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THERAPEUTIC PEROXIDE COMPOSITION

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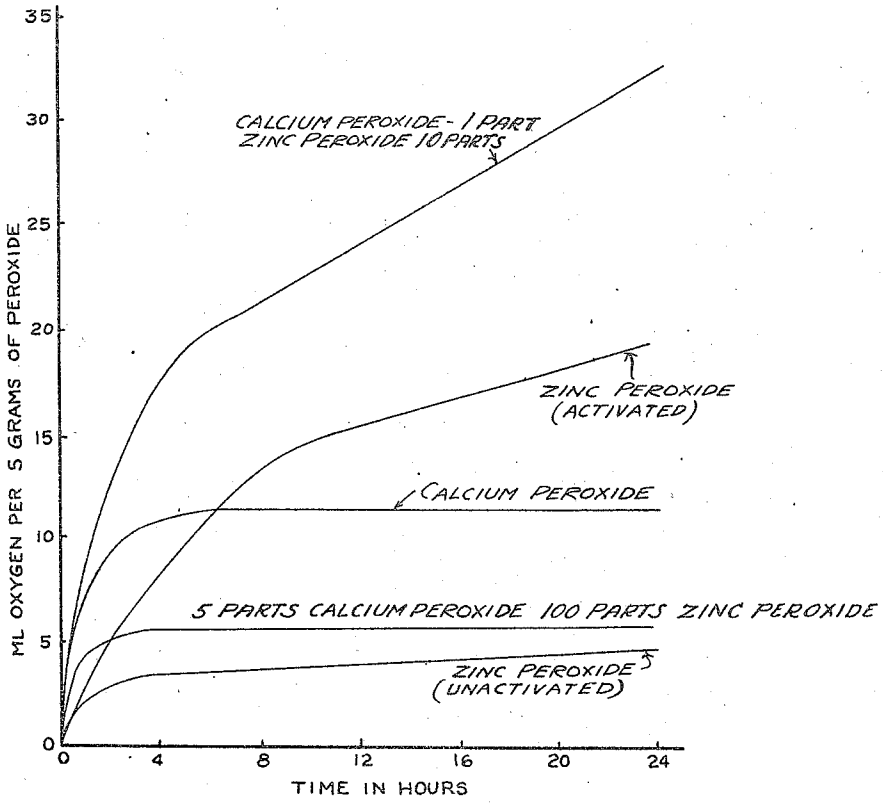

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THERAPEUTIC PEROXIDE COMPOSITION

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5 Claims. (Cl. 167—72)

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This invention relates to compositions of matter and more particularly to peroxide compositions.

For various therapeutic, prophylactic and other purposes, solid peroxides have been found advantageous as a source of active oxygen, since these compounds decompose when brought into contact with water, especially in the presence of various other substances, to give off free oxygen.

In such uses it is commonly required that free oxygen be supplied continuously over a relatively long period of time, e. g. over 24 hours or even several days, but it is desirable that within the time of the desired treatment substantially all of the available oxygen be released and it is likewise highly desirable that the material, during manufacture, storage and shipment, should remain stable and should not lose any material part of its available oxygen until that is required during its use.

Thus in recent years peroxides have been found useful in the treatment of certain persistent and deep-seated infections. Experience has shown zinc peroxide to be most advantageous for this purpose. It has been found necessary, however, before using zinc peroxide for this purpose, to activate it by a special heat treatment, for example, by heating for four hours in a carefully regulated dry oven. The material after this treatment, is unstable and cannot be stored for any considerable length of time or handled under ordinary shipping conditions without loss of activity. This has meant that the material has had to be specially treated immediately before each use; and this type of therapy has, therefore, had to be limited to the larger hospitals and clinics where special equipment for this heat treatment could be made available; moreover, the preparation of the peroxide has substantially increased the cost of such treatment.

It is accordingly an object of my present invention to provide improved peroxide compositions which are stable under practicable conditions of storage and shipment, either dry or when made up in water-free ointment, e. g. of the type set forth and claimed in my co-pending application, Serial No. 462,962, filed October 22, 1942, of which the present application is a continuation-in-part. Another object of the invention is to provide peroxide compositions which give a greater total oxygen yield per unit of peroxide used. Another object of the invention is to provide peroxide compositions which give a greater sustained oxygen yield.

With these ends in view, I have found that

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different peroxides in combination, as hereinafter more particularly described, mutually activate each other so that both the rate of oxygen evolution and the period of sustained oxygen evolution are greatly increased; and it follows that the total oxygen evolution is even more strongly increased.

