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(54) Title: NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREFOR

(57) Abrégé/Abstract:
An orally administered antihyperlipidemia composition according to the present invention includes from about 250 to about 3000 parts by weight of nicotinic acid, and from about 5 to about 50 parts by weight of hydroxypropyl methylcellulose. Also, a method of treating hyperlipidemia in a hyperlipidemic having a substantially periodic physiological loss of consciousness includes the steps of forming a composition having an effective antihyperlipidemic amount of nicotinic acid and a time release sustaining amount of a swelling agent. The method also includes the step of orally administering the composition to the hyperlipidemic once per day "nocturnally", that is in the evening or at night.

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(57) Abstract

An orally administered antihyperlipidemia composition according to the present invention includes from about 250 to about 3000 parts by weight of nicotinic acid, and from about 5 to about 50 parts by weight of hydroxypropyl methylcellulose. Also, a method of treating hyperlipidemia in a hyperlipidemic having a substantially periodic physiological loss of consciousness includes the steps of forming a composition having an effective antihyperlipidemic amount of nicotinic acid and a time release sustaining amount of a swelling agent. The method also includes the step of orally administering the composition to the hyperlipidemic once per day "nocturnally", that is in the evening or at night.

NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREFOR

Field of the Invention

This invention generally relates to compositions of nicotinic acid useful for treating hyperlipidemia and methods of treating hyperlipidemia employing such compositions. More particularly, the present invention employs a composition of nicotinic acid, derivatives and mixtures thereof, and a swelling agent to form a time release sustaining composition for nocturnal or evening dosing. Specifically, the present invention employs a composition of nicotinic acid and hydroxypropyl methylcellulose to treat hyperlipidemia in a once per day oral dosage form given during the evening hours.

Background

Nicotinic acid has been used for many years in the treatment of hyperlipidemia. This compound has long been known to exhibit the beneficial effects of reducing total cholesterol, low density lipoproteins or "LDL cholesterol", triglycerides and apolipoprotein a (Lp(a)) in the human body, while increasing desirable high density lipoproteins or "HDL cholesterol".

Nicotinic acid has normally been administered three times per day after meals. This dosing regimen is known to provide a very beneficial effect on blood lipids as discussed in Knopp et al; "Contrasting Effects of Unmodified and Time-Release Forms of Niacin on Lipoproteins in

Hyperlipidemic Subjects: Clues to Mechanism of Action of Niacin"; Metabolism 34/7, 1985, page 647. The chief advantage of this profile is the ability of nicotinic acid to decrease total cholesterol, LDL cholesterol, triglycerides and Lp(a) while increasing HDL particles. While such a regimen does produce beneficial effects, cutaneous flushing and the like still often occurs in the hyperlipidemics to whom the compound is administered.

In order to avoid or reduce the cutaneous flushing, a number of materials have been suggested for administration with an effective antihyperlipidemic amount of nicotinic acid, including guar gum in U.S. Pat. No. 4,965,252, and mineral salts, as disclosed in U.S. Pat. No. 5,023,245; or inorganic magnesium salts as reported in U.S. Pat. No. 4,911,917. These materials have been reported to avoid or reduce the cutaneous flushing side effect commonly associated with nicotinic acid treatment.

Another method of avoiding or reducing the side effects associated with immediate release niacin is the use of sustained release formulations. Sustained release formulations are designed to slowly release the compound from the tablet or capsule. The slow drug release reduces and prolongs blood levels of drug and thus minimizes the side effects. Sustained release formulations of niacin have been developed, such as Nicobid™ capsules (Rhone-Poulenc Rorer), Endur-acin™ (Innovite Corporation) and Pat. No. 5,126,145 which describes a sustained release niacin formulation containing two different types of hydroxypropyl methylcellulose and a hydrophobic component.

Studies in hyperlipidemic patients have been conducted with a number of sustained release niacin products. These studies have demonstrated that the sustained release products do not have the same advantageous lipid altering effects as immediate release niacin, and in fact often have a worse side effect profile compared to the immediate release product. The major disadvantage of the sustained release formulations, as can be seen in Knopp et al., 1985, is the significantly lower

reduction in triglycerides (-2% for the sustained release versus -38% for the immediate release) and lower increase in HDL cholesterol, represented at HDL_2 particles which are known by the art to be most beneficial, (-5% for the sustained release versus +37% for the immediate release).

Additionally, sustained release niacin formulations have been noted as causing greater incidences of liver toxicity as described in Henken et al (Am J Med 91:1991 1991) and Dalton et al (Am J Med 93: 102 1992). There is also great concern regarding the potential of these formulations in disrupting glucose metabolism and uric acid levels.

In a recent edition of the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA), an articles appeared which presented research results investigating the liver toxicity problems associated with a sustained release form of nicotinic acid. "A Comparison of the Efficacy and Toxic Effects of Sustained- vs. Immediate-Release Niacin in Hypercholsterolemic Patients", McKenney et al., JAMA, Vol. 271, No. 9, March 2, 1994, page 672. The article presented a study of twenty-three patients. Of that number, 12 or 52 percent were forced to withdraw because liver function tests (LFTs) increased indicating potential liver damage. The conclusion of the authors of that article was that the sustained release form of niacin "should be restricted from use."

A similar conclusion was reached in an article authored by representatives of the Food and Drug Administration and entitled "Hepatic Toxicity of Unmodified and Time-Release Preparations of Niacin", Rader, et al., THE AMERICAN JOURNAL OF MEDICINE, Vol. 92, January 1992, page 77. Because of these studies and similar conclusions drawn by other health care professionals, the sustained release forms of niacin have experienced limited utilization.

