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ASPIRIN-MODIFIED COCONUT OIL LIQUID SUSPENSIONS

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This invention relates to a highly palatable and acceptable, stable liquid suspension for oral therapeutic use comprising aspirin and coconut oil.

This application is a continuation-in-part of my prior, co-pending application Serial No. 398,858, filed December 17, 1953, now abandoned.

Many physicians and patients in certain corcumstances prefer to use oral, liquid medication rather than any other form. Such use has been barred in the past by the lack of acceptance by the patient of non-aqueous vehicles or even of aqueous vehicles or lack of sufficient absorption of the drug from aqueous vehicles combined with the chemical instability of many drugs in aqueous media. This is particularly true of aspirin, which is highly unstable in water and must be given as tablets, which are often unacceptable to children and older people.

It is the object of this invention to overcome these obstacles and to provide a liquid suspension of aspirin which is stable for long periods of time, gives good absorption and is highly palatable and acceptable to patients when taken orally. It is essential to avoid the oily, nauseating "taste" or "feel" in the mouth which prohibits oral, therapeutic use as a practical matter.

The objects of this invention have been achieved and there is now provided, according to the present invention, a highly palatable and acceptable, stable liquid composition for oral therapeutic use comprising aspirin and coconut oil.

The product of the present invention is compounded so that one teaspoonful (5 ml.) contains about 1 to 15 grains aspirin, and preferably 5 grains. Other agents may be added in therapeutic dosage to provide increased scope of activity, e.g. codeine, phenacetin, caffeine, p-acetylaminophenol, salicylamide, sodium gentisate.

With respect to particle size, I prefer small particles, e.g. micronized or hammer-milled, to smooth the sensation of the products on the tongue but can also use any commercially available particle size or mixtures thereof. I find it useful, but not essential, to reduce bitter aftertaste by coating the aspirin particles, as by spray-drying, with a hydrophilic, gum-like colloid which is not soluble in oil; examples are Kelmar (potassium alginate), sodium carboxymethyl cellulose, gum acacia, gum tragacanth, gum Karaya, polyvinylpyrrolidone, methyl cellulose and polyvinyl alcohol.

As the liquid portion of these products, I use coconut oil. As available commercially it is essentially anhydrous and suitable for use. I also can use the "intravenous grade" coconut oil or "winterized" coconut oil from which substantially all tristerin has been removed by methods known to the art, e.g. cooling and pressing. This procedure may be carried out according to page 51 of Fats and Oils by H. G. Kirschenbauer (Reinhold Publishing Corp., New York, 1944) to produce a coconut oil having a setting point below 60° F.

I also find useful a coconut oil whose setting point has been reduced below 60° F. by interesterification, ester interchange and/or acidolysis according to the general procedures described by K. S. Markley on pages 292 and 306–313 inclusive (or described by the references cited therein) of his 1947 text titled Fatty Acids (Interscience Publishers Inc., New York). Thus the simple, solid glycerides of saturated acids containing at least ten carbon atoms, e.g. tristearin, are removed, either by conversion to mixed glycerides or by conversion to mixed glycerides of saturated acids containing fewer carbon atoms with simultaneous removal from the mixture of substantial amounts of lauric, myristic, palmitic and particularly stearic acids. It is apparent that for the purposes of the present invention these processes need only be carried out until the setting point of the coconut oil so modified is reduced below 60° F. as determined by simple test. Any free acids present are of course removed by conventional procedures; this includes, for example, stearic acid released by acidolysis or any added acid, e.g. caprylic or acetic acid, not consumed (converted to a glyceride) by acidolysis.

The reduction of the setting point of coconut oil upon such modification is facilitated or increased by conversion to either external or internal eutectic mixtures. By an internal eutectic mixture, I refer to the proper selection of three different acids to be attached to one molecule of glycerine by ester-type linkage so that a minimum freezing point is obtained; this is made possible by a use in combination of both ester-interchange and acidolysis. It is not implied or intended of course, that all the molecules in such modified coconut oil have the same chemical structure; the usual diversity of the natural product is present and applies to the descriptions above.

I find it useful, but not essential, to add many other ingredients. Thus, I can use up to about 20 percent (by weight of the coconut oil) of mineral oil, any edible oil, any injectable oil or such non-toxic fatty acid esters such as butyl stearate or isopropyl myristate in order, for example, to improve such physical properties as freezing point or viscosity at low temperatures and to reduce the setting point of the mixture below 60° F.

