United States Patent Office 3,078,216 Patented Feb. 19, 1963

3,078,216

PROLONGED RELEASE ORAL PHARMACEUTICAL PREPARATIONS

Martin Greif, Bronx, N.Y., assignor to American Cyanamid Company, New York, N.Y., a corporation of Maine

No Drawing. Filed Apr. 11, 1961, Ser. No. 102,098
20 Claims. (Cl. 167—82)

This invention relates to pharmaceutical preparations providing a prolonged release of the medicament.

The administration of drugs orally has presented a serious problem. In very many cases, it is necessary for the drugs to be absorbed from the gastro-intestinal tract into the bloodstream. When a drug is given by mouth, the assimilation is normally fairly rapid and presently the level in the blood reaches a maximum. Then it declines as the drug is excreted or otherwise removed from the bloodstream. The blood level falls and finally reaches a level so low that it is no longer effective and it is then necessary to take, orally, another dose. The peaks and valleys thus caused in blood level have several disadvantages. One is the necessity of taking frequent small doses in order to maintain a therapeutically desired blood level. This is awkward and in some instances presents a serious problem as the patient has to be awakened during the night to take further doses. A second drawback is that in order to have a therapeutically useful blood level, each dose has to be fairly large so that after the blood level peak is reached and begins to subside, there will still remain sufficient of the drug to be useful. The necessity for large doses brings with it some dangers. Nearly all drugs have some undesirable or toxic side effects when administered in sufficiently large doses and the large initial doses may be unacceptable or may produce some undesirable side reactions.

For the reasons set out above, various attempts have been made to slow up the release of drugs taken orally, producing a so-called prolonged release product. Sometimes it is felt desirable only to slow up the release sufficiently so that it extends over a long enough time to even out the more marked peaks and valleys in blood level. In other cases, it may be desirable to prevent assimilation from the stomach but to permit assimilation from the intestine. Various coatings have been developed, the so-called enteric coatings, to achieve this purpose. The present invention constitutes an improved method of prolonging the release of pharmaceuticals taken orally. In the past, a number of methods have been used. A common one is to incorporate a number of so-called "seeds" of drugs in a single capsule. These seeds are small, spherical nuclei of inert material, coated with the drug and finally over-coated with varying amounts of slowly digestible fats with or without dispersible waxes which act as plasticizers. In the digestive tract, the seeds with no wax coating dissolve rapidly and produce the desired initial blood level. Those with coatings more or less thick digest slowly and gradually set the drug free. There is a serious problem in obtaining the right proportion of seeds with the right thicknesses of digestible coatings and the fact that the medicament is coated on inert carriers reduces its content in a particular capsule. With drugs that are used in very small amounts, this latter fact may not be serious, but where the dose is to be substantial, a much larger capsule is needed or it is necessary to ingest a larger number of capsules. It is also relatively expensive to produce the seeds with the varying coatings and this solution to the problem, though useful, leaves much to be desired.

Another method lies in incorporating the desired medicament in a molten medium of the fats and/or waxes

which are slowly digestible or dispersible. The mixture is then cooled forming a cake which is broken up into suitable granules and tabletted or encapsulated. This method gives only an average rate of release.

In the case of drugs capable of adsorption on ion exchange resins, the drugs can be adsorbed on such resins. Alternately, many drugs can be incorporated with plastics from which the digestive juices grandually set free or leach out the medicament. These solutions are not useful where it is necessary to have some of the drug released rapidly but give only an average, slow release. They are far inferior to the seed method and involve just as much or more waste volume of inert material. Finally, another technique has involved the formation of a complex salt of the drug which is not assimilated in its complexed form but is slowly hydrolyzed in the digestive tract and is set free gradually. This is applicable, of course, only to certain drugs that are capable of complexing and again it does not provide for rapid release of a portion of the drug to build up rapidly a satisfactory blood level, the so-called "attack dose." The present invention solves the problems of prolonged release with complete flexibility in rate and with the possibility of making available sufficient drug for rapid release to give a satisfactory attack dose.

