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ENCAPSULATED TIME RELEASE PELLETS AND METHOD FOR ENCAPSULATING THE SAME

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The present invention relates to a novel method of encapsulating solid medicinal pellets, pills or beadlets from which the medicinal material is released at a predetermined rate over a predetermined delayed time interval when the pellets are taken internally. Such pellets are conventional and are referred to herein as time release pellets. The invention also relates to the novel encapsulated time release pellets made in accordance with such method and to a novel intermediate form in which the pellets are placed in order to so encapsulate them.

The controlled rate of release of the medicinal is achieved by formulating the time release pellets so that when taken internally the outer layers thereof disintegrate at a controlled rate to thereby release the medicinal at the desired rate over an extended period of time. While time release pellets are commercially available, and hence per se form no part of this invention, they may be described as consisting of a pellet nucleus built up from a bead of sugar coated with successive layers or coatings of sucrose or simple syrup and alternate layers of starch, to which the medicinal is commonly applied as a powder to a liquid coating of simple syrup during a suitable tumbling process and over which a coating of wax is applied which serves to retard the disintegration of the coating containing the medicinal. The wax coating may conveniently consist of castor wax formulated from hydrogenated castor oil. By selection of medicinal formulations and thicknesses of the medicinal and wax coatings, the rate of release of medicinal from the pellet can be controlled and delayed in a predictable manner.

By varying the make up of different pellets, e.g. the thicknesses of the coatings, the formulation of the medicinal, etc., their rate of release and delay can be varied. By admixing together a number of these different pellets having different release rate and time delay characteristics the medicinal can be released at a controlled rate over a relatively long time interval. For example, the medicinal will be released from one group of pellets over a certain time interval followed by release of medicinal from another group of pellets over a succeeding time interval so that the medicinal will be released at a predetermined rate to maintain the desired blood level of the medicinal over a relatively long total time interval. Such an admixture of pellets having different release rate and time delay characteristics typically includes some pellets on which the wax coating over the medicant coating is omitted entirely so that the period of sustained therapeutic activity commences promptly after a capsule containing the admixture of time release pellets is administered to a patient. In this manner, a predictable, even, smooth, continuous level of therapeutic activity can be achieved over a period of as long as twelve hours or more with no sudden, abrupt rises in blood levels, no "dumping" and no "up-hill-down-dale" effects, as is so often the case with enteric-coated tablets, repeat-action tablets and other substandard action medications. Furthermore, patients are not as likely to interrupt therapy or miss dosage because of forgotten administration since the number of dosages may be reduced.

Each dosage of time release pellets requires a relatively large predetermined quantity of pellets (conventional pellets may vary widely in size over a wide range which typically includes sizes from the opening size of

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a 10 mesh standard screen to the opening size of a 40 mesh screen). In the past, such predetermined quantities of pellets have been encapsulated in a dry state in hard shelled, two piece capsules. However, such capsules have the disadvantage that they may be tampered with, which can result in a loss or removal of pellets to thereby decrease the dosage below that required. Furthermore, these capsules are not hermetically sealed against air and moisture which in many instances are detrimental to the pellets. Since the pellets are encapsulated in a dry state their surfaces are exposed to moisture and air. Also collision of the dry pellets with each other and with the handling equipment during handling, e.g. during encapsulation, may result in damage to the carefully formulated surface coatings which alters the time release characteristics of the pellets.

Accordingly, it is an object of the present invention to provide a method of encapsulating time release pellets in hermetically sealed, tamper-proof capsules in which the surfaces of the pellets are protected from exposure to air and moisture and are protected against damage due to collision during handling.

Although, certain medicinals, such as vitamins, have been encapsulated in hermetically sealed, soft shell (gelatin) capsules, in order to do so automatically with presently existing machinery such as that described in U.S. Patents Nos. 2,549,327 and 2,638,052 the medicinal must be in the form of a liquid or a paste which demonstrates fluidity under the particular feed system employed, that is a gravity feed or a pressure feed. Otherwise it cannot be accurately metered and pumped by the metering valve and pump mechanism (U.S. Patent No. 2,638,052) of such machinery, which mechanism automatically meters out and loads a measured dosage into the capsules. The capsules are formed, loaded and hermetically sealed automatically by the machine.