I find it useful, but not essential, to gel the coconut oil or such mixtures as are disclosed above, with about 0.1 percent to 10 percent, and preferably about two percent, of aluminum salt, particularly stearate, as disclosed in my U.S. Patent 2,507,193. I prefer aluminum monostearate, aluminum distearate, aluminum tristearate and the mixtures thereof which are available commercially. As is obvious to one skilled in the art, the details of choice and concentration of gelling agent are selected to give a suitably fluid product.

I find it useful, but not essential, to add well-known colors, flavors, sweetening agents and preservatives.

I find it useful, but not essential to increase the pharmaceutical elegance and patient-acceptability of the products of my invention by the addition of about 1.0 to 10.0 percent and preferably about 5.0 percent of fillers to reduce further the oiliness of these products, particularly those which are more dilute with respect to the therapeutic agent; I prefer aluminum hydroxide, which also acts as a buffer, but can also use talc, magnesium trisilicate, kaolin, calcium carbonate, magnesium oxide and other such non-toxic fillers which do not "soak up" oil.

I find it useful, but not essential, to add about 0.1 to 6.0 percent of a hydrophilic colloid, e.g. Kelmar (potassium alginate), as a demulcent; I theorize that the soothing action of such agents is due to their swelling and coating the tongue but at any rate they further reduce bitterness and oily texture in the product of this invention.

I find it highly desirable, but not essential, to add a non-toxic acid as a stabilizer in these aspirin suspensions. Citric acid is thus added in amounts of 0.01% to 0.5%,

preferably about 0.1%. Other non-toxic acids such as the crystalline organic acids generally used in pharmaceutical chemistry may be used in place of the citric acid, e.g. tartaric acid.

On occasion, I find it useful, but not essential to add any of the known, non-toxic surface-active agents such as lecithin, Spans (partial esters of the common fatty acids and hexitol anhydrides derived from sorbitol), Tweens (polyoxyethylene ethers of partial esters of the common fatty acids and hexitol anhydrides derived from sorbitol), or polyoxyalkylenesorbitols; in concentration of a few percent or less these are particularly useful when the products of the present invention are mixed with water to form an emulsion, either outside the body or in the gastro-intestinal tract. When used, I prefer those quantities which give a product providing in the gastro-intestinal tract a dispersion of oil in water, the oil particles containing the therapeutic agent and having a diameter of about one micron.

A more comprehensive understanding of this invention is obtained by reference to the following examples which are illustrative only and are not the exclusive embodiment of the invention.

EXAMPLE I

The following ingredients are well mixed, blended or milled into each base:

Ingredients	Formulation Number								
	1	2	3	4	5	6	7	8	9
Soluble Saccharin---g--	0.60	0.60	0.60	0.60	0.60	0.60	0.60		
Sucaryl (cyclohexanesulfamic acid)---g--	4.00	4.00	4.00	4.00	4.00	4.00	4.00		
Powdered Sugar---g--	20.0	60.0	40.0	40.0	40.0	40.0	40.0		
d-Sorbitol---g--			8.00			8.00			
Aluminum Hydroxide---g--				10.0	10.0	10.0			
Kelmar (potassium alginate)---g--					6.00	6.00	6.00		
Asparin---g--	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	36.0
Base—q.s. to---cc--	200	200	200	200	200	200	200	200	200

Thus each of the following bases is used in each of the above formulations:

Base #1 is composed of 100% coconut oil.

Base #2 is composed of 100% coconut oil substantially free of tristearin.

Base #3 is composed of 80% coconut oil and 20% peanut oil.

Base #4 is composed of 90% coconut oil and 10% peanut oil.

Base #5 is composed of 95% coconut oil and 5% peanut oil.

Base #6 is composed of 90% coconut oil and 10% peanut oil gelled with 1% aluminum monostearate.

Base #7 is composed of 90% coconut oil and 10% peanut oil gelled with 2% aluminum monostearate.

Base #8 is composed of 90% coconut oil and 10% mineral oil gelled with 2% aluminum monostearate.

Base #9 is composed of 90% coconut oil and 10% mineral oil gelled with 1% aluminum monostearate.

Base #10 is composed of 90% coconut oil and 10% mineral oil.

Base #11 is composed of 100% coconut oil gelled with 2% aluminum monostearate.

Base #12 is composed of 100% coconut oil chemically modified to reduce the setting point of the product to less than 60° F.

Base #13 is composed of 100% coconut oil chemically modified to reduce the setting point of the product to less than 60° F. and gelled with 2% of the commercially available mixture of aluminum stearates.

The products are stable at room temperature for more than two years and upon oral administration to patients are found to give good absorption upon oral administration and to be highly palatable and acceptable.

EXAMPLE II

Formulations of the present invention were prepared by mixing the following ingredients with an electric mixer, screening, mixing again and filling into bottles.