Therefore, it can be seen from the scientific literature that there is a need for development of a sustained release niacin formulation and a method of delivering said formulation which would provide hyperlipidemic patients with "balanced lipid alteration", i.e. reductions in total cholesterol,

LDL cholesterol, triglycerides and Lp(a) as well as increases in HDL particles, with an acceptable safety profile, especially as regards liver toxicity and effects on glucose metabolism and uric acid levels.

SUMMARY OF THE INVENTION

In brief, the present invention alleviates and overcomes certain of the above-identified problems and shortcomings of the present state of nicotinic acid therapy through the discovery of novel nicotinic acid formulations and methods of treatment.

The present invention seeks to provide a composition of nicotinic acid or any compound which is metabolized by the body to form nicotinic acid for treating hyperlipidemia.

The present invention also seeks to provide a composition as above, which has a time release sustaining characteristic.

The present invention also seeks to provide a method for employing a composition as above, for treating hyperlipidemia, which results in little or no liver damage.

At least one or more of the foregoing, together with the advantages thereof over the known art relating to the treatment of hyperlipidemia, which shall become apparent from the specification which follows, are accomplished by the invention as hereinafter described.

In accordance with one aspect of the invention there is provided an oral dosage pharmaceutical composition for daily treatment of hyperlipidemia in a patient without inducing treatment-limiting liver damage, said composition comprising an effective antihyperlipidemic amount of nicotinic acid for use as an oral dose once per day during the evening or at night, or before bedtime, as a single dose, wherein the nicotinic acid is combined with at least one pharmaceutically acceptable carrier comprising a swelling agent in a total amount which functions as a controlled release agent, to form an oral sustained release solid dosage form, and wherein the oral sustained release solid dosage form does not contain an internal hydrophobic component, said single daily oral dose causing little or no serious damage to the liver of the patient, said nicotinic acid being present in said dosage form in milled agglomerates of the nicotinic acid, a portion of the total swelling agent, and a granulation binder, the agglomerates having been milled to a uniform particle size distribution, and said milled agglomerates being blended, in said dosage form, with the remaining portion of the total amount of swelling agent and an external lubricant.

In accordance with another aspect of the invention there is provided use of a composition of the invention for treating hyperlipidemia in a patient without inducing treatment-limiting (i) hepatotoxicity and (ii) abnormalities in uric acid levels or glucose levels or both.

In accordance with still another aspect of the invention there is provided a method of manufacturing a base granulation for producing a sustained release nicotinic acid solid dosage form, said method comprising:

(a) forming a wet granulation which consists essentially of nicotinic acid, a portion of a total amount of a swelling agent which functions as a controlled release agent, and a granulation binder;

(b) drying the wet granulation to form dry granules;

(c) milling the dry granules to obtain a substantially uniform particle size distribution;

(d) dry blending the milled dry granules, the remaining portion of the total amount of swelling agent, and an external lubricant to form a final dosage blend; and

(e) forming the sustained release nicotinic acid solid dosage form from the final dosage blend.

In particular embodiments the present invention provides an improved antihyperlipidemia composition of the oral type employing an effective antihyperlipidemic amount of nicotinic acid, wherein the improvement comprises compounding the nicotinic acid with from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose per hundred parts by weight of tablet or formulation.

The present invention also provides an orally administered antihyperlipidemia composition which comprises from about 30% to about 90% parts by weight of nicotinic acid; and, from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose.

The present invention also includes a method of treating hyperlipidemia in a hyperlipidemic. The method comprises the steps of forming a composition which comprises an effective antihyperlipidemic amount of nicotinic acid and an amount of excipients to provide sustained release of drug. The method also includes the step of orally administering the composition to the hyperlipidemic nocturnally.

A method of treating hyperlipidemia in a hyperlipidemic according to the invention, comprises dosing the hyperlipidemic with an effective antihyperlipidemic amount of nicotinic acid or compound metabolized to nicotinic acid by the body. The dose is given once per day in the evening or at night, combined with a pharmaceutically acceptable carrier to produce a significant reduction in total and LDL cholesterol as well as a significant reduction in triglycerides and Lp(a), with a significant increase in HDL cholesterol.

The above features and advantages of the present invention will be better understood with reference to the following detailed description and examples. It should also be understood that the particular methods and formulations illustrating the present invention are exemplary only and not to be regarded as limitations of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

By way of illustrating and providing a more complete appreciation of the present invention and many of the attendant advantages thereof, the following detailed description and examples are given concerning the novel methods and formulations.

The present invention employs nicotinic acid or a compound other than nicotinic acid itself which the body metabolizes into nicotinic acid, thus producing the same effect as described herein.

The other compounds specifically include, but are not limited to the following: nicotinyl alcohol tartrate, d-glucitol hexanicotinate, aluminum nicotinate, niceritrol and d,l-alpha-tocopheryl nicotinate. Each such compound will be collectively referred to hereinbelow by "nicotinic acid."

As stated hereabove, nicotinic acid has been employed in the past for the treatment of hyperlipidemia, which condition is characterized by the presence of excess fats such as cholesterol and triglycerides, in the blood stream. According to the present invention, a sustained release composition of nicotinic acid is prepared as an example. By "sustained release" it is understood to mean a composition which when orally administered to a patient to be treated, the active ingredient will be released for absorption into the blood stream over a period of time. For exampled, it is preferred that in a dosage of about 1500 milllgrams (hereinafter "mgs") of nicotinic acid, approximately 100 percent of the nicotinic acid will be released into the blood stream in about 4 to about 24 hours.

