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LIQUID INJECTABLE OIL-PECTIN-DRUG
THERAPEUTIC COMPOSITIONSHenry Welch, Silver Spring, Md., assignor to,
the United States of AmericaNo Drawing. Application June 3, 1947,
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My invention relates to therapeutic products and more particularly to injectable therapeutic products wherein it is desirable or necessary to prolong their therapeutic activity in the animal body.

In the administration of penicillin or in other mold or bacterial excretory or metabolic products, it has been the standard practice to inject an aqueous solution of the substance subcutaneously or intramuscularly. Penicillin in aqueous solution is, however, rapidly absorbed into the blood stream and probably reaches a maximum concentration in the body within fifteen minutes after injection. Following a single intramuscular injection (10,000 to 30,000 units), the concentration of penicillin in the blood rapidly diminishes due to rapid absorption and excretion from the body and is practically zero within two to three hours after injection. This necessitates frequent aqueous penicillin injections intramuscularly to the discomfort and even harm of the patient who may have to be awakened every few hours during the night for such treatments.

Accordingly, many expediences have been proposed directed to the end of maintaining an effective therapeutic penicillin blood level concentration for a prolonged period of time. These include continuous intravenous injections, continuous intramuscular administrations, the establishment of an excretory blockade in the patient by the simultaneous administration of para-aminohippuric acid or diodrast and the use of ice packs at the site of intramuscular injection. Prolongation of therapeutic activity has also been attempted with various slowly absorbed vehicles, such as, peanut oil and beeswax, globin and the like.

With certain of these vehicles, such as globin and the like, prolonged action of penicillin in the blood is not obtained to a sufficient degree.

The development of penicillin in oil and wax overcame the rapid absorption of penicillin but manifested other disadvantages. When penicillin is suspended as a dry salt (e. g. calcium salt) in oil with beeswax and injected into the body a mass is formed in the tissues, consisting of beeswax in which penicillin is entrapped. Water from the tissues gradually dissolves out the penicillin from this beeswax matrix and in a matter of 20 to 24 hours the penicillin has been completely absorbed, although the beeswax itself remains for some time in the tissue.

Beeswax is a well-known sensitizer and thus produces allergic reactions when injected into the body in combination with peanut oil and penicillin. Because of its structure (i. e. insol-

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bility in tissue fluids), beeswax is absorbed with great difficulty by the human body requiring on an average from twenty-five to thirty days to be assimilated by the body. Furthermore, sterile abscesses are frequently formed by beeswax preparations and moreover are painful at the site of injection for prolonged periods. There is, therefore, need for a preparation which will prolong the activity of penicillin in the body while avoiding the disadvantages of the beeswax preparation.

For example, a preparation of beeswax, penicillin and oil, because of the beeswax content is very slowly absorbed by the body due to the inability of the animal tissue to digest and assimilate beeswax from the site of injection. By contrast, and at the other extreme, a solution of sucrose (a polysaccharide), penicillin and water is very rapidly absorbed by the body and no prolonged effect of penicillin is secured since sucrose is readily digested and absorbed by the body along with the penicillin from the site of injection. In between these two extremes there are certain hydrophilic substances which may be substituted for the beeswax and sucrose and which are digested and assimilated by the body. However, because of their colloidal gel-like structure formed on contact with water in the body tissues, they entrap and then slowly release a drug such as penicillin from a repository site in the tissues. Such colloidal gels are not readily absorbed as is sucrose but still are not inordinately delayed in their absorption as is true of beeswax.

Thus, a desirable preparation for prolonging the activity of penicillin in the body would be one that is readily absorbed and assimilated by the body, that is not in aqueous solution, that does not form sterile abscesses on injection, and that does not sensitize the individual injected, and finally that forms a repository site from which the penicillin is gradually released following contact with the watery fluids of the tissue.

