United States Patent Office

3,328,246

Patented June 27, 1967

3,328,246

DENTAL COMPOSITIONS AND METHODS OF MAKING SAME

Siegfried Gottfried, Ilford, and Lily Baxendale, London, England, assignors to Bicrex Laboratories Limited, London, England, a corporation of the United Kingdom

No Drawing. Filed Sept. 18, 1963, Ser. No. 309,862
Claims priority, application Great Britain, Aug. 20, 1957, 26,332/57
5 Claims. (Cl. 167—60)

This application is a continuation-in-part of application Ser. No. 753,609, filed Aug. 7, 1958, now abandoned. The invention is directed primarily to pharmaceutical compositions, particularly those which are useful in the treatment of "dry socket," and to methods of making and using same. Of special import is a new vehicle used in the compositions.

Glycyrrhetinic acid and its active isomers; pharmaceutically acceptable salts thereof, such as the non-toxic alkali metal salts, e.g. the sodium salt of glycyrrhetinic acid; pharmaceutically acceptable esters thereof, e.g. glycyrrhetinic acid hydrogen succinate (see Patent 3,070,623) and glycyrrhetinic acid aminoethanol ester (see Patent 3,070,624); pharmaceutically acceptable glycyrrhetinic acid acryl derivatives e.g. acetyl glycyrrhetinate; xanthoglabrol (see Patent 3,066,072); pharmaceutically acceptable salts of xanthoglabrol with organic bases, e.g. the piperazine, protamine, purine and N-methylglucamine salts; and pharmaceutically acceptable salts of xanthoglabrol with inorganic bases, such as alkali metal salts, e.g. xanthoglabrol sodium salt; have a marked effect in suppressing inflammation. They also potentiate other therapeutics so as to achieve a synergistic effect when employed admixed therewith in a single composition.

It is an object of the present invention to provide a composition containing an active ingredient, e.g. glycyrrhetinic acid, xanthoglabrol or one of their pharmaceutically acceptable derivatives, such as those suggested heretofore, which composition will permit the slow release over an extended period of time of the active ingredient. A further object is to provide an inert and insoluble carrier for the active ingredient. The prime object, however, is to formulate compositions for the treatment of "dry socket." Still further objects will be apparent from the ensuing description.

One of the most distressing complications which may be encountered in dental extraction is "dry socket" which can cause excruciating pain. Although the aetiology of this condition is unknown, it would appear to be closely associated with the absence or loss of the blood clot, which in turn is linked with excessive vascular constriction probably caused by the large-scale use of drugs and possibly aggravated by sclerosis of the bone.

Many medicaments have been tried, the most popular to date being zinc oxide and eugenol, or zinc oxide and "Dentalone." Although these relieve pain, they have the disadvantage of leaving a large empty socket which requires repeated packing, and the cure is rather slow and not always effective. To avoid this there is provided according to the present invention, a composition in the form of a paste, which will not only relieve pain, but will encourage organisation of the socket and suppress inflammation, and which provides a vehicle which can be easily controlled and will slowly release the active therapeutic substances, while at the same time preventing infection in the surrounding area which is, of course, very prone to infection since it is surrounded by a large amount of bacterial flora.

The new composition, according to the present invention, comprises a pharmaceutical agent, preferably glycyrrhetinic acid and/or one of its active isomers and/or derivatives and/or xanthoglabrol and/or its derivatives together with a plastic material of the polythene family with a suitable plasticizer, e.g. lithium hydroxy stearate, in a miscible type of oily or fatty material, e.g. liquid petrolatum. In the following discussion of this invention, each reference to glycyrrhetinic acid is understood to include additionally or in the alternative one of its active isomers and/or one or more of its pharmaceutically acceptable derivatives, such as a salt, ester or acyl derivative thereof. Each reference to xanthoglabrol likewise is understood to include additionally or in the alternative one or more of its pharmaceutically acceptable derivatives such as a salt thereof.