As one example of my invention, I have found specifically that zinc peroxide of pharmaceutical grade, in the stable form in which it is supplied in commerce and without activation by the heat treatment as referred to above, when mixed with calcium peroxide gives off unexpectedly large amounts of oxygen in the presence of water or aqueous liquids.

This I have shown graphically in the accompanying drawing, wherein the oxygen evolution is plotted with the ordinate representing milliliters of oxygen per 5 grams of peroxide and the abscissae representing time in hours. The figures plotted are actual figures for the peroxide in contact with human plasma at 37° C. It will be observed that the unactivated zinc peroxide gives off during the first 24 hours, something less than five milliliters per five grams of peroxide. Calcium peroxide alone is more active, giving off approximately double the amount of oxygen during the first 24 hours, but the oxygen evolution is very quickly over and not sustained, even to a small extent, as in the case of the zinc peroxide. The addition of calcium peroxide in the proportion of five parts of calcium peroxide to 100 parts of zinc peroxide produces an increase in total oxygen much greater than the proportionate increase which might be expected from the greater activity of calcium peroxide. Moreover this small addition of calcium peroxide brings about a sudden initial release of almost the entire oxygen evolution during the first three hours. When the amount of calcium peroxide added to the zinc peroxide is doubled, using one part of calcium peroxide to ten parts of zinc peroxide, the effect is even more startling and much more beneficial. In this case the total oxygen evolution in 24 hours is multiplied more than sevenfold and, what is even more important, this increase in total oxygen evolution is accompanied by an increase in the sustained oxygen evolution. Whereas, after the first four hours oxygen is evolved from the zinc peroxide alone at a rate less than 1½% of the 24 hour total in each hour with the ten to one mixture of zinc peroxide and calcium peroxide, the evolution after the first four hours is at the rate of approximately 4% per hour and when stated in terms of milliliters of oxygen per

gram of peroxide the rate is approximately .01 of a milliliter per gram per hour for the unactivated zinc peroxide alone and approximately .08 for the ten to one zinc peroxide-calcium peroxide mixture.

For purposes of comparison I have also included in this graph a similar plot of zinc peroxide activated by the ordinary oven treatment. It will be observed that, although the ordinary activation treatment greatly improves the peroxide from its unactivated state, a mixture with calcium peroxide in accordance with the present invention produces almost as much improvement again, beyond the ordinary activated zinc peroxide. Moreover, whereas the ordinary activated zinc peroxide becomes unstable when thus activated, a mixture of calcium peroxide and zinc peroxide remains sufficiently stable for handling with reasonable precautions in manufacture, packaging, storage and shipping, and the activity such as is illustrated in the accompanying graph occurs only when the material is exposed to the aqueous liquid.

When the amount of calcium peroxide is increased beyond the 10% ratio, the advantage is decreased for the purposes herein set forth. The reason for this striking advantage in this particular range of proportions is not at present understood, but is well established by experience.

I have found, in fact, that it is entirely feasible to combine such a mixture in pharmaceutical preparations, providing only that the entire composition is water-free and remains so during storage and shipment, to this end advantageously being non-hygroscopic, and that the zinc peroxide and activating peroxide are in such intimate admixture that the zinc peroxide is chemically affected by the activating peroxide whenever it is exposed to moisture sufficient to produce substantial oxygen evolution. For this purpose, I have found particularly desirable a vehicle composed of the waxy polycondensation products of ethylene glycol, more properly described as the polyoxyethylene diols. These may be used in various mixtures and in mixture with the lower liquid polyoxyethylene diols or other glycol solvents, to give any desired consistency. Thus I have used for surgical dressings a soft plastic ointment made up with a waxy polyoxyethylene diol melting in the range 34° C. to 41° C., available commercially under the trade name "Carbowax 1500," mixed with about half its weight of hexa ethylene glycol or nona ethylene glycol.

I have also found that the composition of the present invention can advantageously be used in connection with the invention described and claimed in my co-pending application, Serial No. 462,962, using in the composition one of the quaternary ammonium salt wetting agents and especially one of the germicidal pyridinium salt wetting agents, which serves both to bring the peroxides more quickly and intimately into contact with the aqueous body fluid and likewise to bring the evolved oxygen more readily and completely into the tissues on which the composition is used; and at the same time, as set forth in my said prior co-pending application, the peroxide and the quaternary ammonium germicide each seems to prepare the pathogenic organisms in some way for a more effective action by the other or to support the anti-bacterial action of the other. At least it is found that the combination of the two is more effective in its germicidal action than could be expected from the known activities of each under other conditions.

