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UNITED STATES PATENT OFFICE.

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PREPARATION OF MEDICINAL SUBSTANCES AND METHOD OF MAKING THE SAME.

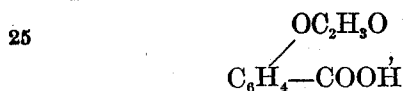
No Drawing.

Application filed September 26, 1922. Serial No. 590,739.

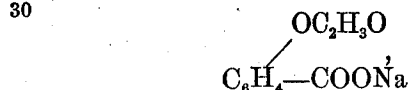
To all whom it may concern:

Be it known that I, JACOB WERSHOW, a citizen of the United States, and resident of New Haven, in the county of New Haven and State of Connecticut, have invented certain new and useful Improvements in Preparations of Medicinal Substances and Methods of Making the Same, of which the following is a specification.

My present invention, like that of my prior Patent No. 1,404,673, granted January 24, 1922, concerns development and application of the medicinal principle of aspirin, the efficacy of which is supposed to be due to production or introduction of sodium acetyl salicylate in the blood. While my present invention is not particularly concerned with the problems or theories as to what compounds are introduced into the blood by the use of aspirin nor with how they operate or re-act when they get into the circulation, it may be well to note that aspirin is acetyl-salicylic acid formula,



and that an alkali salt thereof, usually sodium acetyl-salicylate, formula,



is producible and probably is produced by alkaline re-action in the intestines or upon absorption into the circulation. It may be noted also that according to accepted theory, the value of aspirin resides in the fact that it is not dissolved nor chemically changed by the acid juices of the stomach and hence can reach the intestines and the alkaline juices thereof without producing salicylic acid, even though the stomach may include a two-tenths (.2%) of one per cent solution of hydrochloric acid. This avoids any possible irritant or corrosive effect of salicylic acid because the desired sodium acetyl-salicylate is not produced until the aspirin has passed beyond the reach of the stomach acids. The aspirin is a crystalline solid usually administered in the form of tablets comprising pulverized aspirin combined and compressed with suitable binder and filler materials. This solid vehicle for administering the active medicinal principle of aspirin is objectionable for various rea-

sons set forth in my prior patent and my present invention, as also that of said patent, concerns accomplishing the similar or equivalent effect in the blood and circulation by means of a liquid vehicle embodying the active principle of the aspirin in liquid form.

So far as concerns the thus stated purpose of my invention, it will be understood that the above-described theory of aspirin, while more or less useful as a theory, does not constitute any part of the invention of my said patent nor of my present invention, both of which may be practised without any knowledge of said theory. I will, therefore, describe my invention, referring to theory only to such extent as may seem helpful without thereby limiting my invention to or making it dependent upon how or to what extent the alkali (as sodium) acetyl-salicylates are of medicinal value for the internal economy of a human being.

As before intimated, my present invention has general purposes similar to those of said patent and includes certain generic features covered by the claims of my said patent. Hence it may be considered as being in one aspect an improvement, though in another aspect it also involves broad novelty in the application of a chemical principle, which in so far as I am aware, has never been employed in medicines, certainly not in medicines of this class.

I utilize what is technically known as "mass action" by introducing into the solution a compound suitable for producing a chemical back pressure whereby any carbonic acid, H_2CO_3 , which may be produced in the solution made according to my said patent, may be prevented from producing free salicylic acid and acetic acid in said solution. As a matter of fact the salicylic acid when present in the solution of my prior patent, is advantageous rather than objectionable, apparently because its normally irritant action in the stomach is moderated by reason of its association with the other constituents, particularly the glycerine which latter is made an important element of certain of the claims of said patent. Nevertheless, there is a prejudice against using any salicylic acid in the stomach regardless of its amount or association and there is a demand for a liquid aspirin preparation similar to that of the patent but without any active salicylic acid.

With respect to free salicylic acid in the solution, it will be noted that the reaction whereby the sodium bicarbonate changes the aspirin to sodium acetyl-salicylate, liberates carbon dioxide which produces weak carbonic acid H_2CO_3 , which, in turn, takes sodium from the sodium acetyl-salicylate, breaking it up into salicylic acid $\text{C}_6\text{H}_4\text{COOH}$, and acetic acid, $\text{H}_4\text{C}_2\text{O}_2$. This appears to be one way in which a certain amount of free salicylic acid can be present in the patented solution.

Specifically stated, my present invention contemplates establishing a mass action or chemical back pressure such as will accomplish the above purpose, by introducing acetate ions in excess of sodium ions in the solution. I have discovered that this can be accomplished by introducing medicinally unobjectionable percentages of sodium acetate, thus forcing, by mass action, a chemical reaction toward the re-formation of the sodium acetyl-salicylate, thus maintaining a balance of chemical pressures and preventing free salicylic and acetic acids in the solution.

A further increase in the chemical back pressure of the ions by a further increase in the percentage of sodium acetate will make the solution also immune to similar decomposition by the dilute (.2%) hydrochloric acid of the stomach.

Thus by means of chemical back pressure or mass action, as by sodium acetate or equivalent alkali salt of a weak acid, I may control to any desired extent the production of the free or active salicylic acid in the solution, either as originally prepared or when exposed to the juices of the stomach. An important feature of the invention is the discovery that this control extends to entirely eliminating the salicylic acid, both in the process of manufacture and in the stomach.

