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## ACETYL SALICYLIC ACID PREPARATION

Sverre Quisling, Madison, Wis.

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This invention is a continuation in part of my copending application Serial No. 260,109, filed March 18, 1939.

My invention relates to preparations of acetyl salicylic acid, having new and unpredictable physical, germicidal, and pharmacological properties, and having a particle size far smaller than has been known heretofore in preparations of acetyl salicylic acid.

Another object is to provide acetyl salicylic acid of increased therapeutic efficacy.

Another object is to provide tablets, dusting powder, chewing gum, confections, or lozenges, containing acetyl salicylic acid in a state of increased availability to living organisms.

Another object is to provide tablets of acetyl salicylic acid, which will dissolve more rapidly and be more efficacious as an antiseptic or analgesic than products containing acetyl salicylic in like amount prior to this invention.

Further objects and applications of this invention will become apparent as the following detailed description proceeds.

In previous work conducted in 1933 and disclosed in part in my United States Patent 2,025,399, entitled Topical anaesthetics, I demonstrated the correlation between physical state, therapeutic availability and also germicidal action, particularly of hydroxy aromatic derivatives. This work, and further findings in part disclosed in my U. S. Patent 2,152,917, and my U. S. Patent 2,216,251, indicated that hydroxy aromatic derivatives influence the physical state of colloids, and give valuable unpredictable properties. This conclusion was confirmed and expanded in my copending application, Serial No. 260,109, filed March 6, 1939, of which this application is a continuation in part. These observations and experiences suggested that alteration of physical state of acetyl salicylic acid, such as might be obtained by extreme degree of comminution beyond anything known heretofore, might lead to a product of unpredictably desirable properties.

However, in the case of acetyl salicylic acid, such comminution is difficult, and has not been attained heretofore. For instance, the method of precipitation from solution in colloidal subdivision is inoperable in the instance of acetyl salicylic acid, because any attempt to precipitate this substance in colloidal state leads to decomposition into acetic and salicylic acids, the pharmacological actions both of which substantially differ from that of acetyl salicylic acid.

On comminuting acetyl salicylic acid by methods generally known and practiced by pharmaceutical manufacturers, coalescence of the par-

ticles, or "caking" occurs when the average particle size has been brought to the limit of an average particle diameter of 14 microns; the acetyl salicylic acid then forms a solid coating on the surfaces of the comminuting members and on other surfaces of the comminuting machine, thus rendering impossible further reduction of particle size.

Such preparations, from the viewpoint of this invention, are very coarse, and differ profoundly from the preparations described below in their physical, pharmacological, and germicidal properties.

By a method not previously used in the field of pharmaceuticals, I have prepared comminuted acetyl salicylic acid, having an average diameter of the particles substantially less than 14 microns, preferably less than nine microns and in the order of two to eight microns, and even less than two microns.

These preparations have been found to differ from the previously known acetyl salicylic acid preparations in physical, colloid-chemical, pharmacological, and germicidal properties to a degree far in excess of what might have been expected merely from a consideration of the increased active surface area; and to possess unexpected and unpredictable properties, which could not have been anticipated even by those skilled in the art, prior to the actual preparation and investigation of these preparations.

I have found that by admixture of suitable anti-electrostatic and/or interspersing agents, the coalescence or caking of acetyl salicylic acid on grinding was prevented, so that the acetyl salicylic acid could be milled to any degree of comminution desired, and even to a substantially colloidal state. Suitable interspersing agents include any inorganic or organic substances, or combinations thereof, which are millable, whereby I mean those that are sufficiently hard and brittle to be millable without caking in a mill, such as a ball mill, hammer mill, or the like, or which are otherwise available in an extremely fine state of comminution. Examples of substances usable as interspersing agents are for example almost all inorganic salts, or minerals, with a few exceptions readily discernible and obvious to those skilled in the art. These examples are primarily the highly hygroscopic salts, such as lithium bromide or silver fluoride, which may be used under anhydrous conditions, but are not desirable for practical purposes; the exceptionally soft salts, such as antimony chloride, which can not be readily milled because of their softness; and substances which are incompatible with

