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[54] **DIRECT COMPRESSION CYCLOPHOSPHAMIDE TABLET**

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[58] **Field of Search** 424/489, 464, 465, 470, 424/475, 479, 499

[56] **References Cited**

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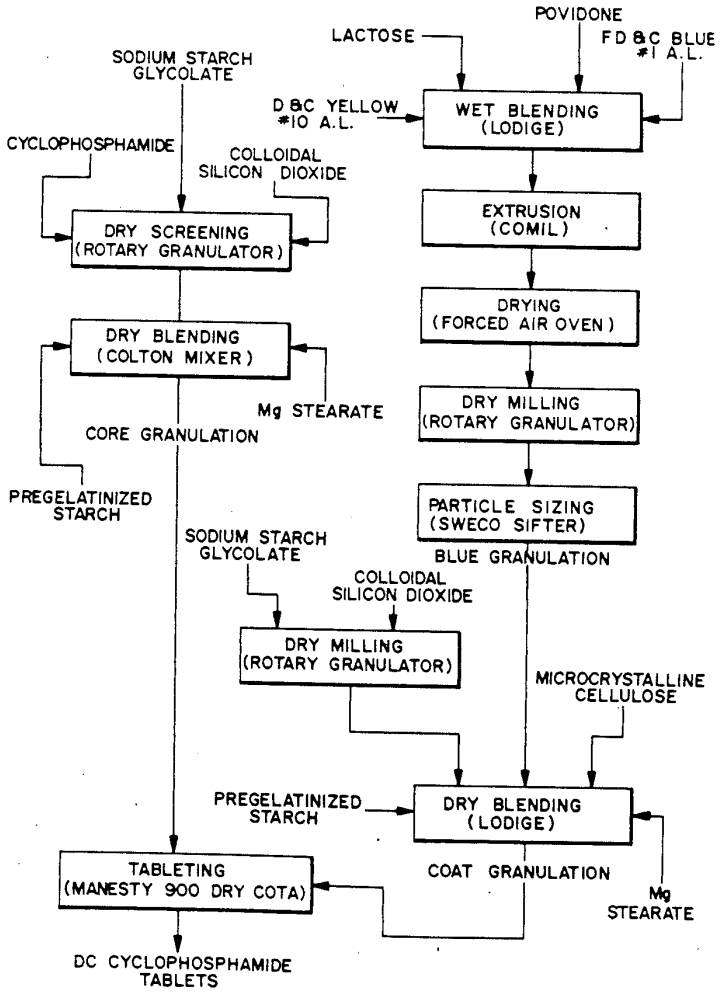
[57] **ABSTRACT**

A directly compressible pharmaceutical composition comprising cyclophosphamide and a partially or fully pregelatinized starch is disclosed. The pharmaceutical composition, when directly compressed into a tablet, exhibits unexpected stability when compared to cyclophosphamide in combination with other direct compression vehicles.