Essentially, the present invention involves granulating the drug, or if it is available in powder form already providing a definite range of particle sizes between predetermined limits, using it as such. These mixtures of granules or particles of different sizes are then coated with a slowly digestible coating of waxes and/or fats. I have found, surprisingly, that the thickness of coating varies directly with the size of the particle. The small particles have very thin coatings and the larger particles have progressively thicker coatings in direct proportion to the particle size. After coating, the particles of random sizes or of a predetermined size range, with the corresponding variation in coating thicknesses, are then assembled into the final dosage unit. They may, for example, be filled into a capsule or they may be compressed into a tablet. If desired, the capsule or the tablet may be provided with an enteric coating if it is desired that release of the drug take place only in the intestinal tract, which is of importance with certain drugs which are destroyed by the stomach acids. An accurately reproducible release rate can be obtained exactly suited for the particular drug in question. For example, a slowly excreted drug may have a relatively large proportion of very small particles which release their medicament rapidly to produce the necessary attack dose. In the case of other drugs which are very rapidly excreted or removed from the bloodstream, the proportion of very small particles is decreased so that the release is more uniform with time. Inasmuch as the rate of release from any particle or granule is determined by the wax content of the coating, which is a function of particle size, it is possible to produce tablets, capsules, or other dosage forms having exactly the desired prolonged release characteristics. At the same time, there is relatively little inert material, such as the cores of the so-called seeds described above or the plastic or resin used in some of the other methods. Except for the dispersible or digestible coating itself, the tablet or capsule can contain the drug but little diluted with inert material, such inert material, in the form of binder, rarely exceeding 5% of the total. It is thus possible in a small tablet or capsule to accommodate a dose that would require a much bigger capsule or tablet or many small ones in the case of other methods in which there is a large amount of inert material present.

While the present invention is not limited to any particular process, in a more specific aspect an improved

process is also included. According to this process, fats and/or waxes for the coating are dissolved in a volatile solvent which need only be of sufficiently low toxicity so that minute residues do not present any toxic problem. One of the best of such solvents is 1,1,1-trichloroethane, but the invention is not in any way limited to this particular solvent. The particles of non-uniform size are then coated by conventional means such as by spraying the solution of fats or waxes onto the particles. At the same time, a sufficient amount of air is passed through the equipment so that the solvent rapidly volatilizes producing a firm coating almost instantly. The temperature of the individual particles should be between that at which the coating material is a hard solid and that at which it is liquid. This is important because if the temperature is too low, non-continuous coating may result which may to a greater or lesser extent defeat the object of the prolonged release by allowing digestive fluids to penetrate through the discontinuities. It is equally undesirable to maintain the temperature high enough so that the fats and waxes remain as liquids on the granules or particles. This can result in sticking or non-uniform coating. The temperature will vary somewhat with the different waxes and fats used in coating. Typically, the temperature may be from about 35° to about 40° C. It should be noted that the air passing through, which volatilizes the solvent, will ordinarily be maintained at a somewhat higher temperature, for example, from about 50° to about 55° C., than that desired on the surface of the particles because of the marked cooling effect resulting from the rapid evaporation of the solvent. The temperature of the air is therefore adjusted to a sufficiently higher temperature than that desired on the surface of the particles or granules. It is not possible to specify exact air temperatures to be used in all cases because this is affected by the volume of air. A larger volume of air will be at a lower temperature than a smaller volume of air. Once the air flow has been established and the temperature determined, it remains constant and an efficient continuous manufacturing process results producing particles which are not cemented to gether by too liquid a coating and which have a smooth, continuous coating over their entire surface. The particles may then be tabletted either with or without other constituents or incorporated in capsules by conventional means.

The fats and waxes used to slow up release are the same fats and waxes which have been used heretofore in similar preparations. As far as the particular coating materials are concerned, the present invention does not change prior practice. The fact that well known materials are used is an advantage of the present invention as it is not necessary to learn new techniques for handling new materials. Typical coating materials are high melting fats such as glyceryl monostearate or glyceryl distearate, waxes like beeswax, or waxy higher alcohols, and the like. Usually, carnauba wax is unsuitable alone but in blends it permits an accurate degree of hardening, especially with drugs having emulsifying properties. Inasmuch as the present invention does not involve the development of new coating materials, it is not limited to any particular ones and any slowly dispersible waxes or digestible hard fats may be used.

Within the range of permissible toxicities, any volatile solvent for the fats and waxes may be used. In addition to the 1,1,1-trichlorethane mentioned above, the following are suitable solvents: chloroform, carbon tetrachloride, other volatile halogenated hydrocarbons, petroleum ether, etc.