A distinct improvement, particularly applicable to my present invention and also useful in the practice of my prior invention, is the method which consists in carefully pulverizing and minutely and intimately comingling the several solid constituents, specifically the aspirin, the acid sodium bicarbonate and the sodium acetate, or equivalents, in the dry state, then introducing said solids into the solvent and dissolving them without heat. The solvents, specifically water and glycerine (with alcohol, aromatic elixir, etc., as desired) are preferably comingled prior to the introduction of the solids. The dry pulverizing and mixing and dissolving without heat, constitute a distinct improvement on the method described in my patent for solution of aspirin and bicarbonate of soda, without sodium acetate.

Formulae illustrative of proportions of

sodium acetate with respect to the sodium bicarbonate and aspirin for certain embodiments of my invention, are as follows:—

Aspirin	10	grams.	70
NaHCO_3	5	grams.	
$\text{NaC}_2\text{H}_3\text{O}_2$	5.6	grams.	
Glycerine	60	grams.	
H_2O	60	cu. centimeters.	

Aspirin	10	grams.	75
NaHCO_3	5	grams.	
$\text{NaC}_2\text{H}_3\text{O}_2$	5.6	grams.	
Glycerine	60	grams.	
Elixir aromatic	60	cu. centimeters.	80

The sodium acetate referred to above is the "fused" acetate from which the water of crystallization has been driven off.

The above percentages of sodium acetate are calculated more particularly for a mass action, or chemical back-pressure of acetate ions such as will afford an initial balance against the tendency to production of free salicylic acid in the solution, especially as concerns the action of the sodium hydroxide $\text{H}_2\text{C}_3\text{O}$ during or after the initial compounding of the liquid preparation. I find that such balanced preparation is modified and protected by the glycerine to such an extent that further action by the weak hydrochloric acid of the stomach, produces very little salicylic acid in the stomach, the quantities producible and their mode of application being such as to make said acid beneficial rather than otherwise.

In the preferred form, requiring a chemical back-pressure of the acetate ions, which will prevail also against the hydrochloric acid of the stomach, the amount of the sodium acetate may be increased, say two-fifths to two-thirds, or more. A typical formula for the latter purpose is as follows:

Aspirin	10	grams.	110
NaHCO_3	5	grams.	
$\text{NaC}_2\text{H}_3\text{O}_2$	8	grams.	
Glycerine	60	grams.	
Elixir	20	cu. centimeters.	
and			
H_2O	40	cu. centimeters.	115
or			
Elixir	60	cu. centimeters.	

It will be noted that in the above formulæ the sodium acetate is by weight equal to or greater than the sodium bicarbonate, the secondary re-actions of which the acetate is intended to control by its mass action, and their combined weight is approximately as great or greater than that of the aspirin.

It will be understood that the above formulæ are merely illustrative and that various degrees of chemical back-pressure may be utilized by varying the percentages of the acetate or its equivalent; also that

the desired mass action may be afforded by salts of alkali or alkaline earth metals, other than sodium, with so-called "weak acids" other than acetic acid, but with a distinct preference for a sodium as the alkaline metal and acetic acid as the weak acid; also that my invention includes broadly the method of preventing undesired chemical re-actions in a medicinal preparation by utilizing a medicinally harmless agent affording mass action or chemical back-pressure of the desired intensity.

It will be noted also that the liquid constituents, aspirin, acid bicarbonate of soda, etc., are preferably used about as in the patent, and the aloin may be used or not, as desired.

It will be evident, however, that the mass action of the sodium acetate in the solution is, in a sense, independent of whether it is sodium hydroxide (H_2CO_3) or dilute hydrochloric acid (HCl) that threatens the integrity of the sodium acetyl-salicylate; and also independent of whether the latter is produced in the preferred manner by action of acid bicarbonate of soda upon aspirin, or otherwise.

Subject to the above-described differences with reference to the methods of making, the use of sodium acetate, and the resulting differences in the product, the various specifications of my prior patent as to the kinds of materials used including most of the proportions, percentages and doses, may be taken as part of my present specification.

I claim:

1. A medicinal liquid preparation made from aspirin rendered soluble by dissolving it simultaneously with acid bicarbonate

of soda and sodium acetate, in a medicinally unobjectionable liquid.

2. A medicinal liquid preparation made from aspirin rendered soluble by dissolving it simultaneously with acid bicarbonate of soda and sodium acetate, in a medicinally unobjectionable liquid, the sodium acetate constituent being by weight approximately equal to or greater than the sodium bicarbonate.

3. A medicinal liquid preparation made from aspirin rendered soluble by dissolving it simultaneously with acid bicarbonate of soda and sodium acetate, in a medicinally unobjectionable liquid, the sodium acetate constituent being by weight approximately equal to or greater than the sodium bicarbonate and their combined weight approximately as great or greater than that of the aspirin.

4. A solution containing sodium acetyl-salicylate and sodium acetate.

5. A solution containing sodium acetyl-salicylate and sodium acetate, the latter in sufficient quantities to afford a chemical balance against formation of salicylic acid by dilute sodium hydroxide.

6. The method of making sodium acetyl-salicylate from aspirin and acid bicarbonate of soda, which method consists in minutely pulverizing and co-mingling the solid aspirin and bicarbonate of soda, together with a suitable percentage of sodium acetate; then dissolving said solids in a suitable solvent.

Signed at New Haven in the county of New Haven and State of Connecticut this 5th day of May, A. D. 1922.

JACOB WERSHOW.