Ingredients	Formulation Number	
	1	2
Soluble Saccharin, dried, 200 mesh---g--	0.180	
Sucaryl, dried, 200 mesh---g--	1.20	1.20
Micronized aspirin---g--	3.60	3.60
Anhydrous Citric Acid, dried, 200 mesh---g--	0.60	0.03
Sugar, dried, 200 mesh---g--		18.0
Vanillin, 200 mesh---g--	0.03	0.03
Flavor---g--	0.1	0.1
Coconut Oil having setting point below 60° F. and gelled with 2% aluminum monostearate, q.s. to---cc--	60	
Coconut Oil having setting point below 60° F., q.s. to---cc--		60

Administration of one teaspoonful (5 ml. or 5 grains aspirin) to fourteen adult patients gave the following blood levels:

Patient	Formulation No.	Blood level of Salicylic Acid in meg./ml—Minutes after administration	
		10	20
TP	1	10	17
MG	1	10	28
NH	1	4	13
KB	1	3	20
CB	1	1	1
JW	1	11	10
JB	2		40
MC	2		13
IM	2		39
IC	2		2
SJ	2	3	20
KS	2	1	1
MW	2	6	16
LS	2	5	13

The following additional blood levels were measured at the indicated time after administration of one teaspoonful of such preparations containing 5 grains aspirin.

Patient	Blood Levels of Salicylic Acid			
	Sample 1		Sample 2	
	Minutes after Administration	Blood Level in mcg./ml.	Time after Administration	Blood Level in mcg./ml.
F	13	6	4 hr., 23 min	6
F	13	16	4 hr., 27 min	6
W	13	16	4 hr., 25 min	40
B	20	6	4 hr., 12 min	16
C	15	23	4 hr	6
S	11	6	4 hr., 8 min	23
M	60	16	4 hr., 20 min	6
A	30	16	4 hr., 15 min	6
T	8.5	23	4 hr., 12 min	6
N	24	40	4 hr., 15 min	6
B	30	6	4 hr., 21 min	6
H	13	6	4 hr., 9 min	16
S	10	16	4 hr	23
N	15	6	5 hr	16
F	10	32	4.5 hr	16
L	10	46	4 hr., 22 min	23
M	10	40	4 hr., 22 min	46
R	10	16	4 hr., 36 min	32
L	10	6	4 hr., 22 min	32
M	10	32	4 hr., 25 min	56
S	10	6	4 hr., 30 min	40
H	10	23	4 hr	16
B	10	23		
F	10	23	5 hr., 5 min	32
W	10	6	4 hr., 18 min	23
S	10	6	3 hr., 55 min	32
R	10	6	4 hr., 53 min	16
T	15	0	5 hr., 6 min	0
F	20	6	5 hr., 12 min	23
N	26	32	5 hr., 20 min	6
M	20	23	5 hr., 30 min	23
O	10	0	4 hr., 40 min	32
H	10	23	4 hr., 40 min	23
D	10	23	4 hr., 32 min	32
F	10	6	4 hr., 35 min	16
F	10	32	4 hr., 35 min	40
S	10	6	4 hr., 38 min	23

It is apparent that the absorption of aspirin from these formulations is more effective, in terms of both the magnitude of the blood level and the duration of the blood level, than is the absorption obtained by the use of the usual commercial aspirin tablets.

The following table summarizes for comparative purposes the blood levels of salicylic acid obtained by administration of twice as much aspirin in the usual tablet form.

Ingestion of 10 grains of U.S.P. aspirin in tablet form

[Salicylate levels in blood plasma micrograms per ml.]

Patient	Initial Sample	Time after Administration		
		10 Minutes ±2	20 Minutes ±2	60 Minutes ±2
AB	0	3.0	4.8	34.0
RG	0	2.5	5.0	12.5
AR	0	2.5	3.0	26.0
FH	0	2.0	3.6	23.8
GS	0	4.5	4.5	34.0
DF	0	2.0	3.4	11.5
PH	0	3.0	4.4	18.0
HS	0	1.5	5.0	22.0
CW	0	2.0	3.2	12.5
SP	0	2.0	3.0	19.0
RE	0	7.5	9.4	36.0
JF	0	4.0	5.0	18.5
HC	0	3.5	4.2	19.0
SC	0	2.0	3.6	11.5
EC	0	3.5	4.0	20.0
FS	0	4.0	6.2	20.0
JK	0	2.0	3.4	11.5
AC	0	3.5	3.8	22.0
BB	0	5.0	6.6	27.5
FG	3.0	10.0	14.0	42.0
DM	0	5.0	6.6	25.5
RT	0	10.0	11.6	37.5
HW	0	3.0	3.8	12.5
ML	0	2.0	4.4	19.0
DV	0	3.5	4.2	33.0
LE	0	4.0	6.0	34.0
ED	0	5.0	7.3	31.5
AY	0	3.0	5.0	15.0
WW	0	4.0	4.1	28.0
ET	0	4.0	5.4	24.0
GF	0	3.5	4.2	37.0
WT	0	4.5	5.6	19.5