The invention requires definite, though fairly wide, limits of particle size of the granules or particles to be coated. The general range is from U.S. standard 12 mesh to U.S. standard 80 mesh. Particles coarser than 12 mesh will not encapsulate or tablet satisfactorily. Any considerable amount of particles finer than 80 mesh tend to clump. Of course, minute amounts of fines resulting from an occasional broken granule can be tolerated but any significant proportion of particles finer than 80 mesh defeats the purpose of the present invention. In the claims, the term "substantially all being from 12 mesh to 80 mesh" is intended to cover this situation and to have no other meaning. In the case of citric acid in which the crystals are dense, it is desirable to use a slightly narrower range of from U.S. standard 16 mesh to U.S. standard 60 mesh. In fact, even with bulkier materials which can be coated up to about 80 mesh, the preferred particle size range is also from 16 mesh to 60 mesh as this gives products of optimum properties.

It should be reiterated that the essence of the present invention lies in the non-uniform coating of non-uniform particle size material in a single coating operation. It should not be confused with a physical mixture of uncoated and uniformly coated material. The uncoated material does, in fact, give a rapid initial release, the so-called "attack dose", but there is not the uniform release thereafter over a period of hours, which is the important advantage of the present invention.

The invention will be described in greater detail in conjunction with the following specific examples. All parts are by weight unless otherwise specified.

Example 1

The powdered anticholinergic agent, tridihexethyl iodide (3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol ethiodide), was granulated as follows:

	Grams
Tridihexethyl iodide	1500
Phenobarbital	900
Lactose	1050
Dicalcium phosphate	1050

The powders were granulated in a Hobart mixer using a mixture of 350 ml. of corn syrup and 300 ml. of a 20% solution of gum acacia in water. The moist mass was then screened on a Stokes oscillating granulator through a 10 mesh screen. The damp granules were then dried at 135° F. in a warm air oven and rescreened through a 16 mesh screen, fines being removed by a 40 mesh screen.

This 16/40 mesh granulation was then coated in a conventional tablet coating pan. A wax coating solution containing 2700 grams of glyceryl monostearate (substantially glycerine free) and 300 grams of white beeswax were dissolved in 10,500 ml. of 1,1,1-trichlorethane. A small amount, 0.75 gram, of D and C Violet Dye No. 2 was added. The coating mixture was heated and held at 60–70° C. and was sprayed onto the granules from a conventional paint spray gun at 10–15 pounds per square inch pressure, 1.5–2.0 cubic feet per minute air flow, and 0.04 inch fluid nozzle orifice. The spray pattern was cone shaped. Spraying was continued until the total wax content reached 44% which required approximately four hours. During the spraying process, a cycle was used whereby the granules were sprayed for ten minutes and then were tumbled in a stream of warm air adjusted to maintain the temperature of the granules at 35–40° C. for ten minutes. After spraying was completed, the granules were tumbled in a stream of warm air for an additional fifteen minutes followed by tumbling in air at room temperature for thirty minutes. The final coated granules were then sifted through a No. 12 mesh screen to remove all clumped granules. The amount of clumped granules constituted less than 2% of the entire batch.

The coated granules were lubricated with a 1% magnesium stearate and tabletted on a standard Stokes tabletting machine with 11/32 inch flat face bevel tablet punches. The average gross tablet weight was approximately 200 milligrams and the final tablet had a honeycomb like physical appearance with an attractive two-tone color of light and dark violet. Release was determined

by a standard method using artificial gastric juice and intestinal fluid. After one hour, one-half of the gastric juice was replaced. After two hours and after three hours, all of the fluid was replaced with artificial intestinal fluid. This was repeated again after five and seven hours. At periodic intervals, a sample was removed and the percent of medicament released was determined. The results were as follows:

1 hour	14% released
2.5 hours	29% released
4.25 hours	62% released
6 hours	82% released
8 hours	98% released

The above indicates that satisfactory blood levels can be maintained for about ten to twelve hours with a single dose of medicament. Ordinarily, the medicament would be given in one or two tablets, three or four times per day. Comparable blood levels were obtained by the tablet of the present invention with a single does of one or two tablets upon arising.

To determine the relative amount of coating, another batch of granules with an average wax content of 29.7% was classified through suitable sieves and the wax contents of the various fractions were determined. The results were as follows:

20/30 mesh	22.1% wax
18/20 mesh	33.4% wax
16/18 mesh	34.8% wax.

Example 2

Six thousand grams of tetracycline was granulated with a 25% solution of corn syrup by the method described in Example 1. It was then screened on the oscillating granulator through a 12 mesh screen and dried with warm air at 140° F. After drying, the granules were rescreened through a 16 mesh screen. The fines were removed by sifting on a 60 mesh screen.