acetyl salicylic acid, reacting with this acid to form unstable compounds, such as sodium carbonate, sodium bicarbonate, magnesium oxide, calcium oxide, or hydroxide, and the like. Numerous organic substances are suitable, particularly those having hard and brittle crystals, such as for example strychnin, tetrachlorophenolphthalein and gentian violet. Even of softer materials, a plurality were found suitable if the comminution was carried out at a reduced temperature, such as for example the temperature of a mixture of acetone with solid carbon dioxide. Even of relatively soft organic materials, some may be used provided their particle size is initially very small: for example, lycopodium spores were found suitable as an interspersing agent.

The above discussion will enable those skilled in the art to select a great number of materials suitable for use as interspersing agents in comminuting acetyl salicylic acid.

From the above disclosure it is obvious that the materials in question as interspersing agents are not confined to any one structural chemical group of substances, but may be selected from chemically extremely heterogeneous materials. For this reason, and to facilitate the determination of adaptability of materials as interspersing agents, I have devised the following simple practical test to aid in the selection of interspersing agents:

Mix intimately 25 parts by volume (calculated from the specific gravity) of the substance to be investigated for suitability as an interspersing agent, in a finely powdered state, with 85 parts by volume of acetyl salicylic acid. (Peculiarly, the specific gravity of acetyl salicylic acid had not previously been reported in the literature, but was found by me to be 1.392. The volume of the acetyl salicylic acid used for this determination was determined by immersing a weighed amount of the acid in a saturated solution of acetyl salicylic acid in benzene, and observing the increase in volume.) Charge the mixture into a ball mill, charged with pebbles of approximately one-half inch average diameter, using a number of pebbles having an apparent volume about equal to that of the charge, including in this apparent volume the space between the pebbles, and mill at a rate of about 70 revolutions of the mill jar per minute.

Under these conditions, pure acetyl salicylic acid, without any interspersing agent, was found to attain average particle size of 14 microns in twenty minutes, but would cake immediately thereafter. Any prolongation of the caking time beyond twenty minutes, or to an average particle size less than 14 microns, showed at least some suitability as an interspersing agent for the purposes of this invention, for the material tested. For practical purposes, it was found the material should preferably delay caking at least 20 additional minutes, but with the preferred interspersing agents and conditions, as further detailed below, no caking took place even when the milling was continued for several days, or even indefinitely.

In this specification, and in the claims, I understand the term "interspersing agent" to mean a substance, which under the test conditions described above will delay the caking of acetyl salicylic acid substantially beyond the time required to comminute it to an average particle size substantially less than 14 microns. The above data and discussion will enable those skilled in the art, in the selection of interspers-

ing agents, to avoid substances likely not to give good results, and the above testing procedure will merely serve as a supplemental aid in the selection, and for definition of substances suitable as interspersing agents.

Among the numerous interspersing agents found suitable, may be mentioned particularly tri-calcium phosphate, and silica aerogel, prepared as disclosed in the U. S. P. 2,093,454, issued September 21, 1937, to S. S. Kistler. It was found that the admixture of only .2% to .9% of either of these substances, and/or 1% to 2% boric acid fully prevented caking of acetyl salicylic acid, even on milling in a pebble mill for eight hours or more, or to an average particle size of 2 microns, or less. The finest particle sizes were generally attained using slightly larger amounts, say 2% of the said interspersing agents. Kaolin was also very suitable, but should preferably be used in amounts of about 7 to 15% by weight. Other suitable interspersing agents were inorganic solids substantially chemically inert to acetyl salicylic acid, such as kaolin, magnesium silicate, carbon, sulphur, calcium phosphates, ferric acetate, boric acid, silver chloride, lead sulphate, barium sulphate, lead bichromate, copper sulfide, mercuric ammonium chloride, aluminum powder and the like. Among organic substances, the suitable materials were found among those having a relatively high degree of hardness and brittleness, at the temperature of the comminution process, or otherwise available in an unusually fine degree of comminution, such as for example strychnin, ephedrin sulphate, galuteolin, lycopodium spores, and the hard black resinous composite materials remaining in the still upon distilling off all material as volatile at 300 degrees C. in 1 mm. vacuum from a petroleum pitch, and the like.