The specified sustained releases composition according to the present invention employs an effective antihyperlipidemic amount of nicotinic acid. By "effective antihyperlipidemic amount" it is understood to mean an amount which when orally administered to a patient to be treated, will have a beneficial effect upon the physiology of the patient, to include at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream. An exemplary effective antihyperlipidemic amount of nicotinic acid would be from about 250 mgs to about 3000 mgs of nicotinic acid to be administered according to the invention as will be more fully described hereinbelow. This amount will vary dependent upon a number of variables, including the psychological needs of the patient to be treated.

Preferably, there is also included in the sustained release composition according to the present invention, a swelling agent which is compounded with the nicotinic acid, such that when

the composition is orally administered to the patient, the swelling agent will swell over time in the patient's gastrointestinal tract, and release the active nicotinic acid, or a compound which produces nicotinic acid into the gastrointestinal system for absorption into the blood stream, over a period of time. As is known in the art, such swelling agents and amounts thereof, may be preselected in order to control the time release of the active ingredient. Such swelling agents include, but are not limited to, polymers such as sodium carboxymethylcellulose and ethylcellulose and waxes such as bees wax and natural materials such as gums and gelatins or mixtures of any of the above. Because the amount of the swelling agent will vary depending upon the nature of the agent, the time release needs of the patient and the like, it is preferred to employ amounts of the agent which will accomplish the objects of the invention.

An exemplary and preferred swelling agent is hydroxypropyl methylcellulose, in an amount ranging from about 5% to about 50% parts by weight per 100 parts by weight of tablet or formulation. The preferred example will ensure a sustained time release over a period of approximately 4-24 hours as demonstrated by in vitro dissolution techniques known to the art.

A binder may also be employed in the present compositions. While any known binding material is useful in the present invention, it is preferred to employ a material such as one or more of a group of polymers having the repeating unit of 1-ethenyl-2-pyrrolidinone. These polymers generally have molecular weights of between about 10,000 and 700,000, and are also known as "povidone".

Amounts of the binder material will of course, vary depending upon the nature of the binder and the amount of other ingredients of the composition. An exemplary amount of povidone in the present compositions would be from about 1% to about 5% by weight of povidone per 100 parts by weight of the total formulation.

Processing aids such as lubricants, including stearic acid, may also be employed, as is known in the art. An exemplary amout of stearic acid in the present compositions would be from about 0.5% to about 2.0% by weight per 100 parts by weight of tablet or formulation.

Examples of various embodiments of the present invention will now be further illustrated with reference to the following examples.

General Experimental

In order to demonstrate the effectiveness of the compositions and method of the present invention over known antihyperlipidemia compositions and methods heretofore known in the art, a number of substantially identical composition were prepared according to the disclosure hereinabove. The composition and ingredients and amounts are listed in TABLE1A hereinbelow.

TABLE IA
Test Tablet Composition

Ingredient	375 mg	500 mg	750 mg
Nicotinic Acid	375.0	500.0	750.0
Hyroxypropyl methylcellulose	188.7	203.0	204.7
Povidone	12.9	17.2	25.9
Stearic Acid	5.8	7.3	9.9
TOTAL	582.4 mg	727.5 mg	990.5 mg

The ingredients were compounded together to form a tablet. More specifically, Niaspan® once-daily tablets in accordance with the present invention utilize a hydrophilic matrix controlled drug delivery system. This is a dynamic system composed of polymer wetting, polymer hydration and polymer disintegration/dissolution. The mechanism by which drug release is controlled depends on, for example, initial polymer wetting, expansion of the gel layer, tablet erosion and niacin solubility. After initial wetting, the hydrophyllic polymer starts to partially hydrate, forming a gel layer. As water permeates into the tablet increasing the thickness of the gel layer, drug

diffuses out of the gel layer. As the outer layer of the tablet becomes fully hydrated it erodes. It is believed that this erosion results in additional drug release. The controlled release from this matrix delivery system can be modified depending on the type and molecular weight of hydrophilic polymer used.

A Niaspan® formulation consists of Niacin, Methocel® E10M Premium, Povidone K90 and Hystrene 5016 (stearic acid). Methocel® E10M Premium is utilized as a controlled-release agent in the Niaspan® formulation. Methocel is a partly O-methylated and O-(2-hydroxypropylated) cellulose and is available in several grades which vary in terms of viscosity and degree of substitution. Methocel is manufactured by Dow Chemical.

Povidone K90 is employed as a granulating/binding agent in a Niaspan® formulation. Povidone is a synthetic polymer consisting of linear l-vinyl-2-pyrrolidone groups, the degree of polymerization of which results in polymers of various molecular weights, or as indicated above. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120. Povidone K90 has an approximate molecular weight of 1,000,000. Povidone is a hygroscopic, water soluble material. Povidone K90 present in a Niaspan® formulation is manufactured by ISP (International Specialty Products). Hystrene 5016 is utilized as an external lubricant in the Niaspan® forumation. Hystrene 5016 is a mixture of stearic acid and palmitic acid. The content of stearic acid is not less than about 40.0% and the sum of the two acids is not less than about 90.0%. Hystrene 5016 is manufactured by Witco. Refer to Table IB for Niaspan® forumlation details.