14 Claims, 1 Drawing Sheet



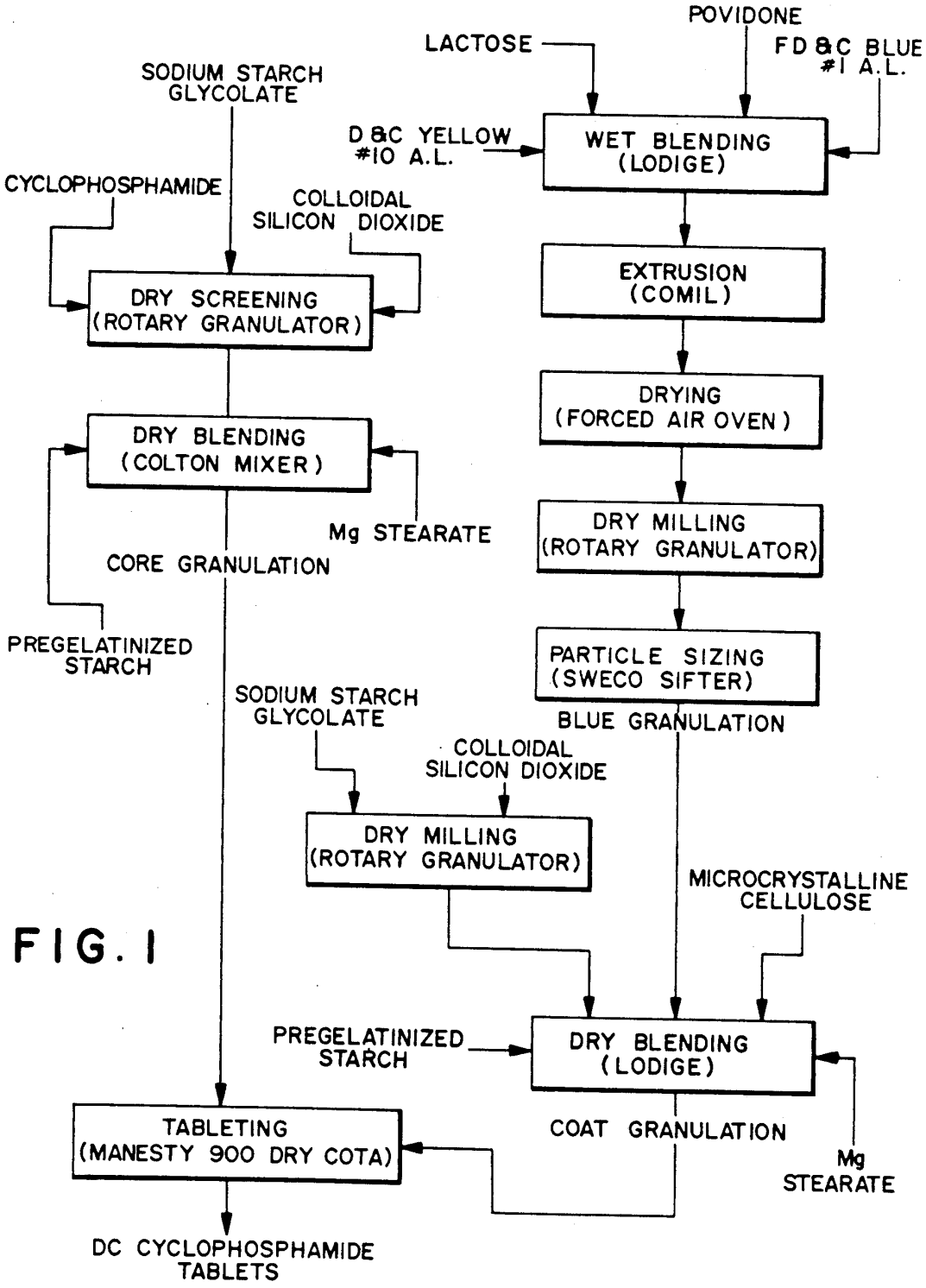


FIG. 1

DIRECT COMPRESSION CYCLOPHOSPHAMIDE TABLET

FIELD OF THE INVENTION

This invention relates to a novel pharmaceutical composition. More particularly, this invention relates to an unexpectedly stable pharmaceutical composition comprising cyclophosphamide and a partially or fully pregelatinized starch, which composition can be directly compressed to form a pharmaceutical tablet.

BACKGROUND OF THE INVENTION

The compressed tablet is one of the oldest and most popular unit dosage forms for medicinal substances. The tablet as a dosage form can be traced to well over 1,000 years ago when a procedure for molding solid forms containing medicinal ingredients was recorded. As a result of the introduction of new carriers and compression vehicles, tablets are replacing many forms of pills, powders and capsules. Accordingly, tablets presently represent the largest production volume of all pharmaceuticals.