In order to provide the desired dosage, the medicinal or medicant in a relatively concentrated form is commonly suspended in a conventional pharmaceutical carrier such as corn oil, cotton seed oil, or some other vegetable oil or the like so that the quantity of the resulting mixture required to fill a capsule will contain the desired dosage. It is essential that the medicant be uniformly suspended in the carrier and that the suspension be stable so that the medicant will remain uniformly distributed in the carrier at the time of loading in order for the measured dosages (measured by volume or weight) loaded into the capsules to contain a predictable uniform quantity of medicant. Consequently, if the medicinal or medicant is originally in the form of a solid, it must first be ground into a fine powder as by a ball milling operation in order to provide the required stable uniform suspension. In such case, the carrier functions to place the solid medicant in a form which can be handled by the metering and pumping mechanism and also functions as a diluent.

A serious problem which has prevented the use of this encapsulating technique to encapsulate the above-mentioned time release pellets is their relatively large sizes (as aforesaid, conventional batches usually include sizes which are substantially larger than the opening size of a 40 mesh screen) as compared to the finely ground powders conventionally used with such techniques. Such large sizes are required in order to achieve the time release characteristics referred to above. On one hand, the pellets are too large to be uniformly distributed in a stable liquid suspension using conventional pharmaceutical liquid carriers. On the other hand, the pellets cannot be ground to a powder fine enough for uniform stable suspension in conventional pharmaceutical liquid carriers without destroying their predetermined and predictable time release characteristics. Finally, since the pellets

in their dry state do not demonstrate all of the fluid properties necessary for successful encapsulation in soft shell capsules using the metering valve and pump mechanism referred to above on the machinery referred to above, these pellets cannot be encapsulated in their dry state with presently existing machinery.

Accordingly, it is another object of the invention to encapsulate predictable and substantially uniform (within acceptable limits) dosages of such time release pellets in soft shell, hermetically sealed capsules utilizing the above-mentioned known encapsulating techniques and without reducing the size of the pellets, whereby the time release characteristics thereof are preserved. This is achieved by metering and loading the pellets in the form of a novel, stable liquid suspension in which the pellets remain uniformly dispersed for a long period of time under normal environmental conditions (including normal storage and encapsulation conditions) and which can be easily handled by the metering and pumping mechanism. This insures that the metered dosages loaded into the capsules by such mechanism will contain substantially uniform quantities of pellets even when the suspension is stored for a substantial period of time before encapsulation. The liquid suspension is formed by suspending the pellets in a novel liquid carrier which not only places the pellets in a form in which they can be successfully utilized with the above-mentioned conventional equipment but also protects the pellets against contact with air or moisture and against damage to their surfaces due to collision during handling.

A number of serious problems had to be overcome in order to do this. The major problem, of course, was to find a way of forming a stable uniform liquid suspension of such large particles. This problem was complicated by the fact the suspension could not contain anything which would unpredictably interfere with the time release characteristics of the pellets. This ruled out the use of most dispersing agents which function as such by collecting, presumably in the form of a coating, on the surfaces of the pellets to thereby alter the surface tension conditions at the interfaces of the carrier and the pellets. Such a coating would interfere with the time release characteristics of the pellets. Furthermore, a carrier could not be used in which the pellets were at all soluble because this would cause the pellet coatings to dissolve to thereby destroy the time release characteristics of the pellets. It was essential that the carrier and its contents (other than the pellets) be inert with respect to the pellets and to the gelatin capsule material which ruled out glycerine and water (water would dissolve the carefully formulated water soluble pellet coatings and glycerine would soften the gelatin capsule material) and wax solvents. Also, it was essential that the carrier and its contents be non-toxic, which ruled out many well known carriers and dispersing agents, and that it be sufficiently flowable with the pellets suspended therein and at the temperatures (usually 72° F.) at which hermetically sealed, soft shell capsules are usually manufactured so as to be readily handled by the metering and pumping mechanism.

Accordingly, it is another object of the present invention to provide a stable, uniform liquid suspension of the above-mentioned time release pellets in a carrier without reducing their size and without unpredictably changing the time release characteristics of the pellets, such carrier being inert with respect to the pellets and capsule, non-toxic and sufficiently flowable with the pellets suspended therein to be readily handled by the metering and pumping mechanism. This is achieved by suspending the pellets in a thick, viscous carrier sufficiently viscous to hold the pellets in stable, uniform suspension for a relatively long period of time under normal environmental conditions (including normal storage and encapsulation conditions) but sufficiently flowable to be readily handled by the metering and loading mechanism. The carrier is

preferably formulated by blending a compound which is normally liquid at room temperature with a compatible thickening compound which is normally solid at room temperature to provide a thick, viscous, homogeneous carrier blend, the thickener being added in an amount sufficient to provide the blend with the desired viscosity.

