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TIMED RELEASE PHARMACEUTICAL PREPARATIONS
AND METHOD OF MAKING THE SAME
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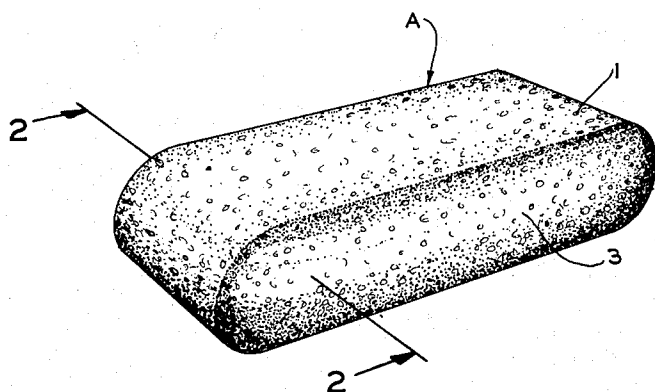


FIG. 1

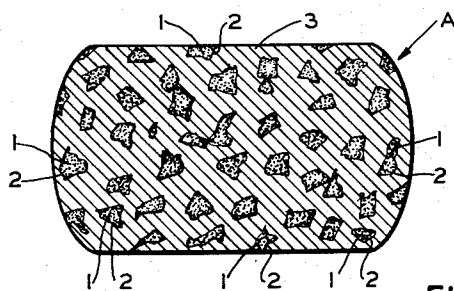


FIG. 2

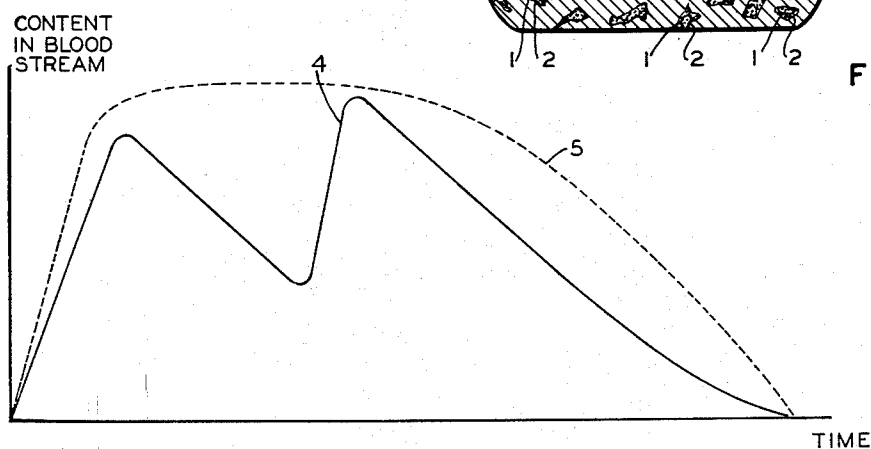


FIG. 3

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TIMED RELEASE PHARMACEUTICAL PREPARATIONS AND METHOD OF MAKING THE SAME

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30 Claims. (Cl. 167—82)

This invention relates in general to certain new and useful improvements in pharmaceutical preparations and, more particularly, to a pharmaceutical preparation having timed release characteristics.

There has long been a need in the medical arts for an analgesic tablet which is capable of releasing the analgesic medication in a relatively constant stream over a rather long period of time. In the case of aspirin, which is one of the best and most universal analgesic drugs, the maximum time of effectiveness is only a few hours and the patient using such medication must take repeated dosages at frequent intervals. This, of course, is inconvenient during waking hours and is extremely undesirable during periods when the patient should be sleeping.

Moreover, analgesic compounds are usually dissolved very readily within the gastric juices of the stomach, and thus the total amount of the dosage is immediately fed into the blood stream. During the interval between dosages, therefore, the analgesic level in the blood stream will constantly decrease due to the biochemical decomposition of the analgesic in the body. Toward the end of the period, the level of the analgesic compound is so low, so that it is practically ineffective. As a result, the degree of pain-relief will fluctuate between dosages.

It is, therefore, the primary object of the present invention to provide a pharmaceutical preparation which is capable of quickly producing an analgesic level within the blood stream of a patient and maintaining such level over a long period of time.