Five thousand grams of the 16/60 mesh granulation was coated as described in Example 1 using a coating solution with 18.9% of glyceryl monostearate, 2.1% of white beeswax and the balance 1,1,1-trichlorethane. Clumps were separated by sieving through a 12 mesh screen and a portion of the sifted granules were tabletted on a Stokes machine with 13/32 inch FFB punch to an average tablet gross weight of 463 milligrams.

The tablets were then submitted to the digestion test as described in Example 1. The release was 18% after one hour and 80% after seven hours.

The balance of the granules were encapsulated in the conventional manner. The resulting capsules were submitted to a standard release rate test and showed satisfactory continual release for a period of ten hours.

Example 3

18,000 gm. of the diuretic, acetazolamide(2-acetylamino-1,3,4-thiadiazole-5-sulfonamide), was granulated with 3900 ml. of a 15% gelatin solution. The material was then screened through a Fitzpatrick comminuting machine, using a No. 4A screen at 1000 r.p.m. The resulting granules were dried in a warm air oven at 140° F. for 15 hours. These granules were then sifted to obtain those finer than No. 16 mesh. The balance of the granules were forced through a No. 16 screen on an oscillating granulator. The fines were removed through a No. 60 mesh screen. All 16/60 mesh granules were combined.

One third of the above granules were set aside and the remainder coated in two phases so as to contain 5% and 10% respectively of the following wax mixture:

	Parts
Glyceryl monostearate	9
White beeswax	1

The wax was applied as a 30% solution in 1,1,1-trichlorethane, as in Example 1. The coated granules were sifted through a No. 12 mesh screen to remove the clumps. The three phases were then mixed in equal proportions and encapsulated in the conventional manner.

Another sample of 10% wax coated granules was compressed into tablets.

When tested, both products showed a sustained release for approximately 9 hours.

Example 4

A granulation was prepared as follows:

	Gm.
Tridihexethyl chloride	5625
Hyoscyamine hydrobromide	35.01
Hyoscine hydrobromide	2.205
Atropine sulfate	6.555
Dicalcium phosphate, USP	5582
Acetazolamide	37,500

All of the powders except the acetazolamide, were mixed in a pony mixer and then screened on a Fitzpatrick comminuting machine, using a No. 80 screen, at 2200 r.p.m. The resulting powder mix was granulated as follows.

The powders were granulated with the following solution:

Ethylcellulose, 50 cps	gm.	30
1,1,1-trichlorethane	ml.	3000
Isopropanol	ml.	2200

This mass was then screened through an oscillating granulator using a No. 8 screen. The granules were dried at 120° F. for five hours and then hand screened through a No. 16 screen.

The fines were removed by shaking through a No. 60 screen.

A portion of the resulting granules were withheld as the immediate release fraction and the balance coated as in Example 3 in three phases, each respective phase containing about 15%, 35% and 50% of the coating materials.

The resulting granules, when mixed as follows, gave a release curve of approximately nine hours duration.

	Percent
Uncoated granules	20
15% coated granules	15
35% coated granules	10
50% coated granules	55

The above mixture of granules was then mixed with the acetazolamide powder in the ratio of one part granules to two parts powder, and encapsulated in the conventional manner. The fill was equal to 400 mg., net, of the powder-granule mixture.

Exampe 5

A bath of granules was prepared exactly as in Example 4, except that the coating material consisted of:

	Parts
Glyceryl monostearate	4.5
Glyceryl distearate	4.5
White beeswax	1

The same prolonged release was obtained as in Example 4.

Example 6

Same as Example 4 except that the coating material consisted of:

	Parts
Glyceryl monostearate	6
Carnauba wax	3
White beeswax	1

The release time was slightly longer than in Example 4.

Example 7

A granulation was prepared as follows:

Tridihexethyl chloride	kg.	10
Dicalcium phosphate, USP	kg.	10
1,1,1-trichloroethane	l.	3.75
Isopropanol, 99% N.F	l.	3.75

The two powders were mixed by barrel rolling for 30 minutes. The resulting blend was screened through a Fitzpatrick comminuting machine using a No. 1 screen, at 5000 r.p.m. and barrel rolled for an additional 30 minutes. The resulting powder was then granulated in a Stokes Model 21H powder mixer using the mixture of 3.75 liters of isopropanol and 3.75 liters of 1,1,1-trichloroethane. The resulting lumpy material was placed directly on trays and dried for 16 hours at 40° C. followed by 2 hours at 50° C. in a forced air drying cabinet. The dried lumps were then sifted on a No. 16 screen to remove the granules and the remaining material was forced through a No. 16 screen on a Stokes oscillating granulator. All of the 16 mesh material was combined and lubricated with 1% magnesium stearate and sifted on a No. 60 mesh screen to remove the finer particles. The following fractions were obtained:

	Kg.
16/60 mesh granules	14
Minus 60 mesh powder	6

Six kg. of the 16/60 mesh granules was placed in a 16 inch coating pan and coated with fully hydrogenated tallow to a content of 18.2% fat. The fatty material was applied as a 33% solution in 1,1,1-trichloroethane, utilizing the standard spraying technique described in Example 1.