Stated briefly, then a substance that could be suspended in a dry state in an injectible vegetable oil, that is in nature hydrophilic, that is readily absorbed by the body yet entraps a drug such as penicillin in its colloidal gel matrix and slowly releases it would be a suitable substance for prolonging the action of the drug.

Examples of such classes of substances are polysaccharides such as pectin, sodium alginate, and certain dextrans, and cellulose compounds all of which are of the group which form gels on contact with water including protein substances such as gelatin.

Although in the above I have referred to this

problem with respect to penicillin, it is also a problem in other therapeutic products including such antibiotics as streptomycin and bacitracin; in insulin therapy; in hormone therapy; in vasoconstrictor therapy and indeed in the use of any injectable drug where it is desired to prolong the therapeutic action of the drug over a relatively long period of time.

It has already been noted that if this drug to be used is, in its dry state, mixed with an agent which on contact with the fluids of the body forms a colloidal gel holding the drug in suspension, the period of absorption of the drug by the body will be extended, particularly where the agent is itself absorbed by the body in substantially the same period of time.

Accordingly, an object of my invention is to provide a novel therapeutic product comprising a drug in such form that its absorption by the body is delayed but which is nevertheless readily assimilated by the body.

Another object of this invention is to provide a therapeutic product comprising an antibiotic mold or bacterial excretory or metabolic product suitable for intramuscular and/or subcutaneous administration.

Still another object is to provide an antibiotic mold or bacterial excretory or metabolic product in combination with a suitable vehicle such that upon parenteral administration to humans or other warm-blooded animals there results a considerably prolonged high blood serum concentration of active material.

Still a further object is to provide a therapeutic product which will not cause the development of sensitization in human beings and one which is readily absorbed and assimilated by the patient.

In general, in accordance with my invention, I suspend the desired drug with a hydrophilic agent such as a polysaccharide, including by way of example, pectin, sodium alginate and certain dextrans; or with cellulose compounds; or with certain protein substances such as gelatin. All of these agents are so selected that they have the common and here essential characteristic that they form colloidal gels on contact with the body fluids. The colloidal gels entrap the drug in the gel matrix and slowly release it while being itself absorbed by the body for which it has an infinity.

In carrying out my invention, I suspend the drug and the selected agent in an injectable oil such as vegetable oil which also has an infinity for body tissue, i. e. is readily absorbed thereby. Such oils by way of example are peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, etc.; or I may use such injectable glycols as propylene glycol.

By way of an example for carrying out my invention in a specific therapeutic composition of penicillin I employ peanut oil mixed with pectin of the proper particle size.

The pectin (National Formulary VIII) having an average particle size of the order of from 50 to 100 microns is mixed with crystalline potassium penicillin G (1500 units per milligram) having an average particle size of the order of from 50 to 100 microns. Two hundred and seventy milligrams of this pectin is mixed with 180 milligrams of the crystalline potassium penicillin G and to this mix there is added sufficient peanut oil of the type described in U. S. P. 13 (highly refined) to make a total of one milliliter. The preparation is then mixed thoroughly in a Waring Blendor until it is homogeneous.

The individual ingredients are preferably sterilized prior to the above mixing operations and are thereafter handled aseptically. Alternatively, the final preparation may be sterilized by dry heat of the order of 110° C. for about 8 hours.

Another preparation of penicillin having greater fluidity comprises 135 milligrams of pectin of the type described above and 180 milligrams of crystalline penicillin, or 67.5 milligrams of the pectin described plus 180 milligrams of the crystalline penicillin. In each of the latter examples peanut oil of the type described above is added to make up one milliliter.

Because of the hydrophilic nature of the product it is advisable to carry out the manufacturing steps described above under conditions where the product will not absorb moisture, as for example, in an air-conditioning room. Although in the above a particle size has been specified for desirable results, it should be understood that other ranges of particle sizes depending upon the desired therapeutic properties may be employed. The product described above may be administered directly in this form to the patient undergoing penicillin therapy.