The reasons for the widespread use of tablets are apparent, since tablets facilitate: (1) administration of medication in an accurate dose; (2) fast and accurate dispensing with less chance of error and contamination: (3) ease of administration: (4) administration in a form in which the time and area of contact between the active ingredient and the taste buds are reduced, thus obviating the physiological problems associated with the oral administration of drugs that possess a bitter taste and, in the case of coated tablets, with drugs that possess a disagreeable odor; (5) release of drugs at specific locations in the gastro-intestinal tract to prevent degradation of drugs sensitive to the low pH environment in the stomach, prevent release of drugs that irritate the gastric mucosa in the stomach, and facilitate local action or preferential absorption at specific sites in the tract: (6) enhanced stability by effecting a marked reduction in the surface of the drug exposed to the environment; (7) rapid production; and (8) economy and ease in storage, packaging and shipping.

There are currently three basic methods for tableting. They are the wet granulation method, the dry granulation method and the direct compression (DC) method. The direct compression method is by far the desired method from the standpoint of processing time and requirements of equipment and materials. However, only a very limited number of pharmaceutical substances possess enough cohesive strength and flowability to allow direct compression without previous granulation. Certain crystalline materials, such as potassium bromide and potassium chloride can be compressed without preliminary treatment. Also, drugs such as aspirin and phenolphthaline can be directly compressed after blending with suitable tableting excipients.

It has been estimated that about 20 percent of the materials used for tableting in the pharmaceutical field may be compressed directly. In order to use this method to a greater extent, many more materials are modified either by treating the material in some special way during early stages of preparation, or by adding a direct compression vehicle, i.e., a dry binder or excipient material which will mix with the active ingredient to provide a flowable powder and form an easily compressible carrier. Exemplary United States patents relating to directly compressible tablets include U.S. Pat. No. 3,584,114 to Cavalli, et al., U.S. Pat. No. 3,725,556 to Hanssen, et al., U.S. Pat. No. 3,873,694 to Kanig, U.S. Pat. No. 4,072,535 to Short, and U.S. Pat. No. 4,439,453 to Vogel.

There are currently several available binders or excipients which can be used as direct compression vehicles. They include spray-dried lactose; anhydrous lactose: microcrystalline cellulose; dicalcium phosphate dihydrate, unmilled; spray-congealed mannitol; ungelatinized starch (e.g., corn starch), and partially or fully pregelatinized starch.

Starch, as defined by the *National Formulary XVI*, "consists of the granules separated from the mature grain of corn {*Zea mays Linne* (Fam.Gramineae)} or of wheat {*Triticum asetivum Linne* (Fam.Gramineae)}, or from tubers of the potato {*Solanum tuberosum Linne* (Fam.Solanaceae)}." Pregelatinized starch is defined by the *National Formulary XVI* as "starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. Some types of pregelatinized starch may be modified to render them compressible and flowable in character." Many types of partially or fully pregelatinized starches are commercially available for use in direct compression tablet formulations.

With the advent of the above described direct compression vehicles, drug manufacturers are seeking to formulate or reformulate pharmaceutically active compounds into compositions which are directly compressible into tablets. One such compound is cyclophosphamide, an anti-neoplastic agent manufactured by Bristol-Myers Company under the trademark CYTOXAN ®, which is currently tableted with specially prepared directly compressible diluent. This DC diluent is produced by a wet granulation process. However, processing cyclophosphamide using wet granulation method has certain drawbacks. A major problem is that it is difficult to control the moisture of the resulting tablet. A second problem is that the dissolution rate, i.e., the rate at which the tablet dissolves in water, decreases over time. The third problem is that the dissolution rate of the tablet varies from batch to batch, with some batches having unacceptably low rates.

Obviously, a direct compression cyclophosphamide tablet would be desirable. Unfortunately, cyclophosphamide is not one of the few known compounds which possesses the cohesive strength and flowability to allow direct compression. Thus, there is a need for a directly compressible composition comprising cyclophosphamide and a direct compression vehicle, which composition obviates the problems resultant from wet processing.

Accordingly, it is an object of this invention to provide a directly compressible pharmaceutical composition comprising cyclophosphamide and a direction compression vehicle.