From the vast number of suitable interspersing agents clearly indicated by the above enumeration of numerous suitable substances of different chemical origin and character, it is obviously easy to select several which have pharmacological or germicidal properties adapted for the particular applications in view, or which are therapeutically inert.

While most of the materials enumerated above by way of example, and not of limitation, were substantially insoluble in water, I may also use water soluble and even hygroscopic substances, provided that the comminution process is carried out under practically anhydrous conditions.

Of most of the above substances, 5 to 25% by volume was required to prevent caking, the most suitable amount of any one interspersing agent being easy to determine by experiment, in a manner obvious to those skilled in the art.

The following example may serve to further illustrate the invention:

#### Example 1

99.7 parts by weight of crystalline acetyl salicylic acid were thoroughly intermixed with .3 part by weight of finely powdered tri-calcium phosphate, and milled in a ball mill with 1/2" pebbles, at 70 revolutions per minute. After four hours the milling was interrupted, and the comminuted product removed. It was found to have an average particle size of 6 microns. The apparent specific gravity was .682, or approximately 50% lower than the apparent specific gravities of the finest powdered acetyl salicylic acid preparations hitherto available. The preparations contemplated in this invention, unless subjected to compression or like treatments, subsequently

to their preparation, have apparent specific gravities below .880, while the most finely comminuted acetyl salicylic acid preparations known heretofore have apparent specific gravities appreciably higher than .880. The preparation offered very little resistance to solid objects; even a relatively light object such as a piece of wood fell through even a foot deep layer of the milled product, while of course such a piece of light material would not at all sink through the finest acetyl salicylic acid previously known. The product of this invention behaved almost like a liquid, or like colloidal carbon: it flowed when handled in a glass container, always forming a substantially horizontal surface, and, on agitation with a glass rod or a pencil, it offered hardly any perceptible resistance. Viewed under the microscope, in the dark field of a cardioid condenser, suspended in a non-solvent liquid medium such as a concentrated solution of acetyl salicylic acid in an oil, or in perchlorethylene, it showed a large number of extremely minute particles, smaller than .1 micron, and having vivid Brownian motion.

In an attempt to separate the interspersing agent, and thus to obtain pure acetyl salicylic acid, I intermixed some of the product of the above experiment with a large excess of perchlorethylene. If a mixture of tri-calcium phosphate, and ordinary finely powdered acetyl salicylic acid, having an average particle size of 14 microns, or larger, were intermixed with perchlorethylene, the acetyl salicylic acid would float up to the surface of the liquid, and the tri-calcium phosphate, having a higher specific gravity, would sink to the bottom. The same was true of a mixture of the most finely ground acetyl salicylic acid heretofore available in commerce, or otherwise, with sodium bicarbonate, as disclosed in the British Patent, No. 25,486 (1912), to Sefton-Jones. However, unexpectedly and surprisingly, it was found that when the product of the above Example 1 was intermixed with perchlorethylene, all of the solid material would float, and no separation took place.

To confirm this finding, another experiment was made, grinding acetyl salicylic acid for two hours with 15% of its weight of kaolin. The average particle size was found to be six microns. This composition again was intermixed with a large excess of perchlorethylene. Again all of the solid material floated to the surface of the liquid, and no separation took place, although if the ingredients were intermixed, prior to the milling step, they would readily separate in two layers, the acetyl salicylic acid floating to the surface and the kaolin sinking to the bottom of the container.