As one particular example of my invention a surgical ointment for use as described above, can be made up with the following composition:

	Per cent
Zinc peroxide	10
Calcium peroxide	1
Cetylpyridinium chloride	0.2
Carbowax 1500	59.8
Hexa ethylene glycol	29

All ingredients are substantially water-free when mixed and all are sufficiently non-hygroscopic so that the material, when handled with ordinary precaution and packaged in moisture-tight packages, can be stored, shipped and used without extraordinary precautions.

Instead of hexa ethylene glycol, one may use nona ethylene glycol or other liquid glycol and instead of the Carbowax 1500 a higher polyoxyethylene diol can be used with suitable adjustment of the proportion of lower polyoxyethylene diol to produce the desired consistency. Instead of the cetylpyridinium chloride other quaternary ammonium wetting agents can be used, and particularly the germicidal wetting agents of this type, e. g. as set forth in my patents Nos. 2,295,504 and 2,295,505 and my co-pending applications, Serial No. 450,616, filed July 11, 1942, now Patent No. 2,357,479, and Serial No. 500,340, filed August 28, 1943. I have found especially advantageous for this purpose the N-propyl tridecyl pyridinium chloride.

As another example of the invention, suppositories, e. g. for treatment of chronic ulcers of the vagina or rectum, may be made of the following composition:

	Per cent
Zinc peroxide	10
Calcium peroxide	1
N-propyl tridecyl pyridinium chloride	0.2
Boric acid	1
Carbowax 1500	72.2
Spermaceti	15
Aromatics and incidental ingredients	0.6

In this composition also we may make substitutions as indicated with Example 1.

Other water-free, water-soluble vehicles as may be, or as may become, available may be substituted for the polyoxyethylene diols.

Numerous other types of pharmaceutical compositions will be suggested to those skilled in the art from what has been said above and for some purposes it may even be desirable to use the dry mixture of peroxides without other ingredients, merely mixing these with water or other aqueous liquid when they are used.

Although I have found this activation effect to be most advantageous with the combination of zinc peroxide and calcium peroxide and to reach a maximum at about the ten to one ratio specified above, it should be understood that my invention is not limited to this particular ratio. As indicated above, there is an unexpected increase in the oxygen evolution even with lower percentages of calcium peroxide and likewise with higher percentages the increased activity persists.

For surgical compositions made up in appropriate vehicles, I have found best results with percentages of the zinc peroxide or other principal peroxide up to 40% of the total, and the activating peroxide in a lesser amount up to 6% of the total.

I claim:

1. A therapeutic and prophylactic composition for use in contact with delicate living tissues and

adapted, when in contact with an aqueous medium, to evolve free oxygen, said composition comprising 100 parts of zinc peroxide intimately mixed with between 5 and 15 parts of calcium peroxide, said composition being free from water and from insoluble diluents which would substantially obstruct interaction of said peroxides in the presence of water.

2. A therapeutic and prophylactic composition for use in contact with delicate living tissues and adapted, when in contact with an aqueous medium, to evolve free oxygen, said composition comprising zinc peroxide intimately mixed with approximately one-tenth its weight of calcium peroxide, said composition being free from water and from insoluble diluents which would substantially obstruct interaction of said peroxides in the presence of water.

3. A therapeutic and prophylactic composition which comprises a mixture of ten parts of calcium peroxide to one hundred parts of zinc peroxide and two parts of a cetyl pyridinium chloride in a soft plastic base comprising 290 parts of hexa ethylene glycol and 598 parts of a higher polyoxyethylene diol of melting range about 34° C. to 40° C.

4. A therapeutic and prophylactic composition which comprises a mixture of ten parts of calcium peroxide to one hundred parts of zinc peroxide

and two parts of a cetyl pyridinium chloride in a soft plastic base comprising 290 parts of nona ethylene glycol and 598 parts of a higher polyoxyethylene diol of melting range about 34° C. to 40° C.

5. A therapeutic and prophylactic composition which comprises a mixture of ten parts of calcium peroxide to one hundred parts of zinc peroxide and two parts of a cetyl pyridinium chloride in a soft plastic base comprising a mixture of nona ethylene glycol and a higher polyoxyethylene diol of melting range about 34° C. to 40° C.

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