A serious problem which arose with the use of such a viscous carrier was that the viscosity required to provide a stable suspension is so high that it is difficult to uniformly mix and disperse the pellets in the carrier, which is necessary in order that the dosages metered out and loaded by the aforementioned metering and pumping mechanism contain substantially uniform and predictable quantities of pellets.

Accordingly, it is another object of the invention to provide a carrier of the type described above having the desired high viscosity to achieve a stable uniform suspension of the time release pellets but in which the pellets can be easily and uniformly dispersed. This is achieved by employing a carrier which has a high viscosity at normal temperatures, including encapsulating temperatures, but the viscosity of which is sharply reduced to a value at which the pellets are easily admixed and uniformly dispersed therein when the temperature thereof is increased, the pellets being mixed and dispersed in the carrier while it is at such elevated temperature.

However, another problem was introduced because the pellets cannot be raised above a relatively low elevated temperature, about 122° F., without detrimentally affecting the pellets. One way in which the pellets are detrimentally affected is that the wax outer coating is melted.

Accordingly, it is yet another object of the invention to provide a carrier which has the desired high viscosity at encapsulating temperature but the viscosity of which is sharply reduced to a relatively low viscosity at which the pellets are easily dispersed uniformly therein by increasing the temperature thereof to a relatively low elevated temperature below the temperature at which the pellets are adversely affected. This is achieved by the use of a carrier comprising a polymerized alkylene glycol, including alkoxy polyalkylene glycols (e.g. methoxy), which is liquid at room temperature and which is thickened to the desired viscosity with a polymerized alkylene glycol, including alkoxy polyalkylene glycols (e.g. methoxy), which is solid at room temperature and which has a greater molecular weight than said first-mentioned polymerized alkylene glycol. Liquid and solid polymerized ethylene glycols are preferred although polypropylene glycols are also satisfactory.

Preferred carriers are normally liquid polymerized polyethylene glycols having approximate average molecular weights ranging from about 190 to 630 and Saybolt viscosities at 210° F., sec., from about 38 to 66 and which are sold by Carbide and Carbon Chemicals Company under the trade names "Polyethylene Glycol 200 to 600," thickened with more highly polymerized, normally solid polyethylene glycols, which have approximate average molecular weights between about 950 and 7500 and Saybolt viscosities at 210° F., sec., from about 85 to 4200 and which are sold by Carbide and Carbon Chemicals Company under trade names "Carbowax" Compounds 1000 to 6000." A preferred liquid polyethylene glycol is one having an approximate average molecular weight of about 380-420 and a Saybolt viscosity at 210° F., sec., from about 45 to 55 and which is sold by Carbide and Carbon Chemicals Company under the trade name "Polyethylene Glycol 400." A preferred solid polyethylene glycol is one having an approximate average molecular weight of about 3000-3700 and a Saybolt viscosity at 210° F., sec., of from about 350 to 400 and which is sold by Carbide and Carbon Chemicals Company under the trade name "Carbowax" Compound 4000."

A polyglycol carrier blend having a viscosity of at least 1000 centipoises measured with a standard Brookfield Synchroelectric Viscometer Model LVF at a tem-

perature of 72° F. (spindle number 4 and a spindle speed of 60 r.p.m.) is preferred to keep the pellets in uniform suspension although the minimum viscosity of the carrier will depend on the size of the pellets. Such minimum viscosity will be greater with greater particle sizes.

The maximum viscosity of the carrier is dictated only by the maximum viscosity of the suspension of the pellets in the carrier which can be handled satisfactorily by the metering and pumping mechanism at normal encapsulating temperatures (between about 70° F. and 90° F.), which temperatures closely approximate room temperature (an encapsulating temperature which is commonly used is 72° F.) with the particular feed system employed.

Since the viscosity of the carrier is increased by increasing the proportion of solid polyglycol to liquid polyglycol, the proper minimum viscosity for any particular particle size can be readily ascertained by increasing or decreasing such proportion until the desired stability of the suspension for that particle size is achieved. A satisfactory carrier viscosity is obtained for a range of pellet sizes passing through a 20 standard mesh screen but being retained on a 25 standard mesh screen where the amount of solid polyglycol is between about 8% and 13% by weight of the carrier, the rest of the carrier comprising the liquid polyglycol.