SUMMARY OF THE INVENTION

Surprisingly, a directly compressible pharmaceutical composition has been discovered comprising cyclophosphamide and a partially or fully pregelatinized starch. It has been found that this composition, when directly compressed into a tablet, exhibits unexpected and remarkable stability when compared to CYTOXAN ® tablets or cyclophosphamide in combination with other directly compressible vehicles.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a schematic diagram of a process for making a direct compression cyclophosphamide tablet in accordance with this invention.

DETAILED DESCRIPTION OF THE INVENTION

Cyclophosphamide is listed as a cytotoxic agent by the Environmental Protection Agency. Accordingly, a "core tablet blend" containing the cyclophosphamide is first prepared and compressed to form a compressed core tablet. The compressed core tablet is then covered or encapsulated by a second compressed coating called a "press coat blend", which contains no active ingredients. Thus, persons handling the tablets do not directly contact the carcinogenic cyclophosphamide.

I. THE CORE TABLET BLEND

The core tablet blend in accordance with this invention comprises a mixture of cyclophosphamide, a partially or fully pregelatinized starch, and optionally, additional diluents or other ingredients such as disintegrants, lubricants, glidants, etc.

A. The Cyclophosphamide and Pregelatinized Starch

The cyclophosphamide used in this invention is the crystalline monohydrate form. For purposes of the procedures described below it is preferred that the particle size be approximately 40 mesh or smaller. Due to its low melting point (46° C.), cyclophosphamide is not conducive to milling. When orally administered, cyclophosphamide is usually prescribed in dosages of 25 mg, 50 mg, or 100 mg.

Several different types of partially or fully pregelatinized starch (hereinafter simply "pregelatinized starch") can be used in accordance with this invention. The pregelatinized starch should meet all *National Formulary XVI* standards and be capable of mixing with cyclophosphamide to form a directly compressible tablet. These skilled in the art can by simple routine experimentation determine those starches capable of forming direct compression tablets with cyclophosphamide, and the optimum mixtures for doing so.

Commercially available pregelatinized starches which can be used include STARCH 1500 (formerly STA-RX 1500), which is a modified, partially gelatinized corn starch produced by Colorcon, Inc., West Point, Penna.; several pregelatinized starches produced by the Hubinger Company, Keokuk, Iowa, including CERI-GEL 300, a five percent modified, fully pregelatinized corn starch, CERI-GEL 433, which is a modified, fully pregelatinized corn starch, PREGEL, which is an unmodified, fully pregelatinized corn starch, INSTANT KEOGEL, which is a 100 percent modified, fully pregelatinized corn starch, and TENDER JEL, which is a 100 percent modified, fully pregelatinized corn starch; WHEATGEL 100, which is a fully pregelatinized wheat starch produced by International Grain Products, Montreal, Canada: and several pregelatinized starches produced by the A. E. Staley Manufacturing Company, Hulton, Ma., including BINASOL 15, which is a modified, fully pregelatinized tapioca starch, BINASOL 81, which is a modified, fully pregelatinized tapioca starch, INSTANT TENDER JEL, which is a 99 percent modified, fully pregelatinized waxy corn starch, and STA-RX, which is a modified, fully pregelatinized corn starch.

It has been found that STARCH 1500 provides the best results, but that the other pregelatinized starches mentioned above will also provide good results. STARCH 1500 is a modified, partially pregelatinized corn starch containing approximately 5 percent amylose, 15 percent amylopectin, and 80 percent unmodified corn starch. STARCH 1500 has a cold water soluble fraction of 10–20 percent.

All starches contain two types of carbohydrate chains, i.e., amylose and amylopectin, which both have the same basic chemical structure. However, they are slightly different, which accounts for their very different individual properties. Amylose has a straight chain molecular make-up, while the amylopectin has a multibranched make-up. In unmodified corn starch, amylose and amylopectin are randomly mixed throughout the starch grains and are held together by hydrogen bonding that prevents them from functioning independently. The gelatinized process breaks that hydrogen bonding and allows the two chains to function separately.