For the preparation of compositions according to the present invention, the oily or fatty material, such as liquid paraffin, e.g. liquid petrolatum, and polythene (polyethylene) are melted together at a temperature of from about 130° to 200° C., but below the decomposition or boiling point of either and preferably at about 180° C. with continuous stirring. The polythene may be added to the pre-heated oily or fatty material either portionwise or continuously or in one amount. The formed liquid admixture is permitted to cool naturally, i.e. in an ambient atmosphere of room temperature (20° to 30° C.) and atmospheric pressure, to about 65° C., at which temperature platicizer, e.g. lithium hydroxy stearate, for the polythene is added gradually to said liquid admixture with constant stirring followed by the remaining ingredients, such as active ingredients, e.g. glycyrrhetinic acid or xanthoglabrol, while still stirring. It is critical that the plasticizer and the active ingredients be added at a temperature which is below their respective decomposition points. The plasticizer must be added at a temperature no higher than about 65° C. and the active ingredients must be added at a temperature no higher than about 65° C.

The polythene is that which is known as the branched chain (as opposed to "linear") or the low-density type, e.g. Bakelite DYNH or Alkathene 20. Preferred polythene has a density from 0.910 to 0.925, but medium density, i.e. from 0.926 to 0.940, polythene can also be employed. Although a crystallinity from 45 to 55% is desirable, the crystallinity can vary considerably as long as the polythene is not completely amorphous. It is also preferred that the polythene have a melting point between 100° and 120° and a molecular weight between 20,000 and 30,000. Alkathene 20 has a molecular weight of 24,000, a density of 0.92 gram/cubic centimeter, a refractive index of 1.52, a melting point between 110° and 120° C., and a decomposition temperature between 280° and 300° C.; it is soluble (at 60° to 75° C.) in many aromatic, aliphatic and halogenated hydrocarbons, but only slightly soluble in polar solvents. Bakelite DYNH has a molecular weight of about 21,000, a melting point of 110° C., a crystallinity of from 50 to 51 percent, a melt viscosity of 1,000,000 poises and a densiy of 0.92.

The polythene is preferably used in powdered or granular form but this is not essential and only serves to reduce the time necessary for dissolving the polythene in the oily or fatty material. It is to be understood that when the final viscosity of the vehicle is the greater, the greater is the molecular weight and/or crystallinity of the polythene used.

It is essential that the compositions be prepared with a plasticizer for the polythene. Any therapeutically acceptable inert (with respect to constituents) plasticizer for polythene may be employed.

A further essential ingredient for the preparation of the compositions of this invention is an oily or fatty mate-

rial. Such materials as petroleum jelly, adeps lanae and lanolin can be employed, but it is preferred to use liquid petrolatum. This ingredient constitutes one of the main components of the vehicle in which the active ingredient(s) is (are) incorporated. It must also be pharmaceutically acceptable and chemically inert toward the remaining ingredients.

The vehicle is prepared from the polythene, the plasticizer therefor and the oily or fatty material. The entire compositions are comprised of the vehicle and active ingredients. It is understood that inert materials can be added, but such addition is not an essential feature of the present invention. The make-up of the compositions with respect to essential constituents is indicated in the following table:

Essential Ingredient	Contemplated Amount (parts [1] by weight)	Preferred Amount (parts [1] by weight)
Polythene [2]	30 to 45	33 to 40
Oily or fatty material [2]	20 to 30	22 to 28
Plasticizer [2]	20 to 35	25 to 30
Active ingredient(s)	1 to 25	10 to 20

[1] The parts by weight are based upon 100 parts by weight of entire essential composition, i.e. vehicle plus active ingredient(s).
[2] Constituent of vehicle. The vehicle constitutes from 80 to 99 parts by weight, based upon 100 parts by weight of the essential composition, or preferably from 80 to 90 parts by weight of the same basis.

By the use of compositions of the present invention wherein glycyrrhetinic acid and/or xanthoglabrol are comprised by the active ingredient, the healing organisation of the socket, the suppression of inflammation, and some degree of relief of pain, are achieved by the glycyrrhetinic acid, and/or the xanthoglabrol.

There may advantageously be provided in the compositions additional active ingredients, such as analgesics, e.g. cinchocaine, amethocaine hydrochloride, and aspirin, and/or anticausative agents, e.g. bactericides and antibiotics, such as neomycin sulphate. The glycyrrhetinic compound and/or the xanthoglabrol potentiates the action of these additional ingredients so that a synergistic effect is obtained. The potentiating action is quite independent of the presence of the polythene.

It is also advantageous when the compositions contain a preservative e.g. sodium benzoate or methyl-p-hydroxybenzoate.