Although the maximum amount of thickener is dictated only by the maximum viscosity of the suspension which can be handled by the above-mentioned conventional metering and pumping mechanism, it is uneconomical for a number of reasons to increase the carrier viscosity beyond what is required for a stable suspension. Examples of such reasons are the increased difficulty in handling the suspension and the increased difficulty in physically mixing the pellets into the carrier. The minimum amount of thickener of course, depends on the minimum carrier viscosity as described above. However, the lower the molecule weight of either or both of the solid and the liquid polyglycol, the greater the proportion of solid polyglycol to liquid polyglycol which is necessary to obtain the same minimum carrier viscosity.

The proportion of pellets in the suspension is not particularly critical and may range from about 10% to 30% by weight, the remainder of the suspension comprising the carrier. However, a range of from 15% to 25% by weight is preferred. The proportion of pellets in any particular suspension will depend on the pellet dosage (quantity of pellets) desired per capsule to provide the required amount of medicant per capsule. Thus, for any given capsule volume, a proportion of pellets is selected to provide the desired quantity of pellets in that volume. Except for this requirement there is no minimum proportion of pellets. The maximum proportion is dictated only by the fact that the proportion of pellets to carrier should not be so great that the suspension becomes too stiff to be efficiently handled by the metering and loading mechanism.

An important advantage of the blended polyglycol carriers of the present invention is that although at normal room temperatures, which include normal storage and encapsulating temperatures, the carrier is sufficiently thick and viscous to hold the pellets in stable suspension, at elevated temperatures below the maximum temperature to which the pellets can be exposed without detrimental effect but well above normal storage and encapsulating temperatures, the viscosity thereof is reduced substantially to a relatively low value at which the pellets can be easily mixed and dispersed uniformly therein. It has been found that when the solid and liquid polyglycol blend is heated from room temperature there is a sudden and substantial drop in viscosity as the blend is heated through a relatively narrow transition temperature range. This transition temperature range at which the sudden drop in viscosity occurs is below the maximum temperature (122° F.) to which the pellets can be exposed and well above normal storage and encapsulating tempera-

tures and depends on the amount of the solid polyglycol which is present, the greater the amount of such solid polyglycol, the higher the temperature at which the sudden drop occurs. For example, with a carrier blend containing 12% solid "Carbowax" Compound 4000" and 88% liquid "Polyethylene Glycol 400" the viscosity drops from 5640 cps. (centipoises using Brookfield Synchroelectric Viscometer Model LVF with spindle No. 4 and a spindle speed of 60 r.p.m.) at 72° F. to 50 cps. (centipoises using Brookfield Viscometer with spindle No. 1 and a spindle speed of 60 r.p.m.) at 120° F., most of this drop in viscosity occurring in the transition temperature range between about 116.6° F. and 120.0° F., and with a carrier formulation of 9% solid "Carbowax" Compound 4000" and 91% liquid "Polyethylene Glycol 400" (using the same viscosity measuring technique and apparatus used with the 12% solid polyglycol blend) the viscosity drops from 1340 cps. at 72° F. to 46 cps. at 120° F., the major portion of this drop occurring in the transition temperature range between about 113.0° F. and 118.4° F. This sudden drop in viscosity occurring in the transition temperature range is accompanied by the blend changing from a thick, viscous opaque state to a thin, fluid transparent state.

It has also been found that when the heated polyglycol blend is cooled the viscosity increases sharply and suddenly within a lower transition temperature range (as compared to the transition temperature range during heating) which is about the same regardless of the relative proportions of solid and liquid polyglycol. Thus, with "Carbowax" Compound 4000" and "Polyethylene Glycol 400" when the temperature is reduced the sudden and substantial increase in viscosity occurs between 105.8° F. and 98.6° F. This sudden increase in viscosity is again accompanied by the blend changing from a thin, fluid transparent state to a thick, viscous opaque state and, as aforesaid, is the same regardless of the relative proportions of solid polyglycol and liquid polyglycol.

The liquid and solid polyglycol blend is preferably formulated by mixing the solid polyglycol into the liquid polyglycol with agitation at a temperature above or at the melting temperature of the solid polyglycol. Such melting temperature for "Carbowax" Compound 4000" is between about 127° F. and 133° F. However, it is different for other solid polyglycols. For example, the melting temperature of "Carbowax" Compound 1000" is between 98.6° F. and 104° F. The maximum temperature at which the solid polyglycol can be added to the liquid polyglycol is dictated only by economics and the maximum temperature to which the polyglycols can be subjected without detrimental effect. From an economic standpoint it is desirable to add the solid polyglycol to the liquid polyglycol at the lowest temperature at which the solid polyglycol melts rapidly and is blended with the liquid polyglycol into a homogeneous liquid of low viscosity. Good results are obtained with a blend of "Carbowax" Compound 4000" and "Polyethylene Glycol 400" when the solid polyglycol is added to the liquid polyglycol at 140° F. The Brookfield viscosity of such blend at that temperature with 9% solid polyglycol and 91% liquid polyglycol is 31 cps. and with 12% solid polyglycol and 88% liquid polyglycol it is 35 cps., both viscosities being measured at 60 r.p.m. with spindle No. 1.