It is another object of the present invention to provide a pharmaceutical preparation of the type stated which contains both immediate action and prolonged release dosage.

It is a further object of the present invention to provide a pharmaceutical preparation of the type stated which is stable and of swallowable size taking into account the quantity required for administration over the prolonged period for which the preparation is designed.

With the above and other objects in view, my invention resides in the novel features of form, construction, arrangement, and combination of parts presently described and pointed out in the claims.

In the accompanying drawing (one sheet)—

FIG. 1 is a perspective view of a prolonged release pharmaceutical preparation constructed in accordance with and embodying the present invention;

FIG. 2 is a sectional view taken along line 2—2 of FIG. 1; and

FIG. 3 is a graphical representation of the quantity of analgesic material in the blood stream over a period of time, when taken in conventional form by a series of successive tablets as compared with the prolonged release dosage form of the present invention.

Referring now in more detail and by reference characters to the drawing, which illustrates a preferred embodiment of the present invention, A designates a pharmaceutical tablet which comprises a plurality of analgesic particles 1 such as acetyl salicylic acid, acetaminophen, salicyl salicylic acid, salicylamide, acetophenetidin, dipyrone, and similar drugs which must be administered in bulky dosages, which are surrounded by a timed-disintegration coating 2. The coated particles are carried in tableted form by a matrix 3 of aspirin and starch.

The analgesic material, such as aspirin, is very finely

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ground by any conventional comminuting device (not shown) and is then tableted in a conventional manner. The tablets are crushed or otherwise broken up to produce particles or granules which are sieved and the particles which are retained between 16 and 20 mesh screens are utilized for coating as hereinafter described. The material which is too large to pass through a 16 mesh screen is crushed and sieved again. The material which passes through a 20 mesh screen is regarded as fines or siftings and is used later as will be presently more fully explained. It has been discovered, in connection with the present invention, that when a drug such as aspirin is compressed into a tablet, a substantially thick case hardened shell is formed around the outside of the tablet and the interior or central portion thereof, although hard and solid, is nevertheless considerably less dense and more porous. Consequently, the mass of particles or granules retained on the 20 mesh screen and utilized for coating purposes will include solid particles of several different degrees of consolidation or, in other words, different degrees of permeability with respect to digestive fluids in the human body.

The granules or particles resulting from the aforementioned screening are placed in a coating pan. While being tumbled therein, the particles are coated with a thin coating of shellac, cellulose acetate phthalate, ethyl cellulose zein, or similar film-forming resin-like materials which are soluble in organic solvents such as alcohol but are insoluble in water. The wetted particles are quickly dusted with stearic acid, kaolin, terra alba, dicalcium phosphate, palmitic acid, linoleic acid, calcium stearate, or any other fatty acids, fatty acid salts, fatty acid esters, or similar non-toxic hydrophobic materials. In this connection, it may be noted that aspirin, for instance, is deleteriously affected by alcohol and water which are the common solvents usually employed in coating materials, but nevertheless, aspirin can tolerate alcohol in limited quantity, for a short period of time. Hence, the particles are given a first quick thin coating, preferably of shellac and stearic acid. This initial coating is thoroughly dried and compacted by tumbling the coated particles for approximately an hour while subjecting them to a gentle stream of cold air.

Thereupon, the coated particles are additionally coated with an aqueous solution of sugar syrup, polyethylene glycols such as carbowaxes, gum such as gum acacia, or other non-toxic materials capable of forming an envelope or integument which resists the penetration of alcohol or similar organic solvents. This second coating is dried by continuous tumbling for a period of 15–30 minutes. Then a third coating just like the second coating is applied and dried. The second and third coatings may, if desired, include an inert non-toxic coloring material.

When the third coating has dried, the granules are removed from the coating pan and placed in thin layers on drying trays which are then placed in a heated drying room and dried overnight. It is essential to dry the particles thoroughly, whereupon the particles are again placed in a coating pan and two successive coatings of shellac and stearic acid are applied as before. At this point in the procedure, a sample is tested in vitro and if the granules have the desired time-delay factor, no further coating is necessary. If, on the other hand, long periods of time-delay are desired, then further shellac-stearic acid coatings are applied.

