Aug. 27, 1957 D. F. SMITH ET AL 2,804,425

CHLORTETRACYCLINE GAUZE AND METHOD FOR PRODUCTION

Filed July 2, 1952

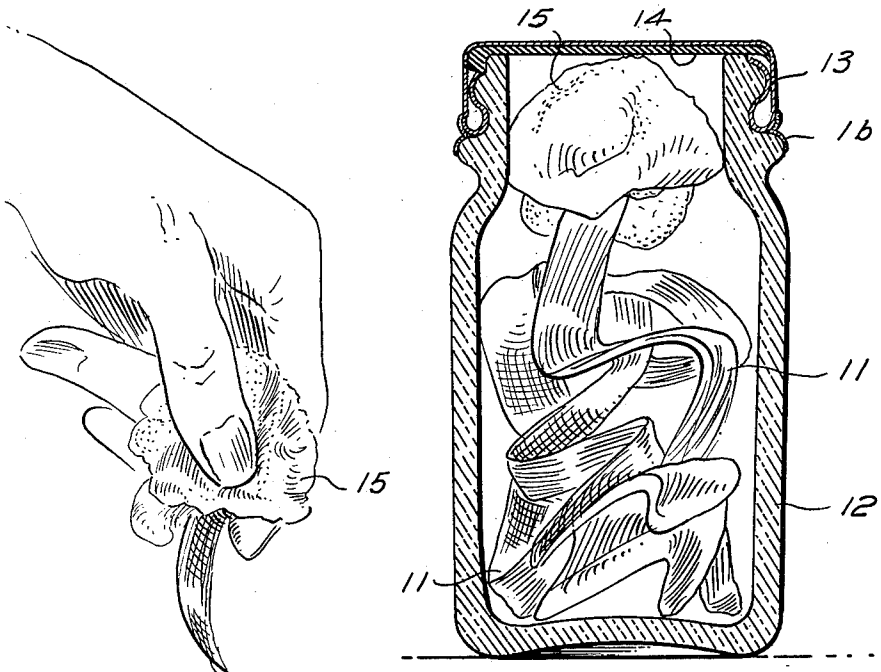


Fig. 1.

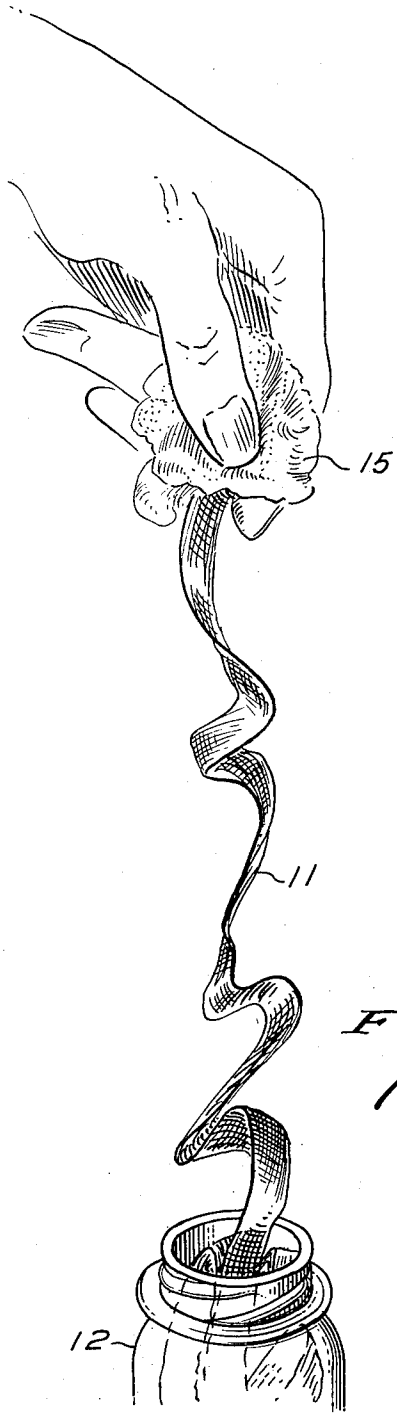


Fig. 2.