To further investigate this observation, using ingredients having a greater difference in specific gravity, and thus presumably easier to separate, acetyl salicylic acid was milled as before, one hour, with twice its weight of lead sulfate as the interspersing agent. The resulting mixture, having an average particle size of 9 microns, was intermixed with an excess of perchlorethylene. Again no separation took place, and all of the solid material sank to the bottom of the container, although prior to the milling step, the ingredients were readily separable.

The experiment was repeated using numerous additional interspersing agents, and in all the proportions tried, the resultant product could not be separated in its constituents by suspension in a liquid having a specific gravity inter-

mediate between the specific gravity of the acetyl salicylic acid and of the interspersing agent. The same was true if the material was compressed to form a tablet, and this tablet was then broken up and dispersed in the liquid.

While I do not wish to confine myself to any theoretical views, it would appear, from the above findings, that the product resulting upon comminution of acetyl salicylic acid with an interspersing agent is not merely a mechanical mixture, but manifestly consists of electrochemically coherent aggregate particles, which are not broken up by such physical means as are ordinarily effective in causing separation of mechanical mixtures.

I believe that in the milling operation, the acetyl salicylic acid particles, and the particles of interspersing agents, having different or at least not exactly identical dielectric constants, assume different electrical charges, and that thus the particles of acetyl salicylic acid will repel other particles of acetyl salicylic acid, having the same electrical charge, and will attract the particles of the interspersing agent, which have electrical charges different from those of the particles of acetyl salicylic acid. If this theory is correct, it may be expected that a substance having exactly the same dielectric constant as acetyl salicylic acid would not be effective as an interspersing agent, even though brittle and millable in itself; but this appears a purely theoretical consideration. I find it much more practical to define the substances suitable as interspersing agents for the process by the simple milling test described above, than to attempt an involved physiochemical procedure, which, though interesting for theoretical study, would be far more involved and less practical to use for those skilled and engaged in the art of pharmaceutical manufacture.

Having failed in the attempt to separate the extremely finely comminuted acetyl salicylic acid from the interspersing agent by a simple gravity procedure as described above, I succeeded in bringing about this separation by preparing an interspersing agent soluble in a substance which is substantially a non-solvent for acetyl salicylic acid, and by then dissolving out the interspersing agent from the product obtained by milling.

For this purpose I dissolved a hard and brittle resinous pitch known to the trade as "Burgundy pitch" in perchlorethylene, and filtered the solution to remove all traces of material insoluble in perchlorethylene. I then distilled off the solvent on an oil bath, and finally removed all traces of the solvent by heating on an oil bath to a temperature of 250 degrees C., in a vacuum of 1 mm.

The resin thus purified was very brittle, and was completely soluble in perchlorethylene.

This resin was comminuted as finely as possible with mortar and pestle, and was then intermixed with twice its weight of acetyl salicylic acid, and the mixture was placed in a pebble mill. The mill jar was immersed in a cooling bath consisting of acetone saturated with solid carbon dioxide. Additional solid carbon dioxide was added from time to time, so that some undissolved carbon dioxide was present throughout the experiment in sufficient amounts to maintain a uniform very low temperature, but not in such quantities as to interfere with the operation of the pebble mill. The mill was not started until after an hour of cooling to allow time for uniform temperature throughout the charge. The mill was then operated two hours. The resultant

powder had an average particle size of 6 microns. This powder was intermixed with an excess of perchlorethylene, which dissolved the resin, but did not dissolve acetyl salicylic acid to any appreciable extent, particularly if the perchlorethylene had been kept in contact with acetyl salicylic acid prior to its use in this process. The acetyl salicylic acid was separated from the resin solution by centrifugation, and was washed from traces of the resin containing solution by repeated suspension in benzene, and centrifugation. It was freed from excess liquid by centrifugation and rapid drying. The resultant acetyl salicylic acid had an average particle size of six microns, and was free from the interspersing agent. By classification, it was possible to separate this preparation in fractions of different fineness. This could be done, for example, by allowing a vertical air current to pass upwardly through the preparation, and by collecting the particles carried upward on a dust filter made of cotton in the upper part of the tube, in manner obvious to those skilled in the art; or by suspending the preparation in perchlorethylene, and skimming off the particles floating up to the surface at suitable time intervals, removing excess liquid by centrifugation, and drying. The largest particles separated first, and the last fraction contained the smallest particle size. The final fraction obtained in this manner, and representing the final 3% of the preparation, was found on inspection under microscope, in the dark field of a cardioid condenser, to have a particle size well below one micron.