Attached hereto are a series of tables showing experimental results using this novel drug. Table I presents data secured employing a product made as described above of crystalline potassium penicillin G, refined peanut oil, and National Formulary VIII pectin following the injection intramuscularly of approximately 250,000 units and 270 milligrams of pectin. Fifteen patients were utilized in this series. Relatively high blood levels of penicillin were obtained in the 12th and 16th hours and the blood levels obtained up to the 24th hour are comparable to those obtained with penicillin in oil and wax. It will be noted that the majority of patients maintained for twenty-four hours a blood level of .03 unit of penicillin which is a therapeutically effective blood concentration of this drug.

In Table 2 results secured from the injection of a number of rabbits of equal weight with 1 cc. of pectin penicillin in oil mixture made in accordance with this invention is shown. As a control, rabbits were similarly injected with 1 cc. of Romansky Formula VIII (300,000 units) (penicillin, beeswax and oil control). Blood levels were taken at one hour and at 24 hours as set forth in the tables.

TABLE I

Penicillin blood levels following single intramuscular injection of 250,000 units of penicillin-pectin

Name	Units of Penicillin per Milliliter of Serum			
	12 Hr.	16 Hr.	20 Hr.	24 Hr.
Bageett	0.125	0.064	0.06	0.03
Griffin	0.5	0.25	0.03	0.06
Calhoun	0.5	1.0	0.5	0.0
Marshall	1.0	1.0	0.03	0.125
Smith	0.06	0.06	0.06	0.06
Davis	1.0	1.0	0.06	0.0
Haves	0.03	0.03	0.03	0.03
Dalley	0.03	0.03	0.03	0.03
Shorts	0.06	0.06	0.06	0.06
Pinkston	0.06	0.125	0.0	0.0
Sullivan	2.0	1.0	0.03	0.03
Thomas	0.5	0.03	0.03	0.06
McFwen	0.05	0.03	0.03	0.0
Williams	1.0	1.0	0.0	0.0
Hood	1.0	1.0	0.06	0.03

¹ 3/4 ampule only injected.

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TABLE 2

Rabbit	1 hr. units/cc. blood	24 hrs. units/cc. blood	Assay pectin prep.
1	13.0	0.0	u./cc. 165,000
2	20.0	0.0	-----
3	7.7	0.1	-----
4	10.0	.05	210,000
5	9.0	.06	-----
6	7.0	.05	270,000
7	-----	.28	240,000
8	-----	.25	-----
9	-----	1.00	264,000
10	-----	.31	264,000
11	-----	.25	285,000
12	-----	.29	-----
13	-----	0.6	-----
14	-----	0.58	270,000
15	-----	0.60	-----
16	-----	0.40	-----

TABLE 2A

	Rabbit	Units/cc. 24 hours	Assay
Peanut Oil	1	.07	u./cc.
Beeswax	2	.14	-----
Control	3	.12	300,000
	4	.35	-----
	5	.07	-----

It will be noted that high penicillin levels were obtained on all rabbits tested with the pectin preparation one hour after injection and except for two rabbits, all showed blood levels of penicillin in the 24th hours. The two that failed to demonstrate twenty-four levels received a preparation containing only 165,000 units per cc.

In the injection in all of the above cases, I found that the pectin preparation (270 or 135 mg./cc. type) could not be packaged in multiple dose vials. This preparation must be put up in cartridges which utilize rubber stoppers as plungers. When the pectin preparation is drawn up into the syringe using glass plungers the plunger invariably binds as it is pushed in the barrel. This apparently is due to the jelly-like nature of pectin which, under the pressure of the glass plunger, creates a sticky substance between the plunger and the walls of the syringe causing it to freeze thereon. I have found, however, that the flexibility of the rubber plunger overcomes this difficulty during injection.

Summarizing the invention, it will now be clear that the formation of a colloidal gel entrapping penicillin outside the body which condition would be obtained from mixing pectin, penicillin and water results in a preparation that is not efficacious in prolonging the activity of penicillin in the body. This may be explained by the fact that in its aqueous condition the absorption of the drug in the body is rapid and is not prolonged.