INVENTORS
DAVID FREDERICK SMITH,
ANDREW JOHN FOGLIA,
JOHN CHARLES CALLAHAN,
BY Samuel Branch Walker
ATTORNEY

United States Patent Office

2,804,425

Patented Aug. 27, 1957

2,804,425

CHLORTETRACYCLINE GAUZE AND METHOD FOR PRODUCTION

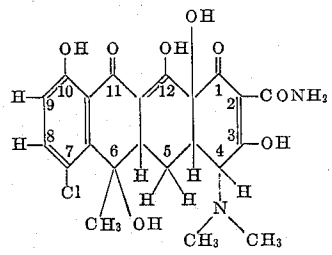
David Frederick Smith, Metuchen, N. J., and Andrew John Foglia, Brooklyn, and John Charles Callahan, Blauvelt, N. Y., assignors to American Cyanamid Company, New York, N. Y., a corporation of Maine

Application July 2, 1952, Serial No. 296,864

2 Claims. (Cl. 167—84)

This invention relates to a stable, physiologically safe and effective wound packing comprising a chlortetracycline impregnated gauze in a moisture-proof container, and a process of producing this wound packing.

Chlortetracycline is produced and sold under the commercial designation "Aueromycin," which, in certain countries, is a trademark of the American Cyanamid Company. Chlortetracycline has been found to be a naphthacene derivative and while having a structure which strongly suggests tautomeric forms, is believed to exist with the following probable structure:



A numbering system is shown. The name under which the compound is indexed in Chemical Abstracts is: 7-chloro- 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a - pentahydroxy - 6 - methyl - 1,11 - dioxo - 2-naphthacenecarboxamide (Chemical Abstracts, vol. 46, page 13363, 1952). Other numbering systems have been used in other U. S. patents, such as 2,658,077, and elsewhere. The accepted generic term for the compound is chlortetracycline (sometimes spelled "chlorotetracycline").

Gauze has been coated with various materials for surgical purposes. For example, a patent to Sobotka, 2,408,818, shows a gauze coated with at least 5% of a sulfa compound and a binding agent such as a cellulose ether. Procedures such as there disclosed and well known in the art, are satisfactory for stable chemicals but they are not satisfactory for labile, moisture or heat sensitive antibiotics such as chlortetracycline.

We have found that if ordinary gauze is impregnated with a therapeutically effective form of chlortetracycline, as for example, chlortetracycline hydrochloride, and permitted to air dry, a chlortetracycline gauze is obtained. However, the product cannot be sterilized without decomposition and is not storage stable under commercial conditions.

We have found that by using a heavy metal-free gauze and that by impregnating and drying the gauze promptly and then sterilizing by heat in the absence of moisture and then hermetically sealing the product, we have been able to provide a sterile, storage stable, chlortetracycline impregnated surgical dressing which is satisfactory for packing into wounds and which may be used as a dressing or elsewhere as is known to the medical profession.

We prefer to use a surgical gauze which is a substantially lint-free, loose woven cotton mesh. Other similar fibrous supports such as a felted or unwoven fabric can be used. We prefer a surgical dressing material which

is a textile material having substantially the feel and flexibility of ordinary surgical gauze.

Cotton gauze is of a cellulosic nature and assumes a negative charge in solution. Amazingly, chlortetracycline, although of an amphoteric nature, particularly in acid solutions, appears to assume a somewhat positive charge and accordingly can be deposited on the cotton fibers. In use on the body, the pH is shifted because the body fluids are around a pH of 7.5 and accordingly, the chlortetracycline is rapidly and readily released and made available at the time when it is needed.

It is necessary that the heavy metal content be comparatively low. For adequate stability, we prefer that the gauze have less than one part per million of heavy metals expressed as iron. Ordinary commercial surgical gauze as procured on the open market contains more than this quantity but may be treated by washing it with dilute hydrochloric acid and then with distilled water to provide a heavy metal-free gauze. Care must be taken to use corrosion resisting materials in the treatment and handling of the product. Surgical gauze which has been processed in stainless steel equipment may become contaminated with sufficient of the heavy metals to be unsatisfactory.