Qualitatively, the four tablet strength formulations are identical. The major component of each formulation is a granulated mixture of Niacin, Methocel E10M and Povidone K90. The granulation process improves compression properties.

TABLE IB

Niaspan® Tablet Formulations

Niaspan® Product	375mg Tablets	500mg Tablets	750mg Tablets	1000mg Tablets
Formulation, % Tablets				
Niacin	64.4	70.5	77.4	83.1
Methocel E10M	7.4	8.1	8.9	9.5
Premium (Intragranular) Povidone K90	2.2	2.4	2.7	2.9
Methocel E10M	25.0	18.0	10.0	3.5
Premium (Extragranular) Hystrene 5016 (Stearic Acid)	1.0	1.0	1.0	1.0
Table weight, mg	582.5	709.5	968.6	1203.6

Niaspan® formulations are presented in white caplet shape tablets. Caplet dimensions differ with respect to product strength. The 375mg and 500mg Niaspan® tablets are compressed with tooling measuring approximately 0.687" in length x 0.281" by width. The length and width of the 750mg and 1000mg tooling measures approximately .0.750" x 0.320". Target tablet weight and hardness dictate thickness across the four Niaspan® products. The production of the Niaspan® tablets will now be described generally as set forth below.

Niaspan® Granulation Process Flow Chart

Raw Materials	Process Flow	Equipment
Niacin Povidone K90 Methocel E10M (Intragranular) Purfied Water	Granulate	High shear granulator (Littleford FM130)
	↓	
	Dry	Fluid bed drier (Glatt fluid bed drier)
	↓	
	Parcel size reduction	Mill (Kemutec Betagrind)

Niaspan® Granulation Process Description

Niaspan® granulation raw materials are dispensed and granulated in a high shear granulator. The wet granules are sieved into a fluid bed drier and are dried. When the drying process is complete, the granules are milled. Milling ensures uniform particle size distribution throughout the Niaspan® granulation.

Niaspan® Tablet Process Flow Chart

Raw Materials	Process Flow Niaspan® Tablet Blend	Equipment
Methocel E10M (Extragranular)	Blend Milled Niaspan® granules with extragranular Methocel E10M and Hystrene 5016	Blender (Patterson-Kelley V-Blender)
Hystrene 5016 (Stearic acid)	↕	
	Niaspan® Table Manufacture	
	Compress Niaspan® Tablet Blend	Rotary tablet press

Niaspan® Tablet Process Description

A Niaspan® tablet blend is manufactured by blending the Niaspan® granulation, extragranular Methocel E10M and Hystrene 5016. The quantities of each Niaspan® tablet blend

component will depend on the particular Niaspan® dose being manufactured (refer to Table IB). A Niaspan® tablet blend is compressed to form Niaspan® tablets. Niaspan® tablet physical properties will vary depending on the particular Niaspan® dose being manufactured.

Production of Niaspan® tablets will now be discussed in greater detail. The initial stage of manufacturing is the same for all four tablet strengths of Niaspan® (375, 500, 750 and 1000mg). One batch of Niaspan® granulation is comprised of four individual 40.0kg units of granulation which are processed separately, but under like conditions. The four individual granulations are sampled and tested individually and subsequently released for blending. The base granulation is not strength specific and may be used to manufacture any tablet strength of Niaspan®.

The ingredients in the base granulation are set froth in Table IC below:

TABLE IC

Component	Function	Quantity per kilogram granulation (kg)	% per kilogram granulation (%)	Quantity per 160.00 kg batch (kg)
Niacin, USP	Drug Substance	0.87	87.00	139.20
Povidine, UPS	Binder	0.03	3.00	4.80
Methocel USP, E10M Premium CR Grade	Controlled-Release Agent	0.10	10.00	16.00
Purified Water, USP*	Granulation Reagent	0.00*	0.00*	48
Total				160

*Purified Water, USP is used as granulation reagent and does not appear in the finished granulation.

Raw materials are quantatively dispensed into appropriately labeled double polyethylene-lined containers using calibrated scales. Purified Water, USP is dispensed into an appropriate vessel from which it is later pumped during the wet-massing operation.

A Littleford FM130 granulator is charged with approximately one half of the Niacin, USP required for the process unit (~17.4 kg) followed by about 4.00kg of Methocel, USP E10M Premium CR Grade; about 1.20kg of Povidine, USP; and the balance of the Niacin, SP (~17.40kg). The powder bed is dry mixed in the Littleford FM130 granulator, with choppers on, for approximately 1 minute. At the completion of the 1-minute pre-mix cycle, about 12.0±0.05kg

of Purified Water, USP are sprayed onto the powder bed at a rate of about 2.40±0.24kg/minute. Immediately following the addition of the Purified Water, USP, the unit is granulated for about 5 minutes.

The granulated unit is discharged into double polyethylene-lined containers and then manually loaded into a Glatt bowl while being passed through a #4 mesh screen. The Glatt bowl is loaded into a Glatt TFO-60 fluid-bed drier with an inlet air temperature setting of about 70°C±5°C. The unit is dried until a moisture level of ≤ 1.0% is obtained as determined using a Computrac® Moisture Analyzer, model MA5A. The dried granulation is discharged into appropriately labeled, double polyethylene-lined drums and reconciled.