The coated granules were allowed to air dry on trays at 0–10% relative humidity for 16 hours.

A screen analysis of the coated granules was performed with the following results:

Size:	Percent
14/16 mesh	1.4
16/20 mesh	12.0
20/30 mesh	40.3
30/40 mesh	21.8
40/60 mesh	24.0
60/80 mesh	0.5
Through No. 80 mesh	0
Total	100

A blend was prepared of 5850 grams of the 16/60 mesh granules with 1540 grams of the 60/80 mesh granules. The drug was mixed with 3500 grams of cottonseed flour, 210 grams magnesium stearate, and 105 grams propylene glycol. The mix was then encapsulated in gelatin capsules with an average fill weight of 321 mg. per capsule, corresponding to a content of 81 mg. per capsule of the drug. It should be noted that the drug granules contain slightly over 25% fat. The capsules gave the same desirable release rate as described in the preceding examples.

Example 8

A methoxypromazine (2-methoxy-10-(3'-dimethylaminopropyl)phenothiazine) maleate granulation was prepared as follows:

	Gm.
Methoxypromazine maleate	4000
Dicalcium phosphate	3000
Sucrose	1000
Powdered acacia	400

The powders were blended and screened through a Fitzpatrick comminuting machine at 5000 r.p.m., using a No. 1 screen. This powder was granulated with a 35% corn syrup solution (a total of 1500 ml. of solution was used). The lumpy material was dried in a circulating air cabinet at 120° F. for 16 hours and then screened through a No. 16 mesh screen on an oscillating granulator. The fines were removed through a No. 60 mesh screen. 6500 gm. of the 16/60 mesh granules were then coated as in Example 7 using a solution of:

Glyceryl monostearate	gm.	1170
White beeswax	gm.	130
Trichloroethane	ml.	4000

The coated granules were sifted on a No. 12 mesh screen to remove clumps. 1500 gm. of 12/60 mesh uncoated granules were mixed with the coated granules and then assayed for methoxypromazine maleate. The granules were encapsulated in a conventional manner. A release rate test was performed and the observed curve provided a sustained release of medicament for 11 hours.

Example 9

Five hundred grams of granular calcium cyanamid was screened through a No. 16 mesh screen and then sifted on a No. 60 mesh screen to remove the fines. 410 gm. of the 16/60 mesh granules were obtained and coated in an 8 inch coating pan with the following solution:

	Gm.
Glyceryl monostearate	45
White beeswax	5
1,1,1-trichloroethane	175

The resulting granules were sifted on a No. 12 mesh screen to remove clumps.

445 gm. of the thus coated granules were intimately mixed with 115 gm. of uncoated granular calcium cyanamid and encapsulated in a conventional manner. On the basis of tests, there was a sustained release of medicament for a period of 12 hours.

Example 10

A granulation of triamcinolone free alcohol was prepared according to the following procedure:

	Gm.
Triamcinolone free alcohol	30
Dicalcium phosphate, USP	870

The powders were blended and screened through a No. 20 mesh screen. Granulation was accomplished with an aqueous solution consisting of 85 gm. sucrose and 30 gm. acacia in 200 ml. of solution. The granules were dried and screened as in Example 1.

Five hundred gm. of the 16/40 mesh granules were coated with a solution consisting of 45 gm. glyceryl monostearate and 5 gm. white beeswax in 150 ml. of total solution, using the method outlined in Example 1.

The resulting granules were mixed with uncoated granules in the ratio of 4 parts coated granules to 1 part uncoated granules, and then encapsulated.

The resulting product produced a sustained release of triamcinolone for a period of approximately 10 hours.

Example 11

The procedure of Example 10 was repeated except that the triamcinolone free alcohol was replaced with 60 gm. of the antihistamine, chlorpheniramine maleate. The resulting product, when tested, showed a sustained release over a 10 hour period.