When the coating of the particles has been completed, they are mixed with a quantity of powdered aspirin and starch and this mixture tableted in a conventional tablet compressing machine. Preferably, the fines or siftings can be used for this purpose. The mixture of aspirin and starch does two things. First; it supplies a readily available initial dosage which enters the patient's blood

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stream very promptly and gives quick initial relief from pain. Second; it serves, uniquely and unexpectedly, as a cushioning matrix for the coated particles so that the latter are not mechanically disrupted or otherwise broken down during compression.

Thus, when a tablet made in accordance with the present invention reaches the patient's stomach, the tablet A disintegrates almost immediately and the initial dosage comprising the matrix is absorbed. The particles 1, however, resist disintegration for about three hours and then the drug begins to leach out in a steady attenuated trickle at a rate which almost identically offsets the rate at which the drug disappears from the blood stream. As a result, a substantially constant level of medication will then be maintained within the blood stream for a period of ten to twelve hours. It will, of course, be understood in this connection, that the length of time during which the patient will be under the influence of the analgesic drug will depend upon the amount of material which has been incorporated into the tablet A, and the size thereof. The tablets of the present invention constitute the only way thus far known by which a time-delay dosage of aspirin or similar analgesic drug can be prepared and still keep the tablet within reasonable limits as to size and also produce a stable product.

It has been found by various in vitro and in vivo tests that when aspirin is taken in the conventional manner, that is to say, one five grain tablet every four hours, the level of drug in the patient's blood stream follows the solid-line curve as shown in FIG. 3. Similar in vitro and in vivo tests show that when aspirin is administered in the prolonged release tablet of the present invention, the analgesic level in the blood stream over a comparable period of time is represented by the dotted-line curve in FIG. 3. It can be seen by further reference to FIG. 3 that in the conventional dosage form, the level of the aspirin within the blood stream is materially increased almost immediately after ingestion thereof. Thereafter, the level of the aspirin in the blood stream begins to decrease rather rapidly over a period of time. The next peak of the solid-line curve occurs when another aspirin tablet is ingested. It can also be seen by reference to FIG. 3 that when aspirin is administered in the prolonged release tablet of the present invention, the analgesic level in the blood stream rises as rapidly as when ingested in the conventional dosage form. However, it is to be noted that the amount of analgesic material in the blood stream is then maintained at a fairly constant level for a prolonged interval.

By way of illustration and not for purposes of limitation, the following are examples of various types of medicinal tablets made in accordance with the present invention:

Example I

360 lbs. of powdered aspirin are mixed with 40 lbs. starch and then tableted into hard slugs. The slugs are crushed through a Stokes oscillator having a 10 mesh screen. The material which passes is sifted through a Sweco separator. Any oversized particles are recrushed through a Stokes oscillator having a 16 mesh screen and again sifted. This series of crushing and sifting steps yields 220 lbs. of granules (16-20 mesh screen) and 180 lbs. of siftings. The 220 lbs. of granules are placed in a coating pan and coated with 450 oz. of 4 lbs. cut shellac and then dusted with 19½ lbs. stearic acid. The coated granules are dried by continued tumbling for approximately one hour while being subjected to a stream of cold air. Then 84 oz. of simple syrup containing 2 oz. of Sunset yellow certified color are applied in two 42 oz. applications with 15-20 minutes' drying after each application. The granules are removed and heat dried on trays overnight at 110° F. The granules are next placed back in a coating pan and coated with three coatings each comprising 150 oz. of 4 lbs. cut shellac and dusted with 11¼ lbs. stearic acid with one hour drying after each ap-

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plication. The coated granules are then heat dried overnight at 110° F. This procedure results in 288¾ lbs. coated granules. These are mixed with the 180 lbs. of siftings and compressed into tablets, each weighing 13 grains and containing 10 grains of aspirin.