In preparing the acetyl salicylic acid of this invention free from the interspersing agents, it was found important to remove as thoroughly as possible the liquid medium in which the separation had been effected, prior to drying the preparation. Even though the solubility of acetyl salicylic acid in perchlorethylene, or in benzol, was but slight, the evaporation of relatively large quantities of this liquid in immediate contact with the acetyl salicylic acid resulted in the deposit of acetyl salicylic acid in sufficient amounts to cause adhesion between the particles. However, if the liquid was drained off rapidly, substantially without evaporation on a centrifuge filter, in manner obvious to those skilled in the art, then the particles remained separated even on drying, and any adhesion between them was so slight as to be readily broken up even by moderate agitation, or vibration.

The acetyl salicylic acid prepared directly by milling with an interspersing agent obviously can be separated into fractions of different particle size by the methods already outlined. Industrially, the most practical method is that of separation of the finer particles by air current, in a "cyclon" type separated, well known in the art. In this manner preparations having an average particle size as low as .1 micron, and less, were found to be obtainable.

While in the above example reference has been made to "Burgundy pitch" as an interspersing agent and to perchlorethylene as a solvent therefore, it is apparent that any interspersing agent which is soluble in a liquid non-solvent for acetyl salicylic acid may be used instead of "Burgundy pitch." For example, Egyptian asphalt and a turpentine resin known to the trade as "Petrex" and produced by the Hercules Powder Company and a synthetic petroleum resin made by the Monsanto Chemical Company, and known as "Santo resin" were also found suitable, the high-

est melting grades of these products being preferable. Instead of perchlorethylene, any other liquid which is substantially a nonsolvent for acetyl salicylic acid, and a solvent for the interspersing agent employed, is suitable, such as for example benzene and carbon-tetrachloride. Thus, using as interspersing agent a mixture of equal parts of "Petrex" and "Santo resin" with three times their combined weight of acetyl salicylic acid, the comminution was carried out successfully in a ball mill at room temperature, and both carbon-tetrachloride and benzene, respectively, were used to separate the interspersing agent from the acetyl salicylic acid.

The pure finely comminuted acetyl salicylic acid preparations thus prepared obviously may be compounded with other ingredients used in medicine, and may be compressed into tablets.

However, for practical applications, I prefer to employ preparations in which the intersecting agent remains present. The number of suitable interspersing agents is so great, and their properties so varied, that it is easy to find one suitable for almost any requirement. For example, a composition comprising less than 5% of a therapeutically inert interspersing agent, such as kaolin, or say .2% to 3% of tricalcium phosphate, and/or silica aerogel can be used freely in therapeutical compositions, the amount of these interspersing agents present being therapeutically negligible.

The finely comminuted acetyl salicylic acid preparations described above are eminently adapted for use as dusting powders for example for local treatment to inflammations of mucous membranes of the human body. The extreme ease of distribution of this powder by blowing or spraying, as well as the surprising antiseptic properties described below render them far superior to acetyl salicylic acid preparations previously available for these purposes, and particularly superior to the preparation contemplated in the British patent to Sefton-Jones, 25,486 (1912), which is chemically unstable and practically devoid of antiseptic properties, as will be described later in this specification.