Example 12

A ferrous fumarate granulation was prepared as follows:

Ferrous fumarate powder	gm.	25000
Corn syrup, 50% aq. soln	ml.	7800

The powder was granulated with the solution, by slowly adding the latter to the former with slow agitation in a Stokes mixer. The resulting mass was dried in a cabinet, on trays, with circulating air at 120° C. for 16 hours. Screening was accomplished with a Stokes oscillating

granulator, using a No. 16 mesh screen. The fines were removed by sifting on a No. 60 mesh screen.

Of the resulting granules, 10,000 gm. was coated with a solution containing 1090 gm. glyceryl monostearate and 110 gm. white beeswax in 3600 ml. of total solution, using the method outlined in Example 1.

The resulting granules were mixed with uncoated granules of ferrous fumarate in a ratio of 4 parts coated granules to 1 part uncoated granules and then encapsulated.

The resulting capsules provided a sustained release of iron for a period of 10–12 hours.

Example 13

A granulation was prepared as follows:

	Gm.
Salicylamide	3080
N-acetyl-p-aminophenol	2200
Caffeine	440
Acacia powder	286

The powders were blended and screened. Granulation was achieved using 1500 ml. of a 35% aqueous solution of corn syrup. The mass was dried at 100° F. for 25 hours and then screened through a No. 16 mesh screen using a Stokes oscillating granulator. The resulting granulation was sifted on a No. 60 mesh screen to remove the fines.

4200 gm. of the resulting 16/60 mesh granules were coated as in Example 1, using a solution consisting of 450 gm. glyceryl monostearate and 50 gm. white beeswax in 1200 ml. of hot (65° C.) 1,1,1-trichloroethane.

The resulting coated granules were sifted through a No. 12 screen to remove the clumps.

4500 gm. of the thus coated granules were blended with 1200 gm. of uncoated granules and the material was encapsulated at 475 mg. per capsule. The resulting product produced a sustained release of medicaments for a period of 10 hours.

Example 14

A granulation of trihexyphenidyl (3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride) was prepared by the procedure of Example 10, starting by blending the following powders:

	Gm.
Trihexyphenidyl	30
Dicalcium phosphate, USP	870

The resulting product produced a sustained release of trihexyphenidyl for a period of approximately 10 hours.

Example 15

A granulation of mephenoxalone (5-(o-methoxyphenoxymethyl)-2-oxazolidinone) was prepared, starting by blending the following powders:

	Gm.
Mephenoxalone	10,000
Acacia powder	500

The powders were blended and screened. Granulation was achieved using 4400 ml. of a 50% aqueous solution of corn syrup. The resulting mass was dried at 110° F. for 20 hours, followed by four hours at 150° F. The dried granulation was then milled through a Fitzpatrick comminuting machine, using a No. 2 screen, at 2200 r.p.m.; and then was screened through a No. 12 mesh screen. The resulting granulation was sifted on a No. 40 mesh screen to remove the fines.

Six thousand grams of this 12/40 mesh granulation was then coated in a conventional 18 inch coating pan. A wax coating solution containing 525 g. of glyceryl monostearate and 58 g. of white beeswax dissolved in 1950 ml. of 1,1,1-trichloroethane was prepared. A small amount, 0.2 g., of D & C Yellow Dye No. 11 was added. The wax coating solution was heated and held at 60° C. and was sprayed onto the granules from a conventional paint spray gun as in Example 1. During the spraying process, a cycle was used whereby the granules were sprayed for 5 minutes at 100 ml. per minute and then were tumbled in a stream of warm air at 50° C. for 5 minutes. This alternating cycle was continued until all of the coating solution had been consumed.

A blend was prepared of 1315 g. of the 12/40 mesh coated granules with 293 g. of the 12/40 mesh uncoated granules and 8 g. of magnesium stearate powder. The ingredients were blended by tumbling in a drum for 10 minutes and then were encapsulated in gelatin capsules in a conventional manner with an average fill weight of 500 mg. per capsule. A release rate test was performed which demonstrated a sustained release of medicament over a period of approximately 10 hours.

Example 16

A granulation of the diuretic, acetazolamide, was prepared as follows:

Acetazolamide	kg.	150
Granular gelatin	kg.	3.85
Distilled water	liters	44

The gelatin was dissolved in the water and the resulting solution was heated to 65° C. The acetazolamide powder was granulated with the gelatin solution in a conventional manner and then dried at 140° F. for 8 hours. The resulting granulation was then milled through a Fitzpatrick comminuting machine, using a No. 4A screen, at 1000 r.p.m.; and then was screened through a No. 12 mesh screen. The resulting granules were sifted on a No. 60 mesh screen to remove the fines.