Ingestion of 10 grains of U.S.P. aspirin in tablet form—Continued

Patient	Initial Sample	Time after Administration		
		10 Minutes ±2	20 Minutes ±2	60 Minutes ±2
JB	4.0	9.0	11.0	39.0
DW	0	5.0	5.4	25.0
BL	0	4.0	6.0	22.0
DR	4.0	9.0	10.2	29.5
HK	0	5.0	7.0	33.0
EF	0	3.0	3.6	23.5
CA	0	4.0	4.0	39.0
OM	0	4.0	4.8	19.5
EL	0	4.0	5.2	16.0
JF	0	5.0	5.8	22.0
JB	0	1.5	3.6	16.0
LG	0	4.5	5.0	25.0
EH	0	6.0	9.2	30.0
GY	0	5.5	6.0	29.0
JW	0	8.0	8.8	43.0
WN	0	3.0	4.6	22.5
BE	0	5.0	7.2	20.0
SN	0	5.0	5.4	22.0
Average		4.24	5.62	24.67

EXAMPLE III

Formulations of the present invention were prepared by mixing the following ingredients with an electric mixer, screening, mixing again and filling into bottles.

Ingredients	Formulation Number				
	1	2	3	4	5
Soluble Saccharin g	3.6	3.6	3.6	3.6	
Sucaryl g	24.0	24.0	24.0	24.0	24.0
Sugar g	360	360	360		360
Light Magnesium Oxide, U.S.P. g				30.0	
Anhydrous Citric Acid g				12.0	0.60
Tributyl Citrate g	1.2	7.0	12.0		
Aspirin, 200 mesh g	72	72	72	72	72
Coconut Oil having setting point below 60° F., q.s. to cc	1,200	1,200	1,200	1,200	1,200

EXAMPLE IV

Formula	Per 2 ounce (60 cc.) Bottle
Aspirin (200 mesh) grams	3.60
Sucaryl Sodium Dried (200 Mesh) do	1.20
Citric Acid Anhydrous Dried (200 mesh) do	0.05
Sucrose Dried (200 mesh) do	12.0
Vanillin (200 Mesh) do	0.03
Lemon Flavor cc	0.24
Lime Flavor cc	0.30
Vehicle Oil (Coconut oil having setting point below 60° F.) cc	60

This product contains 5 grains (300 mgs.) of aspirin per teaspoonful (5 cc.).

Place some of the coconut oil in the batching tank and begin agitation at a moderate rate using a Read-type paddle. With agitation maintained, add the aspirin and sugar. These should be milled as they are being introduced into the tank or on the day the batch is to be run. The aspirin should be checked to be sure that it complies with U.S.P. specifications before incorporating into the product. When the aspirin and sugar have been worked into the vehicle, add the sucaryl (dried at 140° F. overnight in Stokes oven), citric acid (dried at 110° F. overnight in Stokes oven) and vanillin and mix until dispersed. Add the flavors, mix for 15 minutes and q.s. to volume with coconut oil. Mix at a rapid rate for one hour and pass the batch through a 100 mesh screen. Mix again at a rapid rate for an additional two hours before filling.

EXAMPLE V

Formula	Per 2 ounce (60 cc.) Bottle
Aspirin (200 mesh)---grams	3.60
Soluble Saccharin Dried (200 mesh)---do	0.18
Sucaryl Sodium Dried (200 mesh)---do	1.20
Magnesium Oxide Light USP Dried (200 mesh)---do	1.50
Citric Acid anhydrous Dried (200 mesh)---do	0.60
Cherry Flavor---do	0.066
Vanillin (200 mesh)---do	0.0318
Cherry Flavor---cc	0.033
Vehicle Oil (Coconut oil having setting point below 60° F.)---cc	60

This product contains 5 grains (300 mgs.) of aspirin per teaspooonful (5 cc.)