This elevated temperature required for mixing the solid "Carbowax" Compound 4000" with the liquid "Polyethylene Glycol 400" to obtain the carrier blend is too high for the pellets. Consequently, after the two polyglycols have been admixed and before the pellets are added to the carrier blend the temperature of the blend is reduced to a temperature at or below the maximum temperature (122° F.) to which the pellets can be subjected without detrimental effects but above the transition temperature range at which the viscosity of the blend increases sharply as aforesaid. One such temperature

which has been found satisfactory for this particular blend is 120° F. The pellets are added to the blend at this lower elevated temperature at which the viscosity is still relatively low and are uniformly mixed and dispersed throughout the carrier by agitation with a mixer. Thereafter, the blend is cooled while still being mixed, to thereby keep the pellets in suspension, through the transition temperature range, at which the viscosity increases sharply, to room temperature at which the suspension is highly viscous and the pellets remain suspended uniformly in the carrier for long periods of time without mixing. Of course, where the melting temperature of the solid polyglycol is below the maximum temperature to which the pellets can be safely exposed it may not be necessary to reduce the temperature before adding the pellets.

After cooling, the stable, viscous suspension of pellets can be stored before being encapsulated in hermetically sealed, soft shell capsules with the apparatus disclosed in the above-mentioned patents, or it can be so encapsulated immediately. In either case, the time release pellets remain uniformly suspended in the carrier so that there is a predictable uniform quantity of pellets in each dosage automatically loaded into the pellets by the metering and pumping mechanism. Furthermore, although the suspension is thick and viscous it is sufficiently flowable so that it can be readily handled by the metering and pumping mechanism.

As aforesaid, the size of the time release pellets, which are conventional and available on the market, vary over a wide range of sizes which typically includes pellet sizes ranging from a size corresponding to the opening size of a 10 mesh screen to a size corresponding to the opening size of a 40 mesh screen. However, in accordance with the present invention, it is preferable to utilize pellets which are generally uniform in size, e.g. sufficiently uniform so that the difference in the sizes of a screen on which they are held and a screen through which they pass is not much greater than about 5 mesh. Pellets of generally uniform sizes can be obtained by screening conventional batches of time release pellets or by screening a batch of pellets before the coating of medicinal is applied followed by again screening the finished coated pellets.

The highly viscous carrier not only holds the pellets in uniform suspension, thereby placing them in a form in which they can be used with conventional techniques for encapsulation in hermetically sealed, soft shell capsules, but also protects their surfaces from becoming damaged and their shape from being changed by collision with each other and with the handling equipment during handling, e.g. during metering and loading. This is of extreme importance because any damage to the surfaces or any change in shape will damage the coatings that initially were carefully manufactured for the express purpose of potency control in the rate of medication release. The viscous carrier also protects such coatings from contact with moisture and air.

Example I

31.68 lbs. of liquid "Polyethylene Glycol 400" sold under that name by Carbide and Carbon Chemicals Company was heated to 140° F. 4.32 lbs. of solid polyethylene glycol sold under the trade name "Carbowax" Compound 4000" by Carbide and Carbon Chemicals Company was blended into the heated liquid polyglycol by stirring with a stirrer having a 5" blade and rotating at an r.p.m. of 170 r.p.m. which was slow enough to avoid whipping any substantial amount of air into the mix. The mixture was mixed for one hour at 140° F. during which the solid polyglycol melted and was uniformly dispersed in the liquid polyglycol to form 36 lbs. of a thin, transparent homogeneous liquid made up of 12% solid polyglycol and 88% liquid polyglycol and having a Brookfield viscosity at 140° F. (spindle No. 1 and spindle speed of 60 r.p.m.) of 35 cps. (centipoises). The resulting homogeneous blend or carrier was allowed to cool to 120° F.

