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PRODUCTION OF ORALLY ADMINISTRABLE CONTROLLED RELEASE MEDICAMENTS

William E. Gaunt, Shaker Heights, Ohio, assignor to Strong, Cobb and Company, Inc., Cleveland, Ohio, a corporation of Delaware

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The present invention relates to orally administrable controlled release medicaments and more especially to procedure for the production of controlled release granules and tablets formed from a therapeutic agent in a matrix of a metal soap gel or gel-like structure. This application is a continuation-in-part of application Serial No. 741,235, filed June 11, 1958, now abandoned.

In copending applications, Serial Nos. 673,168, filed July 22, 1957, and 741,235, filed June 11, 1958, there have been set forth certain of the significant, basic and important considerations relating to pharmaceutical products of the controlled release type and in those applications certain new procedures have been described and claimed which provide products having an unusual amount of versatility and flexibility in their nature so that controlled release products can be tailor-made to fit the particular medicament involved and the results desired from its administration. It has further been pointed out in said application that the extent of water solubility of various therapeutic agents varies and that such fact can be taken into account by suitable modification of the procedure to adapt it for the production of a particular product.

The earlier applications refer to the use of gels of metal soaps and more specifically of gels of aluminum salts of fatty acids of the 8 to 18 carbon atoms using volatile solvents and, in some instances, heat to prepare the gel, subsequently removing the solvent to give a solvent-free dried gel. The therapeutic material is intimately and uniformly dispersed through the matrix of the solvent-free gel.

It has been found, quite unexpectedly, that the aluminum salts of fatty acid such as aluminum tristearate and aluminum octoate can be made to flow under pressure and that when highly compressed these materials become a translucent mass with the appearance of having been transformed into a gel-like structure similar to that obtained when the volatile solvent is removed by evaporation from a solvent gel of the corresponding aluminum fatty acid salt. Thus when an intimate mixture of a therapeutic material and aluminum tristearate is subjected to compression, the therapeutic material becomes embedded in the aluminum tristearate which flows around and encloses the particles of therapeutic material in a homogeneous gel-like matrix. The amount of compression determines the efficiency of this operation and one or more successive applications of pressure may, in some instances, be utilized to achieve optimum results. The minimum amount of compression used is that which is sufficient to form a gel. The compression necessary to transform the aluminum tristearate into the gel-like mass may be applied by conventional slugging techniques, by pressure rolls or by extrusion processes, but it is understood that other methods and means may be used for compressing the mixed powder of therapeutic material and aluminum soap into the gel-like structure. The compressed products may be broken down into small and uniform particles and used as such for oral administration. Alternatively, the compressed product may be broken down into small particles, lubricated with conventional lubricants and compressed into tablets for oral administration.

The invention is illustrated by the following non-limitative examples:

Example I

10 grams of powdered phenmetrazine hydrochloride (Preludin) (80 mesh) are blended with 15 grams of powdered aluminum tristearate (200 mesh) and mixing continued sufficiently to ensure uniformity, following which the powder blend is compressed on a standard compression machine. The resultant slug is reduced to 20 mesh particles, lubricated and compressed into tablets.

On exposure to artificial gastric juice and intestinal fluid, the following release characteristics were obtained:

Time	Medium	Cumulative Percent Release
Hour 1	Gastric Juice	34.2
Hour 3	Intestinal Fluid	51.8
Hour 5	do	72.6
Hour 7	do	78.8

Example II

280 grams of powdered hydroxazine hydrochloride are blended with 336 grams of aluminum tristearate and when uniformity is achieved the mixture is compressed into slugs and the slugs broken down into small particles through a 20 mesh screen. The particles are lubricated with talc and compressed into tablets.

On exposure to artificial gastric juice and intestinal fluid, the following release characteristics are obtained:

Time	Medium	Cumulative Percent Release
Hour 1	Gastric Juice	44.4
Hour 3	Intestinal Fluid	59.6
Hour 5	do	71.7
Hour 7	do	78.0

Example III

A mixture of 100 parts of meprobamate and 5 parts of aluminum tristearate is intimately blended together. The mixed powder is subjected to high compression between grooved compression rolls. The slivers of compressed materials resulting from this procedure are broken up into small particles by passing through a 20 mesh screen, the particles lubricated with talc and magnesium stearate and compressed into tablets.

On exposure to artificial gastric juice and intestinal fluid, the following release characteristics are obtained:

Time	Medium	Cumulative Percent Release
Hour 1	Gastric Juice	17.2
Hour 3	Intestinal Fluid	37.5
Hour 5	do	54.7
Hour 7	do	73.2

Example IV

A mixture of 100 parts of powdered acetyl salicylic acid and 6.67 parts of aluminum octoate is blended together. The uniform mixture is compressed into hard slugs and the slugs broken down into small particles of 20 mesh size and less. After lubrication the particles are compressed into tablets which, on exposure to artifi-

cial gastric juice and artificial intestinal fluid, show the following release characteristics:

Time	Medium	Cumulative Percent Release
Hour 1	Gastric Juice	22.0
Hour 3	Intestinal Fluid	49.2
Hour 5	do	72.0
Hour 7	do	93.2

Example V

30 grams of powdered potassium antimony tartrate are blended uniformly with 10.75 grams of aluminum tristearate. The resultant mixture is slugged on a compression machine and the slugs granulated to 16 mesh, lubricated with talc and compressed into tablets. On exposure to artificial gastric juice and intestinal fluid, the following release characteristics were obtained:

Time	Medium	Cumulative Percent Release
Hour 1	Gastric Juice	39.9
Hour 3	Intestinal Fluid	80.8
Hour 5	do	94.5
Hour 7	do	108.0

Example VI

3,000 grams of 1,2-diphenyl-4-(2'-phenylsulfinylethyl)-3,5-pyrazolidinedione is blended uniformly with 150 grams of aluminum tristearate and slugged. The resulting slugs are reduced to small particles and reslugged in order to obtain complete transformation of the aluminum tristearate into the gel-like state. The hard slugs are broken up into small particles of 20 mesh size or less, lubricated with talc and compressed into tablets. The tablets show the following release characteristics:

Time	Medium	Cumulative Percent Release
Hour 1	Artificial Gastric Juice.	0.4
Hour 3	Intestinal Fluid	34.1
Hour 5	do	64.9
Hour 7	do	85.1

It will be noted that in this instance there is little release from the tablets during the period of exposure to artificial gastric juice because of the low solubility of 1,2-diphenyl - 4 - (2' - phenylsulfinylethyl) - 3,5 - pyrazolidinedione in acid medium.

It has also been found that the versatility of the procedure can be increased by its adaptation to the manufacture of sustained release forms of therapeutic materials active in such small dosage that it is impractical to prepare a tablet form without the use of some diluent to increase the bulk to compressible size. Suitable diluents have been found to be inert soluble substances such as sucrose, lactose, mannitol etc., themselves embedded in appropriate proportion in the aluminum fatty acid salt matrix. Such diluents are made by blending the soluble substance, such as lactose, with the aluminum soap, such as aluminum tristearate, subjecting the blend to compression and reducing the compressed mixture to small particles. The finely divided therapeutic material, either alone or incorporated in a suitable proportion of matrix, is mixed with the lactose/aluminum tristearate gel-like particles and compressed into tablets.

Example VII

4 kilos of lactose U.S.P. powder and 1 kilo of aluminum tristearate are blended together and the mixture subjected to compression by slugging. The slugs are broken up into small particles (20 mesh or less) and slugged again to ensure that the lactose is unifromly embedded in the aluminum tristearate mixture. The resultant compressed product is broken down into particles of 20 mesh or less.

1 gram of prednisolone (60 mesh) is intimately mixed with 48.5 grams of the above lactose/aluminum tristearate particles and the whole mixture lubricated with 0.5 gram of magnesium stearate. The mixture is compressed into tablets weighing 250 mg., and containing 5 mg. each of prednisolone. On exposure to artificial gastric juice and artificial intestinal juice, the following release data were obtained:

Time	Medium	Cumulative Percent Release
Hour 1	Gastric Juice	12.7
Hour 3	Intestinal Fluid	33.1
Hour 5	do	63.6
Hour 7	do	85.3

Example VIII

To 40.65 grams of the lactose/aluminum tristearate particles referred to in the previous example, are added 8.1 grams of phenobarbital U.S.P. (80 mesh). The materials are blended together and lubricated with 0.75 gram of talc and 0.5 gram of magnesium stearate. The mixture is compressed into tablets weighing 200 mg., containing 32.5 mg. of phenobarbital in each tablet.

On exposure to artificial gastric juice and artificial intestinal fluid, the following release data were obtained:

Time	Medium	Cumulative Percent Release
Hour 1	Gastric Juice	18.1
Hour 3	Intestinal Fluid	40.2
Hour 5	do	66.4
Hour 7	do	97.4

The procedure of the present invention is particularly advantageous for therapeutic materials like acetylsalicylic acid, phenmetrazine hydrochloride, hydroxyzine hydrochloride and potassium antimony tartrate, but is in no way limited thereto as the procedure can be applied to a great variety of therapeutic agents and makes possible the providing of a desired release pattern of reproducible character.

It is understood that the present invention is not limited to the use of aluminum tristearate and aluminum octoate, although these are preferred, since other metal soaps of higher fatty acids containing 8 to 18 carbon atoms can likewise be used satisfactorily.

The present invention is especially characterized by the unique fact that the gel or gel-like structure is produced by compression in the absence of a volatile solvent.

The particles or granules resulting from the subdividing of the gel or gel-like structure are usable as such or in hard shell gelatine capsules or the particles or granules are formed into tablets. All of these dosage forms are adapted for oral administration.

What is claimed is:

1. A method for the production of orally administrable controlled release medicaments which comprises subjecting a therapeutic material and at least about 5%, based on the weight of the therapeutic material, of a metal soap of an 8 to 18 carbon atom fatty acid to compression sufficient to form a gel in which the therapeutic material is embedded and subdividing the gel thus formed into granules.

2. The method of claim 1 in which the metal soap is aluminum tristearate.

3. The method of claim 1 in which the metal soap is aluminum octoate.

4. The method of claim 1 in which compression is effected by means of slugging.

5. The method of claim 1 in which the granules are combined with lubricants and compressed into tablets.

6. The method of claim 5 in which the therapeutic material is phenmetrazine hydrochloride.

7. The method of claim 5 in which the therapeutic material is hydroxazine hydrochloride.

8. The method of claim 5 in which the therapeutic material is meprobamate.

9. The method of claim 5 in which the therapeutic material is acetyl salicylic acid.

10. The method of claim 5 in which the therapeutic material is potassium antimony tartrate.

11. The method of claim 5 in which the therapeutic material is 1,2-diphenyl-4-(2'-phenylsulfinylethyl)-3,5-pyrazolidinedione.

12. The method of claim 1 in which the metal soap is mixed with an inert, soluble bulk-increasing diluent prior to compression.

13. The method of claim 12 in which the diluent is powdered lactose.

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