The dried and reconciled granulation is passed through a Kemutec BetaGrind mill equipped with a 1.5mm screen and running at approximately 1500 RPM. The milled granulation is collected into appropriately labeled, double polyethylene-lined drums and reconciled. The milled granulation is sampled and tested by Quality Control and released prior to further processing.

The released granulation units are charged to a Patterson-Kelley 20 ft^3 V-blender after which they are blended together for about 10 ± 1 minutes and then discharged to appropriately labeled, double polyethylene-lined containers.

As stated above, Niaspan® tablets are formulated from a common granulation which is blended with appropriate quantities of Methocel, USP E10M Premium CR Grade and Stearic Acid, NF to achieve the final dosage formulation. Tables IA and IB describe the formulation for each Niaspan® tablet strength, 375mg, 500mg, 750mg and 1000mg, respectively.

Two study groups consisting of eleven and fourteen patients each were formed. Blood samples were taken from the patients, and tested for total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol to establish baseline levels from which fluctuations in these lipids could be compared. The patients were then placed upon a regimen of the above discussed tablets, totaling approximately 1500 mg of nicotinic acid, once per day before going to bed. After eight weeks of this regimen, the patients were again tested for lipid profiles. The results of tests conducted at eight weeks, showing the changes in the lipid profiles as a percentage change from the baseline, are reported in the table hereinbelow. Positive numbers reflect percentage increases and negative numbers reflect percentage decreases in this table.

TABLE II

Patient Study Lipid Profile Data

Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL-C	Lp(a)
GROUP A							
1	-8.2	-12.0	NA	-17.3	22.0	NA	NA
2	-5.9	-27.0	NA	-28.7	65.0	NA	NA
3	-15.1	-13.0	NA	-22.0	-9.1	NA	NA
4	-3.3	-10.0	NA	61.6	3.8	NA	NA
5	-16.5	-17.7	NA	-28.8	11.1	NA	NA
6	-12.4	-25.9	NA	-42.0	51.6	NA	NA
7	-24.2	-31.4	NA	-39.4	12.5	NA	NA
8	-6.7	-7.4	NA	-42.4	18.8	NA	NA
9	4.5	1.1	NA	7.2	9.2	NA	NA
10	2.8	-0.2	NA	-2.7	22.9	NA	NA
11	-13.0	-9.4	NA	-54.0	44.3	NA	NA
Mean	-8.9	-13.9	NA	-18.9	23.0	NA	NA
p-Valuc	0.0004-8.9	0.0001-13.9		0.0371	0.0068		
GROUP B							
1	-19.2	-27.1	-24.4	-33.4	20.0	22.3	-81.9
2	-32.2	-35.7	-28.0	-60.4	4.3	3.2	-25.3
3	-21.4	-33.6	-35.6	-33.4	30.4	38.6	-17.4
4	-19.9	-24.6	-15.1	-20.8	9.6	16.1	-27.0
5	-3.3	-2.1	-29.4	-41.1	5.8	2.4	-22.4
6	PATIENT WITHDREW FROM STUDY						
7	23.1	-32.6	-42.6	-58.6	49.2	68.9	-14.3
8	24.8	34.0	-28.4	5.5	6.5	-6.8	NA
9	10.1	12.0	-16.8	-11.6	20.7	-12.3	40.6
10	-2.9	-7.7	-28.0	-59.0	53.1	70.5	-41.2
11	-10.5	-18.8	-25.3	-53.4	31.8	39.7	NA
12	-20.0	-30.8	-30.4	11.7	21.1	25.0	-28.4
13	17.4	16.8	-17.5	-17.5	51.3	51.9	38.5

TABLE II (Continued)
Patient Study Lipid Profile Data

Pt. No.	Total-C	LDL-C	Apo B	Trigs	HDL-C	HDL,-C	Lp(a)
14	-9.4	-16.6	-32.0	-46.9	52.3	67.6	17.6
MEAN	-8.7	-12.8	-32.2	-27.2	25.3	30.1	-17.9
p-Value	0.0002	<0.0001	0.0001	<0.001	<0.0001	0.0002	<0.0188
Combined	-8.7	-13.3	Gp B	-26.1	25.3	Gp B	Gp B
p-Value	0.0002	<0.0001	only	<.0001	<0.0001	only	only

The data reported in Table II shows that the LDL levels in the Group A patients had a mean decrease of -13.9% and triglyceride decrease of -18.9% HDL cholesterol levels, the beneficial cholesterol, were raised by 23.0% in this Group. Similar results were obtained with the Group B patients. These studies demonstrate that dosing the sustained release formulation during the evening hours or at night provides reductions in LDL cholesterol levels equal to immediate release niacin on a milligram per milligram basis, but superior reductions in triglyceride reduction when compared to sustained release formulations dosed during daytime hours on a milligram per milligram basis. Additionally, the increases in HDL cholesterol obtained from dosing the sustained release formulation during the evening or at night were +23.0% for one group and +25.3% for the other group. Dosing during the evening therefore provides reduction in LDL cholesterol plus significant decreases in triglycerides and increases in HDL cholesterol with once-a-day dosing.

Groups A and B were also tested for liver enzymes (AST, ALT and Alkaline Phosphatase), uric acid and fasting glucose levels at the start of the study described hereinabove (to form a baseline) and at two, four and eight week intervals. The results of these tests are listed in TABLES III-VII hereinbelow.