If the colloidal gel is formed outside the body by the addition of water, the penicillin being hydrophilic immediately goes into solution and thus on injection acts, for all practical purposes, like aqueous solutions of penicillin which are, as is well known, rapidly absorbed and consequently rapidly excreted from the body.

It is therefore essential to this invention that the pectin in penicillin mix should contain less than 1.0% of water at the time of preparation and that this mixture in turn be suspended in an injectible vegetable oil also containing less than 1% water so that the gel is not formed prior to the injection to the body but rather that the gel is formed only after injection and only as the

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preparation comes in contact with the body fluid.

I offer as an explanation of the prolonged action of penicillin, pectin and oil preparations made in accordance with my invention, that because when it is injected with a minimum moisture content (in the so-called dry state), a repository site is formed in the tissue. As the water body fluids come in contact with the pectin, a colloidal gel is formed. Inasmuch as this contact is, however, inhibited to some degree by the oil which is hydrophobic, the penicillin which has been entrapped in the colloidal gel is only slowly released from the repository site at a rate determined by the tissue fluids' ability to reach the penicillin.

It may be considered that the penicillin at the outer edges of the repository site is relatively rapidly absorbed since it is in contact with the body fluids almost at once. The early relatively high blood levels of the drug which are obtained on injection into both animal and man are explainable on this basis. The delayed absorption and prolonged levels of the drug, i. e., the penicillin demonstrable in the injected individual in the 20th-24th hours are due to the penicillin entrapped deep in the colloidal gel repository site.

As indicated in my experiments, I preferred to use pectin (of all of the examples I have illustrated as useful here) since it is a readily available naturally occurring substance produced in large quantities. Furthermore, pectin is non-toxic and is readily absorbed by the body offering no difficulty to the tissue enzymes which are responsible for its assimilation in the body. In addition, because of its molecular structure, it is non-antigenic, i. e., it will not produce antibodies and thus will not sensitize the body tissues to later contacts with it.

Although, as I have indicated, I prefer a mix with pectin, other polysaccharides, cellulose compounds and proteins may be used when they have the common characteristic that they form colloidal gels on being brought into contact with water. Thus pectin or sodium alginate, both polysaccharides, form gels on contact with water and are satisfactory polysaccharides for use in this invention.

By contrast, sucrose (common table sugar) or lactose (milk sugar) which are also polysaccharides, do not form gels on contact with water but rather form clear solutions. These types of polysaccharides therefore would be unsatisfactory in this invention.

Similarly, gelatin, a protein substance, does form a colloidal gel on contact with water and would be useful in this invention, while casein, the protein of milk, does not form a colloidal gel on contact with water and so would not be suitable.

Streptomycin

Heretofore no procedure has been found for prolonging the therapeutic action of streptomycin. Mixtures of streptomycin and beeswax and oil has speeded up rather than retarded the body absorption rate of the drug.

I have found that my invention is applicable to a preparation of streptomycin and pectin made as follows:

As in the case of the penicillin-pectin preparation, I first prepared the pectin by drying it in a hot air oven until the pectin contained less than 1% moisture. The pectin is milled in a Waring Blender until it is of proper particle size, i. e., 50-100 microns. To 100 mg. of pectin I added .5

gm. of streptomycin calcium chloride trihydrochloride double salt which as with penicillin had also been dried to contain less than 1% moisture. I mixed this thoroughly and added sufficient peanut oil to make 1 milliliter. The whole was then mixed in a Waring Blendor to make it homogeneous and placed in glass tubes and sterilized by dry heat at a temperature of 100°-110° C. for eight to ten hours.

As a control I made a preparation of streptomycin and peanut oil only in a similar manner.