(below the maximum temperature—122° F.—to which the pellets can be safely exposed) at which temperature (120° F.) it had a Brookfield viscosity of 50 cps. (spindle No. 1 and spindle speed of 60 r.p.m.) and was still thin and transparent. Nine lbs. of a batch of conventional time release pellets (sometimes referred to as timed disintegration pellets) having d-amphetamine sulfate medicant coatings over sugar, sucrose and starch bases with wax coatings over the medicant and of a size passing through a 20 mesh standard screen but not through a 25 mesh standard screen (the pellets before being coated with medicant and wax passed through a 30 mesh screen but not through a 35 mesh screen) were added to the carrier at 120° F. while it was being agitated by the stirrer rotating at 170 r.p.m. The carrier was held at this temperature with continued stirring until the pellets were dispersed uniformly throughout the carrier, whereafter the suspension was cooled to 72° F. with continued stirring. During cooling the viscosity of the carrier blend sharply increased over a transition temperature range of from 105.8° F. to 98.6° F. During such transition period the carrier blend changed from a relatively free flowing, thin transparent state to a thick, highly viscous, opaque state. At 72° F. (room temperature) the Brookfield viscosity (spindle No. 4 and spindle speed of 60 r.p.m.) of the carrier blend was 5640 cps., the major portion of the increase in viscosity from 120° F. to 72° taking place in the above-mentioned transition temperature range. The suspension at 72° F. was very thick and viscous but flowable. It was opaque and contained 20% by weight of pellets and 80% by weight of carrier. The pellets remained uniformly suspended with no perceptible settling for a number of days. It was noted that upon heating the carrier it decreased sharply in viscosity in a transition temperature range of between 116.6° F. and 120.2° F. below the maximum temperature (122° F.) to which the pellets can be subjected. The suspension was encapsulated at 72° F. in soft shell, hermetically sealed gelation capsules in a conventional encapsulating machine of the type described in U.S. Patent No. 2,549,327 and having a metering valve and pump of the type described in U.S. Patent No. 2,638,052 with a gravity feed and without concurrent agitation of the suspension. The metering valve and pump satisfactorily and accurately metered and loaded the suspension in the capsules without harming the surfaces or shape of the pellets and the pellets remained uniformly suspended in the suspension throughout the operation so that each load or dosage metered and loaded into each capsule contained a substantially uniform and predictable quantity of pellets (within acceptable limits of uniformity).

The pellets were formulated and mixed by the manufacturer as in conventional practice to achieve a predetermined rate of release of the d-amphetamine sulfate medicant (useful for the control of appetite in weight reduction and for the treatment of depressive states and alcoholism) of about 30–40% of the total medicant after one hour, 50–60% after two hours, 70–80% after five hours and 80–90% after eight hours. The average medicant content of the pellets was 114.8 mg. per gram of pellets and the medicant dosage per capsule was 15 milligrams.

By conventional testing procedure, the release rate of the medicant in the encapsulated suspension of this example was as follows:

	Percent
1 hour-----	36.6
2 hours-----	58.7
5 hours-----	79.1
8 hours-----	82.0

A number of these encapsulated pellets were satisfactorily administered to a number of patients with positive results and with no ill effects.

These results showed that the time release characteristics of the pellets were not altered by the encapsulation

process and that the encapsulated pellets were highly satisfactory.

Example II

Example II was the same as Example I except that the solid polyglycol comprised 9% of the carrier and the liquid polyglycol comprised 91%. The carrier blend had a Brookfield viscosity of 31 cps. at 140° F. and 46 cps. at 120° F. (spindle No. 1 and spindle speed of 60 r.p.m.). The carrier had a Brookfield viscosity of 1340 cps. at 72° F. (spindle No. 4 and spindle speed of 60 r.p.m.). The transition temperature range at which the viscosity of the carrier blend increased sharply during cooling was the same as in Example I. However, the transition temperature range of the carrier during heating was between 113.0° F. and 118.4° F.

Other embodiments of the invention will become apparent from the preceding description, it being understood that such description, especially the specific examples, are only illustrative and that the invention is not limited thereto or thereby but only by the claims hereof and their equivalents.

I claim:

1. An encapsulated, stable liquid suspension of time release medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said pellets being dispersed and suspended in a substantially moisture-free, thick, viscous but flowable liquid carrier in which said pellets are substantially insoluble, said suspension being encapsulated in a soft shell, hermetically sealed capsule, said carrier being inert with respect to said pellets and said capsule and comprising a homogeneous blend of a non-toxic compound which is liquid at room temperature and a non-toxic thickening compound which is solid at room temperature and which is present in an amount to render the carrier sufficiently viscous to hold said pellets in suspension, said carrier being substantially inert with respect to effect on said predetermined rate of medicinal release of said pellets.