Example II

400 lbs. of powdered aspirin are tableted into hard slugs. The slugs are crushed and initially screened (#10 mesh). The material which passes is sifted through a Sweco separator. Any oversized particles are recrushed through a Stokes oscillator having a 16 mesh screen and again sifted. This series of crushing and sifting steps yields 220 lbs. of granules (16-20 mesh screen) and 180 lbs. siftings. The 220 lbs. of granules are placed in a coating pan and coated with 100 oz. of 10% cellulose acetate phthalate in acetone dusted with 2½ lbs. talcum. The coated granules are dried by continued tumbling for approximately one hour while being subjected to a stream of cold air. Then 24 oz. of 25% Carbowax 6000 (aqueous solution) without color are applied in two 42 oz. applications with 15-20 minutes' drying after each application. The granules are removed and heat dried on trays overnight at 110° F. The granules are next placed back in a coating pan and coated with five coatings each comprising 50 oz. of 10% cellulose acetate phthalate dusted with 1¼ oz. of talcum with one hour drying after each application. The coated granules are then heat dried overnight at 110° F. This procedure results in 270 lbs. coated granules. These are mixed with the 180 lbs. of siftings to which 11 lbs. of starch are added. The mixture is then compressed into tablets, each weighing 11.53 grains and containing 10 grains of aspirin.

Example III

400 lbs. powdered acetaminophen (4-hydroxy acetanilide) is tableted into hard slugs. The slugs are crushed and sifted as set forth in Example I again yielding 220 lbs. of granules (16-20 mesh screen) and 180 lbs. siftings. The 220 lbs. of granules are placed in a coating pan and coated with 450 oz. of 4 lbs. cut shellac and dusted with 10 lbs. of calcium stearate. The coated granules are dried by continued tumbling for approximately one hour while being subjected to a stream of cold air. Then 84 oz. of simple syrup containing Sunset yellow certified color are applied in two 42 oz. applications with 15-20 minutes' drying after each application. The granules are removed and heat dried on trays overnight at 110° F. The granules are next placed back in a coating pan and coated with three coatings each comprising 150 oz. of 4 lb. cut shellac and dusted with 6 lbs. of calcium stearate with one hour drying after each application. The coated granules are then heat dried overnight at 110° F. This procedure results in 288¼ lb. coated granules. These are mixed with the 180 lb. of siftings to which 20 lbs. of starch are added. The resulting total mixture is then compressed into tablets each weighing 12.2 grains and containing 10 grains of acetaminophen.

Example IV

400 lbs. powdered salicylamide are tableted into hard slugs. The slugs are crushed and initially screened (#10 mesh). The material which passes is sifted through a Sweco separator to yield 220 lbs. of granules (16-20 mesh screen) and 180 lbs. siftings. The 220 lbs. of granules are coated with the several coatings as described in Example II and results in 288¼ lb. coated granules. These are mixed with the 180 lbs. of siftings and compressed into tablets each weighing 11.53 grains and containing 10 grains of salicylamide.

Example V

400 lbs. powdered salicyl salicylic acid is tableted into hard slugs. The slugs are crushed and sifted as set forth in Example I to yield 220 lbs. of granules (16-20 mesh screen) and 180 lbs. siftings. The 220 lbs. of granules

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are placed in a coating pan and coated with 200 oz. 10% solution of zein in 90% isopropyl alcohol and dusted with 10 lbs. of a mixture of 2 parts kaolin and 1 part calcium stearate. The coated granules are dried by continued tumbling for approximately one hour while being subjected to a stream of cold air. Then 84 oz. of simple syrup containing 2 oz. of Sunset yellow certified color are applied in two 42 oz. applications with 15-20 minutes' drying after each application. The granules are removed and heat dried on trays overnight at 110° F. The granules are next placed back in a coating pan and coated with six coatings each comprising 75 oz. of the above zein solution and dusted with 6 lbs. of the above powder mixture with one hour drying after each application. The coated granules are then heat dried overnight at 110° F. This procedure results in 277 lbs. coated granules. These are mixed with the 180 lbs. of siftings to which 20 lbs. of starch are added. The total mixture is then compressed into tablets, each weighing 11.9 grains and containing 10 grains of salicyl salicylic acid.