TABLE III
THE EFFECT OF NIASPAN® THERAPY ON AST (SGOT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

Pt#	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	28	29	25	24	0-50
2	24	25	24	26	0-50
3	17	18	22	21	0-50
4	14	16	15	17	0-50
5	22	NA	32	52	0-50
6	21	17	17	14	0-50
7	17	17	14	18	0-50
8	20	21	22	22	0-50
9	16	16	17	20	0-50
10	18	21	21	25	0-50
11	21	21	22	21	0-50
GROUP B					
1	23	25	38	33	0-50
2	20	20	21	21	050
3	15	20	18	19	0-50
4	25	22	28	26	0-50
5	23	21	17	18	0-50
6	PATIENT WITHDREW DUE TO FLUSHING				
7	21	18	18	19	0-50
8	18	19	18	19	0-50
9	15	16	18	15	0-50
10	16	15	19	28	0-50
11	20	22	24	28	0-50
12	23	25	28	22	0-50
13	20	15	20	19	0-50

TABLE III (Continued)
THE EFFECT OF NIASPAN® THERAPY ON AST (SGOT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

Pt#	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
14	18	25	20	18	0-50
Combined Mean	19.8	20.4	20.8	21.1	
Change From Baseline		+3.0%	+5.1%	+6.6%	

Level of Significance: p=0.4141

TABLE IV
THE EFFECT OF NIASPAN® THERAPY ON ALT (SGPT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

Pt#	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	32	28	39	30	0-55
2	24	25	23	26	0-55
3	18	23	30	30	0-55
4	7	13	14	14	0-55
5	14	NA	43	46	0-55
6	22	11	14	10	0-55
7	9	7	11	7	0-55
8	16	18	23	21	0-55
9	14	17	20	14	0-55
10	14	15	17	19	0-55
11	18	18	20	16	0-55

TABLE IV (Continued)
THE EFFECT OF NIASPAN® THERAPY ON ALT (SGPT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

Pt#	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP B					
1	16	17	27	29	0-55
2	16	14	15	22	0-55
3	13	21	13	16	0-55
4	23	20	26	17	055
5	21	23	17	15	0-55
6	PATIENT WITHDREW DUE TO FLUSHING				
7	21	16	18	21	0-55
8	18	20	17	18	0-55
9	11	5	11	8	0-55
10	8	10	14	17	0-55
11	17	12	18	16	0-55
12	14	18	20	16	0-55
13	14	NA	11	10	0-55
14	23	23	19	19	0-55
Combined Mean	17.7	17.5	19.3	18.2	
Change From Baseline		-1.1%	9.0%	+2.8%	

Level of Significance: p=0.3424

TABLE V
THE EFFECT OF NIASPAN® THERAPY
ON ALKALINE PHOSPHATASE LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

	Pt#	Baseline	Weeks of Therapy With Niaspan® 2 Wks	4 Wks	8 Wks	Reference Range
GROUP A						
	1	52	56	57	55	20-140
	2	103	100	89	102	20-140
	3	54	45	53	51	20-140
	4	70	68	71	91	20-140
	5	77	NA	74	81	20-140
	6	55	48	49	51	20-140
	7	72	71	79	75	20-140
	8	55	49	47	50	20-140
	9	53	55	56	45	20-140
	10	74	73	75	75	20-140
	11	18	18	20	16	20-140
GROUP B						
	1	73	67	89	95	20-140
	2	82	64	72	71	20-140
	3	73	69	72	82	20-140
	4	37	36	37	38	20-140
	5	65	53	54	61	20-140
	6	PATIENT WITHDREW DUE TO FLUSHING				
	7	64	58	58	58	20-140
	8	79	78	65	73	20-140
	9	94	92	103	93	20-140

TABLE V (Continued)
THE EFFECT OF NIASPAN® THERAPY
ON ALKALINE PHOSPHATASE LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

	Pt#	Baseline	2 Wks	4 Wks	8 Wks	Reference Range
	10	69	67	70	65	20-140
	11	59	67	63	72	20-140
	12	65	59	59	63	20-140
	13	64	68	66	64	20-140
	14	72	61	59	64	20-140
	Combined Mean	66.5	61.5	63.3	65.8	
	Change From Baseline		-6.1%	-3.4%	+0.005%	

Level of Significance: p=0.0236

TABLE VI
THE EFFECT OF NIASPAN® THERAPY ON URIC ACID LEVELS (mg/dL)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

	Pt#	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
	GROUP A					
	1	5.2	5.0	4.8	4.3	4.0-8.5
	2	4.0	4.6	4.5	6.2	2.5-7.5
	3	6.3	7.0	6.5	6.2	4.0-8.5
	4	3.1	4.6	4.2	3.8	2.5-7.5
	5	3.4	NA	3.3	4.2	2.5-7.5
	6	6.6	5.5	5.6	4.7	4.0-8.5
	7	3.8	4.5	4.3	4.9	2.5-7.5
	8	4.4	3.8	5.1	4.5	2.5-7.5
	9	3.9	4.5	4.6	3.5	2.5-7.5
	10	2.6	2.9	2.8	2.7	2.5-7.5
	11	4.7	5.5	5.2	5.3	2.5-7.5
	GROUP B					
	1	3.7	4.2	4.7	3.5	2.5-7.5
	2	2.8	3.5	3.6	2.3	4.0-8.5
	3	4.2	5.3	5.5	5.3	2.5-7.5
	4	4.7	3.9	5.1	3.6	4.0-8.5
	5	3.7	4.1	4.1	3.8	2.5-7.5
	6	PATIENT WITHDREW DUE TO FLUSHING				
	7	5.8	6.6	6.6	6.8	2.5-7.5
	8	4.7	4.3	5.4	5.6	2.5-7.5
	9	3.7	4.6	5.1	3.8	2.5-7.5