2. A stable, liquid suspension of time release medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said pellets being dispersed and suspended in a substantially moisture-free, thick, viscous but flowable liquid carrier in which said pellets are substantially insoluble, said carrier being inert with respect to said pellets and comprising a homogeneous blend of a non-toxic compound which is liquid at room temperature and a non-toxic thickening compound which is solid at room temperature and which is present in an amount to render the carrier sufficiently viscous to hold said pellets in stable suspension, said carrier being substantially inert with respect to effect on said predetermined rate of medicinal release of said pellets.

3. An encapsulated, stable liquid suspension of time release medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said pellets being dispersed and suspended in a thick, viscous but flowable liquid carrier in which said pellets are substantially insoluble, said suspension being encapsulated in a soft shell, hermetically sealed capsule, said carrier comprising a blend of a polyalkylene glycol which is liquid at room temperature and a higher molecular weight polyalkylene glycol which is solid at room temperature, said solid polyethylene glycol being present in an amount to render said carrier sufficiently viscous to hold said pellets in suspension in said carrier.

4. An encapsulated suspension according to claim 3, said solid and liquid polyalkylene glycols comprising polyethylene glycols, said liquid polyethylene glycol having an average molecular weight between about 190 and 630 and having a Saybolt viscosity at 210° F., sec., ranging from about 38 to 66, said solid polyethylene glycol having an average molecular weight between about 950 and 7500 and a Saybolt viscosity at 210° F., sec., ranging from about 85 to 4200.

5. An encapsulated suspension according to claim 3, the Brookfield viscosity of said carrier being at least 1000 centipoises at 72° F. using spindle No. 4 and with a spindle speed of 60 r.p.m., said pellets being larger than the opening size of a 40 mesh screen.

6. A stable liquid suspension of time release medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said pellets being dispersed and suspended in a thick, viscous but flowable carrier comprising a blend of a normally liquid polyalkylene glycol and a normally solid polyalkylene glycol of greater molecular weight than said liquid polyalkylene glycol.

7. A stable liquid suspension according to claim 6, said polyalkylene glycols comprising polyethylene glycols, said liquid polyethylene glycol having an average molecular weight between about 380 and 420 and a Saybolt viscosity at 210° F., sec., ranging from about 45 to 55, said solid polyethylene glycol having an average molecular weight between about 3000 and 3700 and a Saybolt viscosity at 210° F., sec., ranging from about 350 to 400.

8. A method of encapsulating in soft shell hermetically sealed capsules discreet medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval by virtue of the construction of the pellets without interfering with said rate of release, said method comprising homogeneously blending together a non-toxic compound which is liquid at room temperature with a non-toxic thickening compound which is solid at room temperature to provide a carrier which is highly viscous but readily flowable under normal storage and encapsulation conditions and in which said pellets are insoluble, mixing said pellets into said carrier with agitation to thoroughly disperse and suspend said pellets in said carrier, said solid compound being present in a quantity to render said carrier sufficiently viscous under normal storage and encapsulating conditions to hold said pellets in stable suspension, and encapsulating the resulting suspension in a soft shell hermetically sealed capsule, said carrier being substantially inert with respect to said pellets and said capsule material and with respect to predictable rate of medicinal release of said pellets.

9. A method of encapsulating medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said method comprising forming a homogeneous blend of a non-toxic compound which is liquid at room temperature and a non-toxic compound which is solid at room temperature, mixing said pellets in said blend at an elevated temperature and with agitation to disperse said pellets in said blend, said blend having a substantially lower viscosity over a range of higher temperatures including said elevated temperature than over a lower range of temperatures, said blend containing an amount of solid compound to render the blend sufficiently viscous at said lower temperature range to hold said pellets in suspension, reducing said elevated temperature of said suspension to a lower temperature within said lower range to thereby increase its viscosity said elevated temperature being not greater than the maximum temperature which said pellets can withstand without deleterious effects, and encapsulating said suspension in a soft shelled hermetically sealed capsule at a temperature within said lower range, said suspension being agitated while it is cooled from said first elevated temperature to said lower temperature.

10. A method of encapsulating medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said method comprising forming a homogeneous blend of a polyalkylene glycol which is liquid at room temperature and a polyalkylene glycol of greater molecular weight than said liquid polyalkylene glycol and which is solid at room temperature, mixing said pellets in said blend at an elevated temperature and with agitation to disperse said pellets in said blend, said blend having a substantially lower viscosity

over a range of higher temperatures including said elevated temperature than over a lower range of temperatures, said blend containing an amount of solid polyalkylene glycol to render the blend sufficiently viscous at said lower temperature range to hold said pellets in suspension, reducing said elevated temperature of said suspension to a lower temperature within said lower range to thereby increase its viscosity, said elevated temperature being not greater than the maximum temperature which said pellets can withstand without deleterious effects, and encapsulating said suspension in a soft shell hermetically sealed capsule at a temperature within said lower range.