On hundred kilograms of this 12/60 mesh granulation was then coated in a conventional coating pan. A wax coating solution containing 10.125 kg. of glyceryl monostearate and 1.125 kg. of white beeswax dissolved in 37.5 liters of 1,1,1-trichloroethane was prepared. To this solution was added 3 g. of D & C. Yellow Dye No. 11 and 1.5 g. of D & C Red Dye No. 17. The wax coating solution was heated and held at 60° C. and was sprayed onto the granules from a conventional paint spray gun as in Example 1. During the spraying process, a cycle was used whereby the granules were sprayed for 5 minutes at 750 ml. per minute and then were tumbled in a stream of warm air at 50° C. for 5 minutes. This alternating cycle was continued until all of the coating solution had been consumed.

One hundred kilograms of the thus coated 12/60 mesh granules were intimately mixed with 30 kg. of uncoated 12/60 mesh acetazolamide, 1.3 kg. of talc, and 0.65 kg. of magnesium stearate. The ingredients were blended by barrel rolling and then encapsulated in gelatin capsules in a conventional manner with an average fill weight of 550 mg. per capsule. A release rate test was performed which demonstrated a sustained release of medicament over a period of approximately 10 hours..

Example 17

A blend was prepared of 10,000 g. of coated ferrous fumarate granules (prepared as in Example 12), 6,950 g. of a granular fecal softener (72% by weight of dioctyl sodium sulfosuccinate absorbed on 28% by weight of fumed silica aerogel), 215 g. of magnesium stearate, and 254 g. of dried corn starch. Blending was accomplished by barrel rolling for 45 minutes. The resulting blend was encapsulated in gelatin capsules in a conventional manner with an average fill weight of 350 mg. per capsule. When tested, the capsules demonstrated a sustained release of iron over a period of approximately 4 hours.

Example 18

A granulation of meprobamate (2-methyl-2-n-propyl-1,3-propanediol dicarbamate) was prepared as follows:

	Gm.
Meprobamate powder	400,000
Acacia powder	15,000
Corn syrup, U.S.P	40,000
Distilled water, q.s.ad. 60,000 ml.	

The granulating solution was prepared by heating the distilled water to 60° C. and adding the acacia and corn syrup with rapid agitation until an opalescent solution was obtained. The meprobamate powder was granulated with the granulating solution in a conventional manner and then dried. The resulting granulation was then milled through a Fitzpatrick comminuting machine, using a No. 4A screen, at 1,000 r.p.m.; and then was screened through a No. 16 mesh screen. The resulting granules were sifted on a No. 60 mesh screen to remove the fines.

Eighty kilograms of this 16/60 mesh granulation was then coated in a conventional coating pan. A wax coating solution containing 12,600 g. of glyceryl monostearate and 1,400 g. of white beeswax dissolved in 35 liters of 1,1,1-trichloroethane was prepared. The wax coating solution was heated and held at 55°–65° C. and was sprayed onto the granules from a conventional paint spray gun as in Example 1. During the spraying process, a cycle was used whereby the granules were sprayed for 5 minutes at 750 ml. per minute and then were tumbled in a stream of warm air at 50° C. for 5 minutes. This alternating cycle was continued until all of the coating solution had been consumed.

A blend was prepared of 50 kg. of the 16/60 mesh coated granules with 21 kg. of the 16/60 mesh uncoated granules, 700 g. of magnesium stearate, and 700 g. of dried corn starch. The ingredients were blended by tumbling in a drum for 10 minutes and then were encapsulated in gelatin capsules in a conventional manner with an average fill weight of 500 mg. per capsule. When tested, the capsules demonstrated a sustained release of meprobamate over a period of approximately 10 hours.

Example 19

A granulation was prepared; starting by blending the following powders:

	G.
Dextroamphetamine sulfate	30,000
Dibasic calcium phosphate	44,000
Acacia powder	3,700

The powders were blended in a Stokes mixer for 30 minutes. Granulation was achieved using 12,000 ml. of a 50% aqueous solution of corn syrup, and the resulting mass was dried at 110° F. for 20 hours. The dried granulation was then milled through a Fitzpatrick comminuting machine, using a No. 2 screen, at 2,200 r.p.m.; and then was screened through a No. 16 mesh screen. The resulting granulation was sifted on a No. 40 mesh screen to remove the fines.