The compositions of the present invention can be used in the treatment of infectious and infected gum conditions, periodontal diseases and inflammation and infection of the dental nerve canal. They are particularly valuable where they can be applied as a paste or by impregnating a gauze tissue with the composition and applying the impregnated tissue to the affected area. Compositions according to this invention are of especial interest in their utility as packing in the treatment or prevention of "dry socket" following the extraction of a tooth.

Xanthoglabrol and glycyrrhetinic acid have a powerful anti-phlogistic action, assist in tissue organisation, permit swift healing, and act synergistically with analgestics and antibiotics. By using the special vehicle of this invention, containing polythene with a plasticizer, e.g. lithium hydroxy stearate, slow release and full coverage of the area can be achieved without having the active ingredients dissolved.

The following examples ar presented solely for the purpose of illustrating the invention. All parts are by weight and are based upon 100 parts by weight of essential ingredients; all temperatures are expressed in degrees centigrade. By essential ingredients are meant ingredients other than inert constituents.

EXAMPLE 1

Dental paste

Twenty-two and two fifths (22.4) parts of liquid petrolatum are placed in a stainless steel Hobart mixer with a sun and planet movement and heated therein to 180° C. at atmospheric pressure. The agitator (paddle type) is made to rotate at about 89 revolutions per minute (r.p.m.) and is maintained at this speed, except as otherwise stated, until the product is obtained.

Heating is stopped when the temperature of the liquid petrolatum reaches 180° C., and 34 parts of granulated polythene (Alkathene 20) are added to the hot liquid petroleum as it is allowed to cool naturally (in ambient surroundings). The polythene which is added slowly and continuously, dissolves in the liquid petrolatum, and the resulting solution is permitted to cool naturally, while continuing stirring, until its temperature reaches 65° C. At a temperature of 65° C. twenty-five parts of lithium hydroxy stearate are added to polythene/petrolatum solution. The resulting product is the vehicle, which is an essential part of the present invention.

The active ingredients are then incorporated into the vehicle.

Four parts of cinchocaine, 4 parts of amethocaine hydrochloride, 2 parts of glycyrrhetinic acid active isomers, 1 part of neomycin sulphate, 6.6 parts of aspirin and 1 part of methyl-p-hydroxybenzoate (preservative) are uniformly admixed and then added to the vehicle (at a temperature no higher than 65°). The rate of stirring is increased first to 165 r.p.m. and then to 300 r.p.m. to obtain thorough admixture. Natural cooling (to ambient temperature) is permitted to continue until the temperature of the admixture is essentially that of the surroundings (20° C.). The product obtained is a dental paste which is particularly useful in the treatment of "dry socket."

The liquid petrolatum used for the preceding example is a colourless oily liquid, practically tasteless and odorless even when warmed. Its density is about 0.84. All of the solid ingredients are incorporated in the mix in as finely divided (powder for the active ingredients) form as practicable.

The temperature to which the liquid petrolatum is initially heated is not critical per se, but heating initially to a temperature of 180° C. permits the discontinuance of the heating at that point and the carrying out of the entire preparation without any further heating.

The temperature of 65° at which the plasticizer is added is critical. Moreover the addition of the plasticizer at this temperature makes it necessary that the later-added active ingredients are added at a temperature which does not exceed 65° C. This is also critical.

The resulting paste is non-thixotropic and non-gelatinous.

In this example other low density polythenes can be used in place of Alkathene 20. When Bakelite DYNH is employed, the resulting product is essentially the same.

Instead of using a mixture of active ingredients, a single active ingredient can be employed. A composition prepared as above-described from 40 parts of Bakelite DYNH, 29 parts of liquid petrolatum, 30 parts of lithium hydroxy stearate and 1 part of glycyrrhetinic acid provides a dental paste having the anti-phlogistic properties of the glycyrrhetinic acid. The vehicle permits the slow release of the active ingredient.

Each of the compositions 2 to 37 is made according to the procedure of Example 1, but said procedure can be varied as indicated. In place of the Alkathene 20 other low or medium density polythene having a molecular weight between 20,000 and 30,000 can be substituted with comparable results. The liquid petrolatum can be replaced in part or in whole by any other pharmaceutically acceptable inert oily or fatty material which is liquid at a temperature in excess of about 110° C.