Example VI

400 lbs. powdered acetophenetidin is tableted into hard slugs. The slugs are crushed and sifted as set forth in Example I to yield 220 lbs. of granules (16-20 mesh screen) and 180 lbs. siftings. The 220 lbs. of granules are placed in a coating pan and coated with 200 oz. 10% solution of zein in 90% isopropyl alcohol and dusted with 10 lb. of a mixture of 2 parts kaolin and 1 part calcium stearate. The coated granules are dried by continued tumbling for approximately one hour while being subjected to a stream of cold air. Then 84 oz. of simple syrup containing 2 oz. of Sunset yellow certified color are applied in two 42 oz. applications with 15-20 minutes drying after each application. The granules are removed and heat dried on trays overnight at 110° F. The granules are next placed back in a coating pan and coated with six coatings each comprising 75 oz. of the above zein solution and dusted with 6 lbs. of the above powder mixture with one hour drying after each application. The coated granules are then heat dried overnight at 110° F. This procedure results in 277 lbs. coated granules. These are mixed with the 180 lbs. of siftings to which 20 lbs. of starch are added. The total mixture is then compressed into tablets, each weighing 11.9 grains and containing 10 grains of acetophenetidin.

Example VII

400 lbs. powdered dipyrone is tableted into hard slugs. The slugs are crushed and sifted as set forth in Example I to yield 220 lbs. of granules (16-20 mesh screen) and 180 lbs. siftings. The 220 lbs. of granules are placed in a coating pan and coated with 200 oz. 10% solution of zein in 90% isopropyl alcohol and dusted with 10 lbs. of a mixture of 2 parts kaolin and 1 part calcium stearate. The coated granules are dried by continued tumbling for approximately one hour while being subjected to a stream of cold air. Then 84 oz. of simple syrup containing 2 oz. of Sunset yellow certified color are applied in two 42 oz. applications with 15-20 minutes' drying after each application. The granules are removed and heat dried on trays overnight at 110° F. The granules are next placed back in a coating pan and coated with six coatings each comprising 75 oz. of the above zein solution and dusted with 6 lbs. of the above powder mixture with one hour drying after each application. The coated granules are then heat dried overnight at 110° F. This procedure results in 277 lbs. coated granules. These are mixed with the 180 lbs. of siftings to which 20 lbs. of starch are added. The total mixture is then compressed into tablets, each weighing 11.9 grains and containing 10 grains of dipyrone.

It should be understood that changes and modifications in the form, construction, arrangement, and combination of the several parts of the timed release pharmaceutical preparations and method of making the same, may

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be made and substituted for those herein shown and described without departing from the nature and principle of my invention.

Having thus described my invention, what I claim and desire to secure by Letters Patent is:

1. A prolonged release analgesic tablet comprising a plurality of finely divided hard particles of an analgesic drug, each particle being individually coated with a permeable solution-resistant coating, said particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug.

2. A prolonged release analgesic tablet comprising a plurality of finely divided hard particles of an analgesic drug, each particle being individually coated with a permeable solution-resistant coating, and particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug intermixed with a small amount of an inert material.

3. A prolonged release analgesic tablet comprising a plurality of finely divided hard particles of an analgesic drug, each particle being individually coated with a permeable solution-resistant coating, said particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug intermixed with a small amount of starch.

4. A prolonged analgesic tablet comprising a plurality of finely divided discrete particles of an analgesic drug, each of said particles being individually coated with a permeable solution-resistant coating, said coated particles being carried by and being randomly dispersed throughout a matrix consisting predominantly of an analgesic drug.

5. A prolonged analgesic tablet comprising a plurality of finely divided discrete particles of an analgesic drug, each of said particles being individually coated with a permeable solution-resistant coating, said coated particles being carried by and being randomly dispersed throughout a matrix consisting predominantly of an analgesic drug intermixed with a small amount of an inert material.

6. A prolonged analgesic tablet comprising a plurality of finely divided discrete particles of an analgesic drug, each of said particles being individually coated with a permeable solution-resistant coating, said coated particles being carried by and being randomly dispersed throughout a matrix consisting predominantly of an analgesic drug intermixed with a small amount of starch.