Fifty-five kilograms of this 16/40 mesh granulation was then coated in a conventional coating pan. A wax coating solution containing 13,950 g. of glyceryl monostearate and 1,550 g. of white beeswax dissolved in 40 liters of 1,1,1-trichloroethane was prepared. The wax coating solution was heated and held at 55°–65° C. and was sprayed onto the granules from a conventional paint spray gun as in Example 1. During the spraying process, a cycle was used whereby the granules were sprayed for 5 minutes at 750 ml. per minute and then were tumbled in a stream of warm air at 50° C. for 5 minutes. This alternating cycle was continued until all of the coating solution had been consumed.

A blend was prepared of 235,930 g. of coated meprobamate granules (prepared as in Example 18), 133,820 g. of uncoated meprobamate granules (also prepared as in Example 18), 38,190 g. of coated dextroamphetamine sulfate, 14,220 g. of uncoated dextroamphetamine sulfate, 5,000 g. of fumed silica aerogel, 2,500 g. of dried corn starch, and 31,120 g. of sugar-starch filler. The ingredients were blended by barrel rolling and then encapsulated in gelatin capsules in a conventional manner with an average fill weight of 460 mg. per capsule. A release rate test was performed which demonstrated a sustained release of both meprobamate and dextroamphetamine over a period of approximately 10 hours.

This application is a continuation-in-part of my copending application Serial No. 812,794, filed May 13, 1959, now abandoned.

What is claimed is:

1. An oral pharmaceutical preparation having a prolonged release comprising a plurality of medicament granules, substantially all being from 12 mesh to 80 mesh, each coated with a layer of water insoluble, partly digestible hydrophobic material, the thickness of coating varying directly with particle size whereby in oral use the very fine granules rapidly release their medicament and the granules of increasing size release their medicament more and more slowly.

2. A product according to claim 1 in which the medicament comprises tetracycline.

3. A product according to claim 1 in which the medicament comprises tridihexethyl halide.

4. A product according to claim 1 in which the medicament comprises tridihexethyl halide and phenobarbital.

5. A product according to claim 1 in which the medicament comprises tridihexethyl halide and mixed belladonna alkaloids.

6. A product according to claim 1 in which the medicament comprises 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide.

7. A product according to claim 1 in which the medicament comprises 5-(o-methoxyphenoxymethyl)-2-oxazolidinone.

8. A product according to claim 1 in which the medicament comprises 2-methyl-2-n-propyl-1,3-propanediol dicarbamate.

9. A product according to claim 1 in which the medicament comprises 2-methyl-2-n-propyl-1,3-propanediol dicarbamate and dextroamphetamine sulfate.

10. A product according to claim 1 in which the medicament comprises ferrous fumarate.

11. A product according to claim 1 in which the medicament comprises ferrous fumarate and a fecal softener.

12. A product according to claim 1 in which the medicament comprises calcium cyanamide.

13. A product according to claim 1 in which the medicament comprises trihexyphenidyl.

14. A product according to claim 1 in which the medicament comprises triamcinolone free alcohol.

15. A product according to claim 1 in which the medicament comprises methoxypromazine maleate.

16. An oral pharmaceutical preparation having a prolonged release comprising a plurality of medicament granules, substantially all being from 16 mesh to 60 mesh, each coated with a layer of water insoluble, partly digestible hydrophobic material, the thickness of coating varying directly with particle size whereby in oral use the very fine granules rapidly release their medicament and the granules of increasing size release their medicament more and more slowly.

17. A method of making oral pharmaceutical preparations having a prolonged medicament release which comprises sizing granules of medicament to produce a mixture having granules substantially all being from 12 mesh to 80 mesh, and spraying them with a solution in a volatile solvent of water insoluble, partially digestible hydrophobic materials whereby the granules are coated with a coating of the hydrophobic material, increasing in thickness with increased particle size.

18. A method according to claim 17 in which the volatile solvent is 1,1,1-trichloroethane.

19. A method of making oral pharmaceutical preparations having a prolonged medicament release which comprises sizing granules of medicament to produce a mixture having granules substantially all being from 16 mesh to 60 mesh, and spraying them with a solution in a volatile solvent of water insoluble, partially digestible hydrophobic materials whereby the granules are coated with a coating of the hydrophobic material, increasing in thickness with increased particle size.

20. A method according to claim 19 in which the volatile solvent is 1,1,1-trichloroethane.

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