TABLE VI (Continued)
THE EFFECT OF NIASPAN® THERAPY ON URIC ACID LEVELS (mg/dL)
(1500 mgs dosed once-a-day at night)
(n = 28)

		Weeks of Therapy With Niaspan®				
Pt#	**Baseline**	**2 Wks.**	**4 Wks.**	**8 Wks.**	**Reference Range**
10	4.2	5.0	4.4	8.5	2.5-7.5
11	1.9	3.0	2.8	5.0	2.5-7.5
12	5.6	5.4	6.2	5.6	4.0-8.5
13	4.2	4.6	4.6	5.3	2.5-7.5
14	5.5	5.4	6.1	5.3	2.5-7.5
Combined Mean	4.54	4.82	4.92	4.86	*p=0.3450
Change From Baseline		+6.2%	+8.4%	+7.0%	

*Level of Significance: p=0.3450

TABLE VII
THE EFFECT OF NIASPAN® THERAPY
ON FASTING GLUCOSE LEVELS (mg/dL)
(n = 28)

Weeks of Therapy With Niaspan®

Pt#	Baseline	2 Wks	4 Wks.	8 Wks	Reference Range
GROUP A					
1	114	122	123	110	70-115
2	101	105	107	101	80-125
3	99	98	109	103	70-115
4	100	118	94	94	80-125
5	89	NA	82	103	80-125
6	97	103	94	107	70-115
7	85	107	100	94	80-125
8	98	107	103	101	80-125
9	97	97	100	110	80-125
10	94	101	111	97	70-115
11	102	103	95	95	80-125
GROUP B					
1	101	97	83	99	70-115
2	90	95	96	89	80-125
3	96	98	95	97	70-115
4	116	139	113	125	80-125
5	88	98	91	95	70-115
6	PATIENT WITHDREW DUE TO FLUSHING				
7	106	114	118	117	70-115
8	95	106	106	108	70-115
9	81	92	84	92	70-115
10	108	117	122	105	70-115

TABLE VII (Continued)
THE EFFECT OF NIASPAN® THERAPY
ON FASTING GLUCOSE LEVELS (mg/dL)
(n = 28)

	Weeks of Therapy With Niaspan®				
Pt#	**Baseline**	**2 Wks**	**4 Wks.**	**8 Wks**	**Reference Range**
11	85	106	106	108	70-115
12	92	89	101	86	80-125
13	99	105	94	100	70-125
14	100	108	84	107	70-125
Combined Mean	98.4	105.8	101.6	102.3	
Change From Baseline		+7.5%	+3.3%	+4.0%	

Level of Significance: p=0.0021

In order to provide a comparison between the state of the art prior to the present invention, and in order to quantify the magnitude of the improvement that the invention provides over the prior art, another study was conducted. This study included 240 patients dosed with the sustained release formulation according to the present invention as described hereinabove. Compared to this group was the group of patients studied by McKenney et al, as reported hereinabove. The results of this study are reported in TABLE VIII hereinbelow.

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TABLE VIII
A Comparison of Changes in Liver Function Tests

DOSE

	0	500	1000	1500	2000	2500	3000	TOTAL
McKenney Sr[b] Niacin[a]								
AST	23.8	27.9	40.4	36.6	56.5	na	97.0	
%	--	117	170	154	237	na	408	
Invention Dosage[c]								
AST	24.3	na	23.7	17.5	26.6	27.6	27.8	
%	--	na	98	113	109	114	114	
McKenney SR Niacin								
ALT	25.6	29.5	36.3	39.0	59.1	NA	100 0	
%	--	115	142	152	231	NA	391	
Invention Dosage								
ALT	21.4	na	18.7	22.6	21.3	22.4	21 8	
%	--	na	87	106	100	105	102	
McKenney SR Niacin								
ALK	95	95	106	105	136	na	135	

TABLE VIII (Continued)
A Comparison of Changes in Liver Function Tests

DOSE

	0	500	1000	1500	2000	2500	3000	TOTAL
%	--	100	112	111	143	na	142	
Invention Dosage								
ALK	74.7	na	73.9	76.1	73.4	76.7	78.0	
%	--	na	99	102	98	103	104	
McKenney SR Niacin								
Drop	--	0	1	2	4	na	5	12
n	--	--	--	--	--	--	--	23
%	--	0	4	9	17	na	22	52
Invention Dosage								
Drop	--	--	0	0	0	0	0	0
n	--	--	26	67	97	35	15	240
%	--	--	0	0	0	0	0	0
1 year	--	--	15	46	77	31	15	184
1 year	--	--	58	69	79	89	100	77

[a] Dosed twice-per-day as described in "A Comparison of the Efficacy and Toxic Effects of Sustained - vs Immediate - Release Niacin in Hypercholesterolemic Patients" by McKenney et al. Journal of the American Medical Association, March 2, 1994; Vol. 271, No. 9, pages 672-677.
[b] SR is "sustained release"
[c] Dosed once-per-day at night

The results of the comparison of the studies reported in Table VIII show that the control group (the McKenney group) had 12 of 23, or 52 percent of the patients therein drop out of the test because of an increase in their respective liver function tests. The patients withdrew at the direction of the investigator. In comparison, a group of 240 patients treated according to the present invention had zero patients drop out, based upon the same criteria for withdrawal. The test results reported above indicate that this sustained release dosage form caused no elevation in liver function tests (i.e., no liver damage), no elevations in uric acid and only a small, 7.5% increase in fasting glucose levels which in fact decreased during continued therapy.