7. A prolonged release analgesic tablet comprising a plurality of finely divided discrete particles of an analgesic drug, each particle being individually coated with a permeable solution-resistant coating, said coating being a member of the class consisting of shellac and stearic acid, shellac and palmitic acid, shellac and linoleic acid, shellac and calcium stearate, shellac and a dry non-toxic hydrophobic powder, cellulose acetate phthalate and stearic acid, cellulose acetate phthalate and palmitic acid, cellulose acetate phthalate and linoleic acid, cellulose acetate phthalate and calcium stearate, cellulose acetate phthalate and a dry non-toxic hydrophobic powder, ethyl cellulose and stearic acid, ethyl cellulose and palmitic acid, ethyl cellulose and linoleic acid, ethyl cellulose and calcium stearate, ethyl cellulose and a dry non-toxic hydrophobic powder, zein and stearic acid, zein and palmitic acid, zein and linoleic acid, zein and calcium stearate, and zein and a dry non-toxic hydrophobic powder, said particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug.

8. A prolonged release analgesic tablet comprising a plurality of finely divided hard particles of an analgesic drug, each particle being individually coated with a permeable solution-resistant coating consisting of shellac and stearic acid, said particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug.

9. A prolonged release analgesic tablet comprising a

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28. The method of releasing an analgesic drug in the blood stream of a person over a prolonged period of time, said method comprising ingestion of a plurality of finely divided particles of the analgesic drug in tablet form, each particle being individually coated with a permeable solution-resistant coating, said coating being a member of the class consisting of shellac and stearic acid, shellac and palmitic acid, shellac and linoleic acid, shellac and calcium stearate, shellac and a dry non-toxic hydrophobic powder, cellulose acetate phthalate and stearic acid, cellulose acetate phthalate and palmitic acid, cellulose acetate phthalate and linoleic acid, cellulose acetate phthalate and calcium stearate, cellulose acetate phthalate and a dry non-toxic hydrophobic powder, ethyl cellulose and stearic acid, ethyl cellulose and palmitic acid, ethyl cellulose and linoleic acid, ethyl cellulose and calcium stearate, ethyl cellulose and a dry non-toxic hydrophobic

powder, zein and stearic acid, zein and palmitic acid, zein and linoleic acid, zein and calcium stearate, and zein and a dry non-toxic hydrophobic powder, said particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug.

29. The method of releasing an analgesic drug in the blood stream of a person over a prolonged period of time, said method comprising ingestion of a plurality of finely divided particles of the analgesic drug in tablet form, each particle being individually coated with a permeable solution-resistant coating, said coating being a member of the class consisting of shellac and stearic acid, shellac and palmitic acid, shellac and linoleic acid, shellac and calcium stearate, shellac and a dry non-toxic hydrophobic powder, cellulose acetate phthalate and stearic acid, cellulose acetate phthalate and palmitic acid, cellulose acetate phthalate and linoleic acid, cellulose acetate phthalate and calcium stearate, cellulose acetate phthalate and a dry non-toxic hydrophobic powder, ethyl cellulose and stearic acid, ethyl cellulose and palmitic acid, ethyl cellulose and linoleic acid, ethyl cellulose and calcium stearate, ethyl cellulose and a dry non-toxic hydrophobic powder, zein and stearic acid, zein and palmitic acid, zein and linoleic acid, zein and calcium stearate, and zein and a dry non-toxic hydrophobic powder, said particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug intermixed with a small amount of inert material.

30. The method of releasing an analgesic drug in the blood stream of a person over a prolonged period of time, said method comprising ingestion of a plurality of finely divided particles of the analgesic drug in tablet form, each particle being individually coated with a permeable solution-resistant coating, said coating being a member of the class consisting of shellac and stearic acid, shellac and

palmitic acid, shellac and linoleic acid, shellac and calcium stearate, shellac and a dry non-toxic hydrophobic powder, cellulose acetate phthalate and stearic acid, cellulose acetate phthalate and palmitic acid, cellulose acetate phthalate and linoleic acid, cellulose acetate phthalate and calcium stearate, cellulose acetate phthalate and a dry non-toxic hydrophobic powder, ethyl cellulose and stearic acid, ethyl cellulose and palmitic acid, ethyl cellulose and linoleic acid, ethyl cellulose and calcium stearate, ethyl cellulose and a dry non-toxic hydrophobic powder, zein and stearic acid, zein and palmitic acid, zein and linoleic acid, zein and calcium stearate, and zein and a dry non-toxic hydrophobic powder, said particles being dispersed throughout a compressed matrix consisting predominantly of the same analgesic drug.

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