Both of the above preparations were injected intramuscularly in the right rear legs of rabbits. Blood samples were withdrawn at suitable intervals and the quantity of streptomycin determined by the *B. subtilis* cup plate assay method. The results are shown in the following Table 3.

TABLE 3

Streptomycin in micrograms per milliliter of serum

Animal No.	Material Injected	17 Hr.	21 Hr.	24 Hr.
S-23	Mycin-Pectin-oil	6.9	1.2	.82
S-28	do.	10.2	3.3	4.6
S-29	do.	1.55	.85	.58
S-31	do.	7.2	1.55	.78
S-32	do.	1.2	.66	.20
	(Averages)	(5.41)	(1.51)	(1.39)
S-33	Mycin-Oil	1.0	1.85	.46
S-36	do.	.6	.3	.0
S-38	do.	.9	.48	.33
S-39 ¹	do.	.52		
	(Averages)	(0.75)	(0.94)	(0.26)

¹ S-39 died following 17 hour bleeding.

It will be noted from the Table 3 that all five rabbits injected with the pectin preparation had relatively high blood concentrations of this drug through the 24th hour. In contrast one of the three rabbits injected with the preparation containing no pectin failed to show streptomycin in the 24th hour. Moreover, the average blood levels with the pectin preparations were more than seven times higher at the 17th hour, more than 1.5 times higher in the 21st hour and more than 5 times higher in the 24th hour than those obtained with preparations which had no pectin in it.

In the above example I have described preparations and tests of two antibiotics from molds. Other antibiotic molds or bacterial metabolic or biological excretory products which can be made in accordance with this invention include besides penicillin and streptomycin, penicillin X, penicillin F, penicillin G, penicillin dihydro F, penicillin K, derived from various strains of *Penicillium notatum*, and *Penicillium chrysogenum*; bacitracin, eumycin and subtilin derived from *B. subtilis* and other similar mold or bacterial excretory products possessing antibiotic properties.

Preferably the mold or bacterial excretory products is in the form of a neutral salt which is highly water soluble, as for example, penicillin potassium. However, both the molds and the bacterial excretory products may be in the form of salts such as penicillin sodium or penicillin calcium, streptomycin sulphate, streptomycin phosphate, streptomycin hydrochloride, streptomycin calcium chloride, trihydrochloride double salt, etc.

Drugs such as insulin, epinephrine, ephedrine and hormones, including estrin, estradiol and

still-besterol; vitamins such as folic acid, vitamin E₁ complex, vitamin C (ascorbic acid), liver extract and drugs where the therapeutic effect is to be prolonged, can also be made and used in accordance with this invention, and I do not wish to be limited by the specific examples herein given of my invention except as set forth in the appended claims.

The invention described herein may be manufactured and used by or for the Government of the United States for governmental purposes without the payment to me of any royalty thereon in accordance with the provisions of the act of April 30, 1928 (Ch. 460, 45 Stat. L. 467).

I claim:

1. An injectable therapeutic composition comprising an oleaginous normally-liquid vehicle having combined therewith a drug which is normally rapidly assimilated upon injection, and pectin, said composition containing less than 1% free water.

2. The composition of claim 1 wherein the oleaginous vehicle is peanut oil.

3. The composition of claim 1 wherein the drug is streptomycin.

4. The composition of claim 1 wherein the drug is a hormone.

5. The composition of claim 1 wherein the oleaginous vehicle is propylene glycol.

6. An injectable therapeutic composition comprising an oleaginous normally-liquid vehicle having penicillin and pectin combined therewith, said composition containing less than 1% free water.

7. An injectable therapeutic composition comprising peanut oil having penicillin and pectin dispersed therein, said composition containing less than 1% free water, whereby said composition is readily injectable but upon contact with aqueous body fluids becomes slowly resorbable to yield prolonged medication.

8. The composition of claim 7 wherein each cubic centimeter thereof contains about 180 milligrams of penicillin and about 270 milligrams of pectin, the balance being substantially all peanut oil.

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