We prefer to use all glass or ceramic gauze contacting parts although resins or noble metals may be used.

We have found that the chlortetracycline may be supplied as the free base or the hydrochloride or other salt with an acid. The chlortetracycline may be dissolved in a volatile, oxygenated solvent such as methyl alcohol, 2-methoxy ethanol, acetone, or methylethyl ketone. We prefer a concentration of from about 1 to 10 grams per liter of solvent. The gauze may be immersed in and then removed from the solution of chlortetracycline in the solvent and then permitted to dry. In drying it is necessary that the material be comparatively free from moisture. The drying air should have a relative humidity such that the drop in temperature due to the evaporation of the solvent does not cause disposition of moisture on the gauze.

In drying the solvent from the gauze after impregnation, it is also very important to dry quickly at a somewhat elevated temperature in order to obtain an even distribution of chlortetracycline on the gauze. If the gauze is dried slowly, the solution apparently creeps over the gauze resulting in spottiness. Such spottiness appears to be due to the relatively high surface tension of the solvent—thus, any device that serves to reduce surface tension will improve the distribution. For example, the surface tension of the solution may be reduced by warming.

We find that if a heavy stream of air with a relative humidity of approximately less than 50% is used, the solvent is rapidly evaporated and no moisture is condensed from the drying air. If appreciable moisture is present at this point, the chlortetracycline does not remain stable. The moisture content in the solvent itself must be considered and if an appreciable amount of moisture is present in the solvent, the drying air must have a lower moisture content to partially compensate therefor. We find that methanol with less than 1% of water is an excellent solvent.

The gauze is then sterilized. For purposes of convenience, we prefer to pack the gauze in its final container before sterilization. Open metallic envelopes or glass vials may be used. We prefer to pack the material in a glass vial and partially apply the top. The gauze is then sterilized by heat, as for example, 110° C. for 10 hours or other sterilizing conditions which are well known to the trade. The container being partially open permits any moisture or other volatile products to pass off in the ambient air. If free access to the air is not provided during sterilization, excessive loss of chlortetracycline occurs. We then close and seal the containers.

We have found that an ordinary rubber gasket and a metal cover against a glass vial does not provide sufficient security for moisture for the product to remain stable under commercial storage conditions.

We apply a seal of microcrystalline wax to the juncture between the glass and the metal of the cover in order that a more moisture resistant layer be present to prevent the diffusion of atmospheric moisture through the rubber seal into the vial. It is of course possible to dip the end of the vial in the microcrystalline wax; however, we find that by applying the wax only to the juncture between the glass and the metal a marked economy in the quantity of microcrystalline wax required is obtained. Metallic envelopes or all-glass containers may be used to provide a completely moisture-proof hermetical seal.

In the drawings:

Figure 1 shows a finished bottle containing the chlortetracycline impregnated gauze.

Figure 2 shows the gauze being removed from the bottle.

Example 1

A 500 foot spool of double selvage edged gauze ½ inch wide was washed in 6 normal hydrochloric acid and then rinsed through distilled water, and dried. 3.2 grams of chlortetracycline hydrochloride were dissolved in one liter of absolute methanol. The gauze from the spool was threaded under a glass guide in a glass container containing the methanolic chlortetracycline solution and then drawn up and on to a reel. 850 cubic feet per minute of air which was warmed to a temperature of approximately 20° F. above the prevailing outside temperature by electric heaters totalling 6400 watts, was passed over the gauze as it travelled from the impregnating solution. The gauze was exposed to the dry air for approximately 2½ minutes as it passed zigzag over glass guides. The gauze was passed through the solution and the drying chamber at the rate of approximately 10 feet per minute. The thus dried gauze was separated into 2 foot segments 11 and packed into small glass vials 12. Cotton swedgies 15 were provided into which the end of the gauze segment was tamped to provide a sterile handle when using the chlortetracycline gauze, as shown in Figure 2. The vials were loosely capped with a metal cap 13 having a rubber gasket 14 and then placed in a sterilizing oven at 110° C. for 10 hours, care being taken to insure that none of the caps was tight on the vials. The vials were heated to 110° C. for 10 hours, removed from the sterilizing oven and the caps immediately tightened. As soon as the vials had cooled to room temperature, microcrystalline wax 16 was run around the juncture between the metal cap and the glass bottle so as to provide a moisture proof seal.