Place some of the coconut oil in the batching tank and begin agitation at a moderate rate using a Read-type paddle. With agitation maintained, add the aspirin. This should be milled as it is being introduced into the tank or on the day the formula is being batched. The aspirin should be checked to be sure that it complies with U.S.P. specifications before incorporating into the product. When the aspirin has been worked into the vehicle, add the soluble saccharin, sucaryl, magnesium oxide, citric acid and vanillin and mix until dispersed. The soluble saccharin, sucaryl and magnesium oxide should be dried at 140° F. overnight in a Stokes oven and the citric acid should be dried at 110° F. overnight in a Stokes oven. Add the flavors, mix for 15 minutes and q.s. to volume with coconut oil. Mix at a rapid rate for one hour, discontinue stirring and allow the batch to stand undisturbed until the product develops a "set" (becomes thixotropic). Resume stirring at a rapid rate until the batch becomes fluid and passes through a 100 mesh screen. Mix again at a rapid rate for an additional two hours. Allow the batch to stand undisturbed overnight to be sure that the thixotropic properties have been entirely removed.

EXAMPLE VI

Formula	Per 10 cc. Bottle
Aspirin (200 mesh)---grams	0.75
Soluble Saccharin Dried (200 mesh)---do	0.03
Sucaryl Sodium Dried (200 mesh)---do	0.15
Magnesium Oxide Light U.S.P. Dried (200 mesh)---do	0.25
Citric Acid Anhydrous Dried (200 mesh)---do	0.15
Sucrose Dried (200 mesh)---do	2.00
Cherry Flavor---do	0.011
Vanillin (200 mesh)---do	0.005
Cherry Flavor---cc	0.0055
Vehicle Oil (Coconut oil having setting point below 60° F.)---cc	10

This product contains 1¼ grains or 75 mgs. of aspirin per cc.

Place some of the coconut oil in the batching tank and begin agitation at a moderate rate using a Read-type paddle. With agitation maintained, add the aspirin and sugar. These should be milled as they are being introduced into the tank or on the day the batch is to be run. The aspirin should be checked to be sure that it complies with U.S.P. specifications before incorporating into the product. When the aspirin and sugar have been worked into the vehicle, add the soluble saccharin, sucaryl, magnesium oxide, citric acid and vanillin and mix until dispersed. The soluble saccharin, sucaryl and magnesium oxide should be dried at 140° F. overnight in a Stokes oven and the citric acid should be dried at 110° F. overnight in a Stokes oven. Add the flavors, mix for 15 minutes and q.s. to volume with coconut oil. Mix at a rapid rate for one hour, discontinue stirring and allow the batch to stand undisturbed until the product develops a "set" (becomes thixotropic). Resume stirring at a rapid rate until the batch becomes fluid and pass through a 100 mesh screen. Mix again at a rapid rate for an additional two hours. Allow the batch to stand undisturbed overnight to be sure that the thixotropic properties have been entirely removed.

I claim:

1. A highly palatable and acceptable, stable liquid suspension for oral therapeutic use comprising aspirin and modified coconut oil having a setting point below 60° F., said suspension upon oral administration to man in an amount providing a dose of five grains of aspirin giving higher average blood levels of salicyclic acid than those obtained by oral administration of ten grains of aspirin in tablet form in the period from ten to twenty minutes after administration.

2. A highly palatable and acceptable, stable liquid suspension for oral therapeutic use comprising aspirin and coconut oil substantially free of tristearin, said suspension upon oral administration to man in an amount providing a dose of five grains of aspirin giving higher average blood levels of salicyclic acid than those obtained by oral administration of ten grains of aspirin in tablet form in the period from ten to twenty minutes after administration.

3. A highly palatable and acceptable, stable suspension for oral therapeutic use which is liquid above 60° F. and which comprises aspirin and coconut oil which has been chemically modified to reduce the setting point of the product to less than 60° F., said suspension upon oral administration to man in an amount providing a dose of five grains of aspirin giving higher average blood levels of salicylic acid than those obtained by oral administration of ten grains of aspirin in tablet form in the period from ten to twenty minutes after administration.

4. A process for obtaining more efficient absorption of aspirin in man upon oral administration than is obtained by the use of tablets of aspirin which comprises orally administering to man an amount containing at least one grain of aspirin of a highly palatable and acceptable, stable liquid suspension for oral therapeutic use comprising aspirin and modified coconut oil having a setting point below 60° F.

5. A process for obtaining more efficient absorption of aspirin in man upon oral administration than is obtained by the use of tablets of aspirin which comprises orally administering to man an amount containing five grains of aspirin of a highly palatable and acceptable, stable liquid suspension for oral therapeutic use comprising aspirin and modified coconut oil having a setting point below 60° F., said process giving higher blood levels of salicylic acid than those obtained by oral administration of ten grains of aspirin in tablet form in the period from ten to twenty minutes after administration.

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