11. A method according to claim 10, said solid and liquid polyglycols being mixed at a second elevated temperature higher than said first elevated temperature, said second elevated temperature being at least the melting temperature of said solid polyalkylene glycol and being within said higher range, whereby said solid polyalkylene glycol is melted and dispersed in said liquid polyalkylene glycol in a melted state to form said homogeneous blend, said method including reducing the temperature from said second elevated temperature to said first elevated temperature and thereafter adding said pellets at said first elevated temperature, said suspension being agitated while it is cooled from said first elevated temperature to said lower temperature.

12. A method according to claim 10, said pellets being of a size passing through a screen of one size and being retained on a screen of a size which is about 5 mesh greater than said screen of said one size.

13. A method according to claim 10, said polyalkylene glycols comprising polyethylene glycols.

14. A method according to claim 13, said liquid polyethylene glycol having an average molecular weight between about 190 and 630 and a Saybolt viscosity at 210° F., sec., ranging from about 38 to 66 and said solid polyethylene glycol having an average molecular weight between about 950 and 7500 and a Saybolt viscosity at 210° F., sec., ranging from about 85 to 4200.

15. A method according to claim 13, said blend having a Brookfield viscosity of at least 1000 centipoises at 72° F. with spindle No. 4 and a spindle speed of 60 r.p.m.

16. A method of forming a stable suspension of medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said method comprising forming a homogeneous blend of a non-toxic compound which is liquid at room temperature and a non-toxic compound which is solid at room temperature, mixing said pellets in said blend at an elevated temperature and with agitation to disperse said pellets in said blend in the form of a suspension, said blend having a substantially lower viscosity at said elevated temperature than at a lower temperature, said blend containing an amount of solid compound to render said suspension sufficiently viscous at said lower temperature to hold said pellets in suspension, reducing said elevated temperature of said suspension to said lower temperature to thereby increase its viscosity, said elevated temperature being not greater than the maximum temperature which said pellets can withstand without deleterious effects, said suspension being agitated during said cooling step.

17. A method of forming a stable suspension of medicinal pellets having a predetermined rate of medicinal release over a predetermined delayed time interval, said method comprising forming a homogeneous blend of a polyalkylene glycol which is liquid at room temperature and a polyalkylene glycol of greater molecular weight than said liquid polyalkylene glycol and which is solid at room temperature, mixing said pellets in said blend at an elevated temperature and with agitation to disperse said pellets in said blend, said blend having a substantially lower viscosity at said elevated temperature than at a lower temperature, said blend containing an amount of solid polyalkylene glycol to render said suspension sufficiently viscous at said lower temperature to hold said pellets in suspension, reducing said elevated temperature of said suspension to said lower temperature to thereby increase its viscosity, said elevated temperature being not greater than the maximum temperature which said pellets can withstand without deleterious effects, said suspension being agitated during said cooling step.

18. A method according to claim 17, said polyalkylene glycols comprising polyethylene glycols, said liquid polyethylene glycol having an average molecular weight between about 190 and 630 and a Saybolt viscosity at 210° F., sec., ranging from about 38 to 66 and said solid polyethylene glycol having an average molecular weight between about 950 and 7500 and a Saybolt viscosity at 210° F., sec., ranging from about 85 to 4200, the Brookfield viscosity of said blend at 72° F. with spindle No. 4 and a spindle speed of 60 r.p.m. being at least 1000 centipoises.

19. A method according to claim 17, said polyalkylene glycols comprising polyethylene glycols, said liquid polyethylene glycol having an average molecular weight of between about 380 and 420 and a Saybolt viscosity at 210° F., sec., ranging from about 45 to 55 and said solid polyethylene glycol having an average molecular weight of between about 3000 and 3700 and a Saybolt viscosity at 210° F., sec., from about 350 to 400, said blend comprising at least about 8% by weight of said solid polyethylene glycol.

20. A method according to claim 17, said solid polyalkylene glycol being mixed with said liquid polyalkylene glycol to form said homogeneous blend at a second elevated temperature at least as high as the melting temperature of said solid polyalkylene glycol, said method including reducing the temperature of said blend from said second elevated temperature to said first elevated temperature at which said pellets are added thereto, said first elevated temperature being not substantially greater than 122° F.

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