The gauze was found to contain approximately 6 milligrams of chlortetracycline hydrochloride per gram of gauze and was found to be stable on standing for prolonged periods at room temperature even under moist conditions. Comparable gauze in unsealed containers lost a large proportion of its chlortetracycline content on standing for 30 days in moist eastern seaboard climate.

Example 2

The above example was repeated using a solution of 1 gram of neutral chlortetracycline per liter of methanol.

Example 3

Example 1 was repeated using 10 grams per liter of chlortetracycline hydrochloride in methanol. The gauze contained approximately 20 milligrams of chlortetracycline per gram of gauze.

Example 4

Example 1 was repeated using 4 grams of chlortetracycline hydrobromide in 2-methoxy ethanol. The product gauze contained approximately 8 milligrams of chlortetracycline hydrobromide per gram of gauze.

Obviously the chlortetracycline may be present in a mixture of forms and mixtures of our solvents may be used. The concentration of the chlortetracycline in the solvent may be adjusted to give a product having the desired concentration of chlortetracycline in the finished gauze. Normally from 1 to 10 grams of chlortetracycline per liter of solution gives the most satisfactory concentration of chlortetracycline in the finished product. Other modifications and variations within the scope of the appended claims will suggest themselves to those skilled in the art.

As our invention, we claim:

1. A sterile, anhydrous, storage stable, chlortetracycline-containing wound packing comprising a lintless, heavy metal-free gauze impregnated with from about 1 milligram to 10 milligrams per gram of gauze of a therapeutically effective form of chlortetracycline selected from the group consisting of neutral chlortetracycline and its acid addition salts, said form of chlortetracycline being that resultant from anhydrous evaporation of a solution of said chlortetracycline in an organic solvent selected from the group consisting of methanol, 2-methoxy ethanol, acetone, and methyl ethyl ketone.

2. A method for the production of a sterile, anhydrous, storage stable chlortetracycline impregnated wound packing comprising dipping a lintless, heavy metal-free cotton gauze into a solution of a therapeutically effective form of chlortetracycline selected from the group consisting of neutral chlortetracycline and its acid addition salts and a solvent from the group consisting of methanol, 2-methoxy ethanol, acetone, and methyl-ethyl ketone, removing the solvent with air whose moisture content is so low that the cooling due to the evaporation of the solvent does not cause the deposition of moisture on the gauze, for a sufficient time to remove substantially all of the solvent, and sterilizing the thus impregnated gauze.

References Cited in the file of this patent

UNITED STATES PATENTS

2,512,616	Eberl	June 27, 1950
2,571,849	Elson	Oct. 16, 1951
2,640,842	Weidenheimer	June 2, 1953
2,680,701	Cusumano	June 8, 1954

FOREIGN PATENTS

581,234	Great Britain	Oct. 4, 1946

OTHER REFERENCES

Finland et al.: Aureomycin, A New Antibiotic, J. A. M. A., November 27, 1948, pp. 946 to 948.

Abraham: New Antibiotics, Jour. Pharm. and Pharmacol., May 1951, pp. 257–270, esp. 261.

Am. Druggist, November 1945, p. 45, Tyrothricin Band-Aid.

Drug Trade News, Dressing Utilizes Triple Antibiotics, June 25, 1951, p. 39.

Warth: The Chemistry and Technology of Waxes, Reinhold Pub. Co., New York, 1947, pp. 254 and 255.