STARCH 1500, when used as a capsule excipient for aspirin, is known to provide better stability than either anhydrous lactose or microcrystalline cellulose excipients. It is also known that aspirin is an ester that easily undergoes hydrolysis in the solid state when exposed to ambient moisture. STARCH 1500 has a high moisture content; however, this moisture is apparently not available to hydrolyze the aspirin molecule. In contrast, degradation of cyclophosphamide (CY) monohydrate in solid dose forms is initiated by dehydration resulting in the loss of CY monohydrate crystalline structure. CY monohydrate degrades rapidly when the moisture content is less than the monohydrate equivalent. Without being bound by theory, the improved stability is believed to be due to the moisture of STARCH 1500 maintaining the CY in its monohydrate state. This is surprising and unexpected since the moisture is tightly bound and essentially unavailable as indicated by the stability of aspirin in the presence of STARCH 1500.

The pregelatinized starch can be dried prior to mixing with cyclophosphamide. However, no significant differences have been observed using dried pregelatinized starches versus using undried pregelatinized starches.

Using STARCH 1500, it has been found that a cyclophosphamide/pregelatinized starch ratio of approximately 2:1 provides an adequate blend compatibility to produce core tablets that can be transferred intact for compression coating on a tablet press. Such a blend is advantageous because it is predominantly cyclophosphamide, resulting in a smaller, more easily swallowable tablet.

B. Additional Diluents

Optionally, other direct compression vehicles can be added to the core tablet blend. However, such diluents are not necessary because a core tablet blend of cyclophosphamide and pregelatinized starch is usually sufficiently compressible to provide an acceptable compressed core tablet. Moreover, the presence of other diluents might have a detrimental effect on stability. Other diluents include lactose monohydrate, microcrystalline cellulose, calcium phosphate (dibasic, milled), ungelatinized corn starch, and dextrates.

C. Disintegrants

Disintegrants are substances that are added to the ingredients of a pharmaceutical tablet to facilitate its

disintegration in the presence of water or biological fluids, and thus hasten the release of the active ingredients. In experiments with the core tablet blend of this invention, sodium starch glycolate was used to facilitate disintegration. Experiments in which the level of disintegrant was 0.0 percent, 4.0 percent and 8.0 percent were carried out to evaluate the effects on tablet dissolution, disintegration, hardness, durability and weight variation. The test results indicated that increasing or decreasing the disintegrant level had no adverse effect on the physical attributes of the tablet. Even though the test results indicated that a disintegrant is unnecessary, it is preferred to include sodium starch glycolate at a 4.0 percent level to assure disintegration and performance of aged tablets or tablets made with different batches of excipients.

D. Lubricants

Lubricants are ingredients that can be added to a tablet blend to facilitate ejection of the tablets from the dies after compression and to prevent tablets from sticking to the punch faces. Acceptable tablets can be manufactured using magnesium stearate in concentrations of 0.25 percent, 0.5 percent and 1.0 percent of the tablet weight, with no tablet picking or sticking to the punch faces. However, a 1.0 percent concentration has a detrimental effect on tablet durability and maximum achievable hardness. Prolonged mixing of the powder blend containing 0.5 percent does not significantly effect the dissolution characteristics, durability or tablet compressibility, and therefore, approximately 0.5 percent magnesium stearate is a preferred level of lubricant.

E. Glidants

Glidants are compounds which are used to improve the flow of the powder blend and to minimize tablet weight variation. Core blends and the resulting tablets containing 0.0 percent, 0.2 percent and 0.5 percent colloidal silicon dioxide have been evaluated for flowability and weight variation. These results show that the addition of 0.2 percent and 0.5 percent improves core blend flowability and decreases tablet weight variation. The results also indicate that increasing the level of colloidal silicon dioxide beyond 0.2 percent does not further improve the flowability or weight variation. Therefore, 0.2 percent colloidal silicon dioxide is a preferred level of glidant in the core tablet blend.