The preparations of pure acetyl salicylic acid of an average particle size substantially below 14 microns, as well as the preparations in which the interspersing agents are present, are for most purposes conveniently used in the form of tablets. To facilitate the disintegration of such tablets, the preparations are intermixed with a tablet disintegrating agent having the property of swelling, so as to break up the tablets when in contact with aqueous fluids, such as for example, water, or gastric juice. To secure the full advantage of the high speed of dissolution of the preparations of this invention, I prefer to use a somewhat higher percentage of the tablet disintegrating agent preferably starch, than is usual; for example I find 25% by weight of unswollen corn starch to be a suitable amount. In tableting the material, I generally first prepare a granulation by stamping out slugs of the mixture of finely comminuted material with the starch, breaking up these slugs, and sifting them, returning the fines to the slug stamping machine and the particles coarser than the size desired for the granulation to the breaking machine. The material thus granulated is fed to tableting machines, and tableted as well known to the art.

In some cases, particularly when the desired product is made up in tablet form in a tablet-forming machine or the like, I found it advan-

tageous to include as an ingredient in the preparation a wetting agent, such as sodium lauryl sulfate or the like, for example, in the amount of one-tenth of one per cent, to further facilitate the disintegration and dissolution.

In these manufacturing operations I prefer to maintain the relative humidity of the atmosphere at a point lower than 40% to 45%, or if the relative humidity has been higher, to keep the tablets, or the acetyl salicylic acid preparation in thin layers in contact with dry air, until their moisture content is lower than that corresponding to an equilibrium with air of a relative humidity of 45%. I have found that the acetyl salicylic acid products made with stable, substantially inert interspersing agents, when prepared at a relative humidity below 45%, are at least as stable as any acetyl salicylic acid preparation previously available, and that they conform with the requirements of the U. S. Pharmacopoea in regard to salicylic acid content even after more than a year of storage, but that if the manufacturing processes have been carried out at a relative humidity higher than 45%, without a subsequent drying operation, then the product will be less stable, probably due to some absorption effect peculiar to these highly surface active preparations. The stability is particularly favorable in those preparations which contain less than 5% of the interspersing agent, such as preparations made with .2% to 5% of silica aerogel or of tricalcium phosphate as interspersing agents.

This high stability of the preparations of this invention is commercially very important, and is a significant distinction over preparations of prior art which contain acetyl salicylic acid in combination with substances which are not inert to acetyl salicylic acid, but react therewith to form soluble salts. Such preparations of prior art (for example the mixture of "finely pulverized" acetyl salicylic acid with sodium bicarbonate disclosed in the British Patent 25,486 (1912) to Sefton-Jones, or with magnesium oxide as disclosed in the Dutch Patent 12,268 to Wulffing) even when stored under cool and dry conditions, are unstable and will decompose to the extent of at least several per cent monthly.

The preparations of this invention are far more rapidly soluble than any preparations of acetyl salicylic acid previously known. This is illustrated in the following experiments:

#### Example 2

Acetyl salicylic acid was milled 2 hours in a ball mill with .6% of silica aerogel. The average particle size of this preparation was 6 microns. The product was granulated with 25% of corn starch and tableted to give tablets containing 5 grains each of acetyl salicylic acid. In the following tabulations these tablets are referred to as (I).

Other tablets were prepared containing the identical amounts of the identical ingredients, except that the acetyl salicylic acid was milled before the addition of the silica aerogel to the finest degree of comminution attainable without the aid of interspersing agents, or to an average particle size of 14 microns. In the following tabulations, these tablets are referred to as (II).

The rates of dissolution of these tablets were determined by allowing the tablets to disintegrate in 250 cc. of water at 25 degrees C., then shaking them up twice, vigorously, filtering immediately, on suction filter, and determining by

titration the amount of acetyl salicylic acid in true solution, (not merely dispersion).