PARTS BY WEIGHT OF INGREDIENTS

Ingredient	Example									
	2	3	4	5	6	7	8	9	10	11
Alkathene 20	39	39	38	39	39	39	44	43	44	44
Liquid petrolatum	24	24	24	24	24	24	23	23	23	23
Adeps lanae							2	2	2	2
Lithium hydroxystearate	28	28	28	28.5	28	27	25	25	25	25
Glycyrrhetinic acid:										
Active isomer	0.75	.5					2	1.5		
N-methylglucamine salt			1							
Piperazine salt				1						
Hemisuccinate					1				2	
Di-sodium salt						1				2
Xanthoglabrol		.5						.5		
Cinchocaine	2	2	2	2	2	2	1	1	1	1
Amethocaine hydrochloride	2	2	2	2	2	2	.5	.5	.5	.5
Hydrocortisone	.25									
Neomycin sulphate	.5	.5	.5		.5	.5	.5	.5	.5	.5
Aspirin	2.5	2.5	3.5	3.5	3.5	2	2	2	2	2
Sodium benzoate	1							1		
Methyl p-hydroxybenzoate		1	1			1				

Ingredient	Example								
	12	13	14	15	16	17	18	19	20
Alkathene 20	36	30	34	33	38	35	36	38	38
Liquid petrolatum	22	30	26	27	21	26	25	26	24
Adeps lanae	2						2		
Lanolin						2			
Lithium hydroxystearate	34	30	31	32	30	30	30	31	31
Glycyrrhetinic acid:									
Active isomer						2			
N-methylglucamine salt		3					2		
Piperazine salt	2							2	
Hemisuccinate									2
Sodium salt			8	2					
Acetyl					3				
Xanthoglabrol					2				
N-methylglucamine salt		3							
Sodium salt				3					
Cinchocaine	1	1			2	2			
Amethocaine hydrochloride	.5	.5		.5				2	
Neomycin sulphate	.5	.5		.5			.5	1	1
Aspirin	2	2		2		3	3.5		3
Sodium benzoate									1
Methyl p-hydroxybenzoate			1				1		

Ingredient	Example								
	21	22	23	24	25	26	27	28	29
Alkathene 20	43	45	40	40	41	43	34	32	35
Liquid petrolatum	30	20	22	24	17	25	23	25	22
Lanolin					6				
Lithium hydroxystearate	20	26	32	30	30	26	26	27	25
Glycyrrhetinic acid:									
Hemisuccinate							1		5
Di-sodium salt	2								
Sodium salt		2							
Acetyl			2						
Xanthoglabrol				2	2				
Piperazine salt						2			
Protamine salt							2		
N-methyl-glucamine salt								2	
Sodium salt									2
Cinchocaine	2	1	1		2	1	3	4	2
Amethocaine hydrochloride	2	2			1	1	3	4	
Neomycin sulphate		.5				1			3
Aspirin		3.5	2	3	1	1	7	6	5
Sodium benzoate			1						
Methyl p-hydrobenzoate	1			1			1		1

Ingredient	Example							
	30	31	32	33	34	35	36	37
Alkathene 20	38	38	40	35	40	45	44	43
Liquid petrolatum	26	22	21	24	20	22	22	24
Lithium hydroxystearate	30	30	30	26	32	30	29	26
Glycyrrhetinic acid	2			2				
Active isomer			2					1
N-methylglucamine salt				2				
Piperazine salt		4						
Sodium salt					2			
Xanthoglabrol			2			2		
Piperazine salt		1						
N-methylglucamine salt				1				
Sodium salt					4			
Cinchocaine	2		1	4			2	2
Neomycin sulphate		.5	.5	1		1	2	.5
Aspirin	2	3.5	3.5	4	2			3.5
Sodium benzoate		1						
Methyl p-hydroxybenzoate				1			1	

Although lithium hydroxystearate is exemplified as the polythene plasticizer, it can be replaced by a corresponding amount of any pharmaceutically acceptable polythene plasticizer with comparable results. Plasticizer for the polythene, however, cannot be omitted.

In the preceding table the indicated parts by weight of derivatives of glycyrrhetinic acid and xanthoglabrol are those of the corresponding parent material so that a ready comparison can be effected.

Some of the compositions, e.g. those of Examples 8 to 12, are most useful as a gauze impregnant for packing a "dry socket," whereas others, e.g. those of Examples 1 to 7, are readily used per se for this purpose.

EXAMPLE 38

Following the extraction of a tooth the resulting cavity in the jaw is syringed with a large quantity of liquid using a Higginson's syringe and then packed with the composition of Example 32.