It will be readily apparent to those skilled in the art that pregelatinized starches, diluents, disintegrants, lubricants and glidants other than those specifically recited can be used. Determining the optimum levels of such ingredients is well within the ordinary skill of such persons using routine experimentation similar to that described above.

II. THE PRESS COAT BLEND

As discussed above, cyclophosphamide is cytotoxic, and therefore direct contact with cyclophoshhamide is a potential health risk. Accordingly, after compressing the core tablet blend containing cyclophosphamide, a press coat blend of inert, edible materials is used to encapsulate the compressed core tablet blend.

It is preferable that the composition of the press coat blend contain pregelatinized starch, most preferably STARCH 1500. While pregelatinized starch is the only diluent required in the core tablet blend, tableting characteristics are poor when used as the only diluent in the press coat. For instance, tablet weight loss during durability testing was generally greater than 1.0 percent and tablet picking and sticking often occurred. Therefore, mixtures of pregelatinized starch and microcrystalline cellulose at concentrations of 3:1, 1:1 and 1:3 have been evaluated. When microcrystalline cellulose comprises at least 50 percent of the diluent, the resulting tablets have acceptable tableting characteristics. The stability of the cyclophosphamide is not influenced significantly by these ratios of pregelatinized starch to microcrystalline cellulose. Thus, it is preferred to use a press coat blend comprising one part pregelatinized starch and three parts microcrystalline cellulose.

The press coat blend can, of course, be comprised of other additives such as disintegrants, lubricants and glidants useful in preparing any direct compression tablets. The press coat can also include coloring additives to enable visual recognition of the tablet. In the case of CYTOXAN ®, the press coat blend contains blue flecks which give the finished tablet a distinctive appearance. A discussion of how to color the tablets with blue flecks is given below.

III. PROCESSING THE TABLETS

A. Preparing the Core Tablet and Press Coat Blends

A schematic diagram of an overall process for preparing direct compression tablets in accordance with this invention is shown in FIG. 1.

The first step in preparing the core tablet blend is to deagglomerate the cyclophosphamide and additives such as sodium starch glycolate (disintegrant) and colloidal silicon dioxide (glidant) by dry screening in a rotary granulator. The deagglomeration step is used to break up aggregates of the cyclophosphamide and additives.

Experiments were carried out to determine whether a Model D. Fitzmill or a Colton Rotary Granulator could sufficiently deagglomerate cyclophosphamide, sodium starch glycolate and colloidal silicon dioxide. That was accomplished by passing the ingredients concurrently through the Fitzmill or Granulator. Laboratory experiments demonstrated that the Fitzmill equipped with a number 2A plate, knives forward and medium speed could sufficiently break apart aggregates of those excipients. That is, there were no visual lumps in the excipients after passing through the Fitzmill. Also, the Fitzmill and a rotary granulator equipped with a 12 mesh screen were both shown to be operable when large scale laboratory or production batches were prepared.

After deagglomeration, the mixture is dry blended together with the pregelatinized starch and other additives such as magnesium stearate (lubricant). A 2.5 cubic foot Peerless Radial Arm mixer can be used for the dry blending. Aliquots of core tablet blends have been taken from six different areas of the Peerless mixer and assayed for cyclophosphamide content. The results indicate that cyclophosphamide is adequately distributed throughout the core tablet blends after 2, 5 and 30 minutes of blending. Therefore, a blending time of five minutes is preferred. It is noted that blending for 30 minutes does not cause a slowing of the disintegration/dissolution rates of the resulting tablets.

To determine whether there is any significant variability among different mixers, both the core tablet and press coat blends were prepared in four different mixers, i.e., a 2.5 cubic foot Peerless Radial Arm mixer, a 5.0 cubic foot Patterson-Kelley Twin Shell blender, and a 3.3 cubic foot and a 22.2 cubic foot Lodige mixer.

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