#### Amount of acetyl salicylic acid dissolved, in per cent

|                 | Number of tablets in 250 cc. water |            |              |
|-----------------|------------------------------------|------------|--------------|
|                 | 1                                  | 3          | 5            |
| Tablets I.....  | Percent 74.9                       | Percent 57 | Percent 51.4 |
| Tablets II..... | Percent 28.1                       | Percent 26 | Percent 25.1 |

This test shows a much faster solution of the acetyl salicylic acid preparation of this invention, under conditions of dissolution resembling those of preparing a gargle. For these purposes, it is seen that the preparation of this invention gives a solution more than twice as concentrated, and correspondingly more efficient, therapeutically, than a preparation containing an identical quantity of acetyl salicylic acid comminuted to the finest degree known heretofore.

A comparison between the germicidal potency of the preparations I and II resulted in the unexpected discovery of a germicidal potency of the preparations of this invention far exceeding what might have been anticipated even in view of the increase of solubility produced. This is illustrated by the following example:

#### Example 3

One of the tablets (I), the composition of which is described in the preceding example, was shaken thoroughly with 30 cc. of water. The solution was tested according to the Food and Drug Administration method, in comparison with one of the tablets (II), made from the finest comminuted acetyl salicylic acid (aspirin) previously known, and the details of the composition of which are given in the preceding example, and also a tablet (III) containing an identical amount of the most finely comminuted acetyl salicylic acid heretofore available, intermixed with sodium bicarbonate, as disclosed in the British Patent 25,486 (1912), to Sefton-Jones. All of the tablets tested were disintegrated, dissolved, or suspended by shaking thoroughly for several minutes with 30 cc. of water. The shaking was continued until even the more slowly dissolving preparation II had given a substantially saturated solution. On filtration, and subsequent analysis, from the clear filtrate, it was found that the concentration of truly dissolved acetyl salicylic acid was the same for all three preparations, within a limit of 5%, and that therefore the differences found in germicidal potency cannot be ascribed merely to differences in concentration of the active ingredient.

It was found that under the conditions of the test (Food and Drug Administration method) the suspension of the tablet (I) killed 100% of the test organisms (*Staphylococcus aureus*, 24 hour culture) within 3 minutes, but not within 2 minutes; that the suspension of the tablet (II) killed the same test organisms in 15 minutes, but not in 10 minutes; and that the tablet (III) did not kill the same test organisms even on continued exposure for 150 minutes.

To compare the germicidal potency of acetyl salicylic acid, prepared according to my invention, using 1% of silica aerogel as an interspersing agent, having an average particle diameter of from 4 to 6 microns, with acetyl sal-

cylic acid of the finest average particle diameter heretofore available, found to be 14 microns, tests were made using *bacillus coli* (*Escherichia coli*) and *Staphylococcus aureus* as test organisms. The former organism commonly causes infections of the intestinal tract, kidney, and bladder; the latter of the nose, throat, and skin. Several types of tests were made with conforming results. In one test 5% and 20% of acetyl salicylic acid powder, having an average particle diameter of from 4 to 6 microns, prepared as stated above in Example 2, was suspended in water by shaking. One cc. of a water suspension of *B. coli* was then intermixed with 5 cc. of the suspension. From a plate count it was determined that 2,080,000 bacteria were present in each cc. of inoculum. At intervals of 30 seconds, 1 minute, 3 minutes, 5 minutes, 10 minutes, 20 minutes, and 1 hour, one loop full of the mixture was inoculated into tubes of sterile beef peptone broth at pH 7.0. The cultures were incubated at 37 degrees C. and were examined at 12 hour intervals for growth, as indicated by a distinct and heavy cloudiness of the medium.

It was found that preparations of acetyl salicylic acid having an average particle diameter of 4 to 6 microns, made according to the method described above, killed 100% of the test organisms within 5 minutes, under the conditions stated above in contradistinction to the preparations of commercially available acetyl salicylic acid, having an average particle diameter of 14 to 26 microns, which did not completely kill the test organisms even after 20 to 30 minutes. To determine whether the difference might not have been due to differences in the rates of dissolution, the suspensions were filtered through Whatman filter paper #1, and the content of dissolved acetyl salicylic acid determined by titration. The difference in concentration was found to be less than 5%, and entirely insufficient to explain the very great difference in germicidal potency.