In view of the nature of the vehicle, the composition remains in the cavity and permits the active ingredients to escape slowly and continuously to the surrounding area. The active isomers of glycyrrhetinic acid, which are powerful anti-inflammatory agents, not only depress inflammation but assist in the organisation of the socket, as well as promoting swift healing.

The new vehicle, i.e. the product formed from the polythene, plasticizer and fatty or oily material, has been found to produce good results in compositions containing glycyrrhetinic acid and/or xanthoglabrol as the active ingredient or as one of the active ingredients. The use of the vehicle, however, is not limited to this purpose. As is apparent to the art-skilled, said vehicle can readily be employed with different active ingredients without the concurrent presence of either glycyrrhetinic acid or xanthoglabrol.

In the preceding description reference is made to acyl derivatives and esters of active ingredients. The acyl derivatives of particular import are the glycyrrhetinic acid lower acyls. Among the esters of interest are the lower alkyl esters of glycyrrhetinic acid.

It is thought that the invention will be understood from the foregoing description. Various changes can be made in the process and in the products without departing from the spirit and the scope of the invention or sacrificing its material advantages, the process and products hereinbefore described being merely illustrative of the embodiments of the invention.

What is claimed is:

1. A non-thixotropic non-gelatinuous vehicle consisting essentially of (a) branched-chain polyethylene having a molecular weight between 20,000 and 30,000 (b) a member selected from the group consisting of petroleum jelly, lanolin and liquid petrolatum, and (c) lithium hydroxy stearate, the weight ratio of (a):(b):(c) being within the range of 30 to 45:20 to 30:20 to 35 based on from about 80 to 99 parts by weight of vehicle.

2. A non-thixotropic non-gelatinous vehicle consisting essentially of branched-chain low density polyethylene having a molecular weight between 20,000 and 30,000, liquid petrolatum and lithium hydroxy stearate, the weight ratio of polyethylene:liquid petrolatum:lithium hydroxy stearate being within the range of 30 to 45:20 to 30:20 to 35, based on from 80 to 99 parts by weight of vehicle.

3. A process which consists essentially of dissolving low density polyethylene, having a molecular weight between 20,000 and 30,000 in liquid paraffin at a temperature in excess of 65° C. and below the decomposition point of both the polyethylene and the paraffin, permitting the resulting solution to cool naturally at ambient temperature and atmospheric pressure to 65° C., admixing lithium hydroxy stearate as plasticizer for said polyethylene with said solution at a temperature of at most 65° C., and permitting the resulting product to cool to ambient temperature.

4. A process which consists essentially of dissolving low density polyethylene, having a molecular weight between 20,000 and 30,000, in liquid paraffin at a temperature in excess of 65° C. and below the decomposition point of both the polyethylene and the paraffin, permitting the resulting solution to cool naturally at ambient temperature and atmospheric pressure to 65° C., admixing lithium hydroxy stearate as plasticizer for said polyethylene with said solution at a temperature of at most 65° C., thereafter admixing topical dental therapeutically active ingredients with the resulting product and allowing same to cool naturally to ambient temperature.

5. A uniform pharmaceutically acceptable composition consisting essentially of vehicle and active ingredient; the vehicle being non-thixotropic and non-gelatinous and consisting essentially of (a) branched-chain polyethylene having a molecular weight between 20,000 and 30,000, (b) a member selected from the group consisting of petroleum jelly, lanolin and liquid petrolatum and (c) lithium hydroxy stearate, the weight ratio of (a):(b):(c) being within the range of 30 to 45:20 to 30:20 to 35, and the active ingredient being a member selected from the group consisting of glycyrrhetinic acid, N-methyl-glucamine salt of glycyrrhetinic acid, piperazine salt of glycyrrhetinic acid, glycyrrhetinic acid hemisuccinate, glycyrrhetinic acid hemisuccinate disodium salt, lower acyl glycyrrhetinic acid, xanthoglabrol, piperazine salt of xanthoglabrol, protamine salt of xanthoglabrol, and N-methyl-glucamine salt of xanthoglabrol.

References Cited

UNITED STATES PATENTS

2,628,187	2/1953	Frohmader et al.	167—82
2,628,205	2/1953	Shoemaker	167—82

OTHER REFERENCES

Mitchell, Manufacturing Chemist, May 1956, pages 169–172.

Mutimer, J.A.P.A. (Sci. Ed.), February 1956, pages 101–105.

SAM ROSEN, *Primary Examiner.*