton, Wis.
[3] Cerelose, Corn Products Co., New York, N.Y.
[4] Foremost Dairies Inc., San Francisco, Calif.
[5] Catalog No. PAF-2011, Celutab, Penic and Ford Ltd., Cedar Rapids, Iowa.
[6] Sta-Rx 1500, A. E. Staley Manufacturing Co., Decatur, Ill.
[7] Avicel, F.M.C. Corp., New York, N.Y.
[8] Polyox WSR-35, WSR-205, and WSR-301, Carbon and Carbide Chemicals Co.
[9] Carbowax 6000, Union Carbide Chemicals Co., New York, NY 10017.
[10] Manesty model D3A.
[11] Monsanto, distributed by F. J. Stokes Co.
[12] Thermonic tablet disintegration machine, B. P. Standard, Campbell Electronics, Bombay-28, India.
[13] Fitzmill model D, 5000 rpm, W. T. Fitzpatric Co., Chicago, Ill.
[14] Gamaquil, Siegfried Ltd., Zofingen, Switzerland.
[15] Chugai Pharmaceuticals Ltd., Tokyo 101, Japan.
[16] Mebinol, Carlo Erba Sp.A., Milan, Italy.

Table I—Weight Variation and Friability of the Tablets at the Time of Preparation and Hardness Data of the Tablets for 3 Years

Tablet	Weight Variation[a] Mean Weight, mg	*SD*	Hardness[b], kg 0	1	2	3	Friability[c], %
Ascorbic acid	602	2.3	4	5.3	7.1	7.3	0.33
Diethylcarbamazine citrate	203	1.4	3.2	3.5	3.3	3.1	0.17
B complex	147.3	1.5	2.4	2.3	2.7	2.5	0.15
Chloramphenicol[d] (film coated)	302 (cores)	1.9	6.1	6.3	6.2	6.5	—
Tetracycline[d] (film coated)	268 (cores)	1.8	7.1	6.8	6.7	7	—
Sulfisomidine	631	3	4	3.8	4.1	4.2	0.37

[a] Average of 20 tablets. [b] Average of 10 readings taken at: 0, the time of preparation; 1, the end of the 1st year; 2, the end of the 2nd year; and 3, the end of the 3rd year. [c] Average of two readings. [d] Friability data are not given because both tablets are film coated.

400-mg phenprobamate tablets had satisfactory compressibility and hardness but very high disintegration time. The 100-mg isoniazid and 37.5-mg thiacetazone tablets showed appreciable capping. The 250-mg clefamide tablets displayed sticking to the punches and die even when 2% magnesium stearate was used. The 150-mg glucuronolactone tablets discolored on heating, resulting in mottled tablets.

The following six formulations gave satisfactory tablets:

1. Ascorbic acid tablets containing 500 mg of ascorbic acid and 100 mg of polyethylene glycol 6000.
2. Diethylcarbamazine citrate tablets containing 50 mg of diethylcarbamazine citrate, 20 mg of starch, 104 mg of lactose, 25.4 mg of polyethylene glycol 6000, and 0.6 mg of magnesium stearate.
3. B complex tablets containing 6 mg of thiamine mononitrate, 2 mg of riboflavin, 0.5 mg of pyridoxine hydrochloride, 1.5 mg of calcium pantothenate, 0.55 mg of folic acid, 25 mg of niacinamide, 50 mg of lactose, 40 mg of starch, and 24.45 mg of polyethylene glycol 6000.
4. Chloramphenicol tablets containing 250 mg of chloramphenicol, 30 mg of starch, and 30 mg of polyethylene glycol 6000.
5. Tetracycline hydrochloride tablets containing 250 mg of tetracycline hydrochloride and 20 mg of polyethylene glycol 6000.
6. Sulfisomidine tablets containing 500 mg of sulfisomidine, 37 mg of starch, 12 mg of talc, 70 mg of polyethylene glycol 6000, and 6 mg of magnesium stearate.

The granules of all satisfactory formulations were uniform and free flowing. The flow of sulfisomidine granules was not satisfactory, and it was necessary to use talc as a glidant.

The data for weight variation and friability of the fresh samples and for hardness of the fresh as well as the aged samples of the six satisfactory formulations are given in Table I. Disintegration times and 50% dissolution times for the fresh as well as the aged samples are given in Table II. From these tables, it is evident that the weight variation, hardness, friability, disintegration time, and 50% dissolution time of all fresh samples fell within the prescribed limits.

There was no significant change in hardness, disintegration time, and 50% dissolution time during the shelflife period of 3 years with diethylcarbamazine citrate, B complex, chloramphenicol (film-coated green), tetracycline hydrochloride (film-coated orange), and sulfisomidine tablets. With ascorbic acid tablets, there was a stepwise increase in hardness, disintegration time, and 50% dissolution time. The content uniformity of diethylcarbamazine citrate and B complex tablets was well within the limits prescribed in NF XIV.

Diethylcarbamazine citrate and sulfisomidine tablets maintained their original whiteness throughout the 3 years. The coatings of chloramphenicol (film-coated green) and tetracycline hydrochloride (film-coated orange) maintained their original color and gloss and remained intact without any cracks during this period. The inside cores of chloramphenicol and tetracycline hydrochloride tablets did not show any sign of discoloration. These two cores were subjected to TLC, and decomposition products were totally absent at the end of 3 years.

B complex tablets, which usually need a protective coating to prevent decomposition and development of unpleasant odor, maintained freshness throughout the 3 years. A slight deepening of the yellow color of B complex tablets at the end of 3 years was not significant. With ascorbic acid tablets, there was a progressive discoloration; the tablets were light brown at the end of 3 years.

The complete analytical data for the fresh and aged samples are given in Table III. The ascorbic acid formulation decomposed to an extent of 17% in 3 years. The other five formulations were reasonably stable for 3 years.

Table II—Disintegration and Dissolution Data of the Tablets for 3 Years

Tablet	Disintegration Time[a], sec 0	1	2	3	Time for 50% Dissolution[a], sec 0	1	2	3
Ascorbic acid	510	630	1260	1530	180	330	420	420
Diethylcarbamazine citrate	270	270	330	300	60	90	90	60
B complex	300	270	360	330	120	150	120	120
Chloramphenicol (film coated)	510	450	420	450	300	330	300	390
Tetracycline (film coated)	720	840	810	930	480	450	510	390
Sulfisomidine[b]	420	510	390	450	—	—	—	—

[a] Average of five readings taken at: 0, the time of preparation; 1, the end of the 1st year; 2, the end of the 2nd year; and 3, the end of the 3rd year. [b] It was not possible to get dissolution data for sulfisomidine tablets because a perfect sink condition could not be attained.

Table III—Assay[a] of Active Ingredients

Tablet	At Time of Preparation, %	After 3 Years, %
Ascorbic acid	107	90
Diethylcarbamazine citrate	103	105
B complex	—	—
Thiamine mononitrate	98	90
Riboflavin	97	94.5
Folic acid	103	105
Pyridoxine hydrochloride	98	103
Calcium pantothenate	105	103
Niacinamide	95	98
Chloramphenicol (film coated)	97.5	95
Tetracycline (film coated)	105.5	108
Sulfisomidine	95	96.5

[a] Average of two readings.

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