These germicidal properties were equally pronounced whether acetyl salicylic acid powder of a mean particle diameter of materially less than 14 microns was used in bulk as obtained directly from the comminution process, or whether said powder was compounded or compressed into tablets or the like, pure or comingled with excipients, or with agents such as starches, dextrose, or the like, which, by their swelling, promote the disintegration of the tablets upon immersion in water. Without wishing to commit myself to any theory regarding the cause of this surprising and unpredictable enhancement of germicidal action, I believe that bacteria are attracted, electrostatically to colloidal particles of acetyl salicylic acid present in the preparations of this invention, and that they are thus brought in intimate contact with pauci-molecular layers of highly supersaturated acetyl salicylic acid solution surrounding such colloidal particles. The presence of such peculiar forces of surface attraction is at least strongly indicated by the fact that it proved impossible to effect separation of the interspersing agent from the acetyl salicylic acid of my preparations, by gravity separation means, as fully discussed above. It is also probable that a sharp concentration gradient exists in the immediate proximity of such colloidal particles, so that the different parts of a bacterium contacting such a colloidal particle will be in contact with solutions of different concentration, whereby osmotic cur-

rents may be generated facilitating penetration of the acetyl salicylic acid into the bacterial cell.

This latter assumption would explain the abrupt cessation of germicidal potency which takes place upon the addition of sodium bicarbonate, or similar substances causing complete dissolution of solid colloidal particles of acetyl salicylic acid.

The tests with the product of the Sefton-Jones patent (British, 25,486 (1912)), which is a mixture of acetyl salicylic acid with sodium bicarbonate, adapted to react chemically on contact with water to form readily soluble sodium acetyl salicylate, show that this compound has hardly any germicidal potency. Similar tests with mixtures of acetyl salicylic acid and magnesia and calcium oxide, hydroxide or carbonate, confirm that the salts of acetyl salicylic acid formed on dissolution in water of such compounds are germicidally very much less potent than the free acid, in spite of their higher solubility. This is another practically important distinction between the product of this invention, and that of the Sefton-Jones patent.

The average particle sizes of the preparations disclosed in this specification, except where otherwise expressly stated, were determined by the method described by E. L. Gooden and Charles M. Smith, in *Industrial and Engineering Chemistry*, pages 479 to 482, August, 1940, with suggested modifications supplied by these authors for use in connection with the study of powders of extremely fine particle size. The references made in the claims to preparations of certain average particle sizes, have in view values obtained by this method.

Pharmacologically, I have observed that the comparative rate of therapeutic activity of preparations made by my process of acetyl salicylic acid is distinctly shorter and more intense than when similar dosages of preparations made by manufacturers now selling similar products are employed. However, the therapeutic action of drugs on human beings is difficult to measure accurately and, although I have compared the results using my preparations with others on the market, on a number of patients for the indicated therapeutic applicability of this product with results that seem to greatly favor my preparation, I have preferred to characterize and define the preparations of the present invention particularly in terms of physical and chemical properties more objectively determinable.

It is understood that the invention has many pharmaceutical applications and that procedures and ingredients referred to in the application are for the purpose of illustration only and not to limit the scope of the claims, in which it is intended to claim all novelty inherent in this invention as broadly as possible, in view of prior art.

I claim:

1. A composition of matter comprising acetyl salicylic acid having an average particle size substantially smaller than 14 microns.
2. A composition of matter comprising acetyl salicylic acid having an average particle size smaller than 9 microns.
3. A composition of matter comprising acetyl salicylic acid particles, a substantial proportion of which have a diameter smaller than 2 microns.
4. A composition of matter comprising acetyl salicylic acid and an interspersing agent, and having an average particle size less than 9 microns.

SVERRE QUISLING.