Thus it should be evident that the compositions and method of the present invention are highly effective in controlling hyperlipidemia in hyperlipidemics, by reducing the levels of LDL cholesterol, triglyceride and Lp(a) while increasing HDL cholesterol levels. The present invention is also demonstrated not to cause elevations in liver function tests, uric acid or glucose levels for the hyperlipidemics.

Based upon the foregoing disclosure, it should now be apparent that the use of the compositions and methods described herein will carry out the objects set forth hereinabove. It is, therefore, to be understood that any variations in sustained release formulation evident fall within the scope of the claimed invention and thus, the selection of specific component elements can be determined without departing from the spirit of the invention herein disclosed and described. In particular, sustained release excipients, binders and processing aids according to the present invention are not necessarily limited to those exemplified hereinabove. Thus, the scope of the invention shall include all modifications and variations that may fall within the scope of the attached claims.

CLAIMS:

1. An oral dosage sustained release pharmaceutical formulation for use once per day during the evening or at night, or before bedtime, as a single dose, for daily treatment of hyperlipidemia in a patient without inducing treatment-limiting liver damage, said formulation comprising a blend of:

(a) an effective antihyperlipidemic amount of nicotinic acid in milled agglomerates of the nicotinic acid, a portion of the total amount of swelling agent, and a granulation binder, the milled agglomerates being of a uniform particle size distribution, and

(b) the remaining portion of the total amount of swelling agent and an external lubricant;

wherein said total amount of swelling agent functions as a controlled release agent, to form an oral sustained release solid dosage form, and wherein the oral sustained release solid dosage form does not contain an internal hydrophobic component,

said single daily oral dose causing no treatment-limiting damage to the liver of the patient.

2. A formulation as set forth in claim 1, wherein the oral dose is from about 250 mg to about 3000 mg of nicotinic acid.

3. A formulation as set forth in claim 1, wherein the oral dose is about 1000 mg of nicotinic acid.

4. A formulation as set forth in claim 1, wherein the oral sustained release solid dosage form contains nicotinic acid in an amount selected from the group consisting of about 375 mg, about 500 mg and about 750 mg.

5. A formulation as set forth in claim 1, 2, 3 or 4, wherein the oral sustained release solid dosage form is an oral sustained release tablet.

6. A formulation as set forth in claim 1, 2, 3, 4 or 5, wherein said single daily dose is effective to elevate HDL cholesterol in the patient.

7. A formulation as set forth in claim 1, 2, 3, 4 or 5, wherein said single daily dose is effective to induce at least some decrease in levels of total cholesterol, LDL cholesterol, triglycerides and Lp(a) in the patient.

8. A formulation as set forth in any one of claims 1 to 7, wherein said single daily dose causes no treatment-limiting increase in uric acid in the patient.

9. A formulation as set forth in any one of claims 1 to 8, wherein said single daily dose treatment causes no treatment-limiting increase in free fasting glucose in the patient.

10. A formulation as set forth in any one of claims 1 to 9, wherein said single daily dose treatment causes no anomalies in a liver function test in the patient to an extent which would require daily treatment to be discontinued, and wherein the liver function test is selected from the group consisting of an AST, ALT and alkaline phosphatase liver function test.

11. A formulation, as set forth in any one of claims 1 to 10, wherein said oral sustained release formulation is in the form of a tablet which contains:

(a) about 30% to about 90% parts by weight nicotinic acid, and

(b) about 5% to about 50% parts by weight hydroxypropyl methylcellulose as said swelling agent.

12. A formulation for treating hyperlipidemia in a patient with an effective amount of nicotinic acid once per day during the evening or at night, or before bedtime, comprising a blend of:

(a) milled agglomerates of nicotinic acid, a portion of a total amount of swelling agent, and a granulation binder, the milled agglomerates having a uniform particle size distribution, and

(b) the remaining portion of the total amount of swelling agent and an external lubricant,

wherein the swelling agent in said total amount functions as a controlled release agent, to form an oral sustained release solid dosage form, and wherein said oral sustained release solid dosage form does not contain an internal hydrophobic component.

13. A formulation as set forth in claim 12, wherein said oral sustained release solid dosage form comprises from about 250 mg to about 3000 mg of nicotinic acid.

14. A formulation as set forth in claim 12, wherein said oral sustained release solid dosage form comprises about 1000 mg of nicotinic acid.

15. A formulation as set forth in claim 12, wherein said oral sustained release solid dosage form contains nicotinic acid in an amount selected from the group consisting of about 375 mg, about 500 mg and about 750 mg.

16. A formulation as set forth in claim 12, 13 or 15, wherein said oral sustained release solid dosage form is an oral sustained release tablet.

17. A formulation as set forth in claim 16, wherein said oral sustained release tablet contains

(a) about 375 mg nicotinic acid,

(b) about 189 mg hydroxypropyl methylcellulose as said total amount of the swelling agent,

(c) about 13 mg polyvinyl pyrrolidone as said granulation binder, and

(d) about 6 mg of stearic acid as said lubricant.

18. A formulation as set forth in claim 16, wherein said oral sustained release tablet contains

(a) about 500 mg nicotinic acid,

(b) about 203 mg hydroxypropyl methylcellulose as said total amount of the swelling agent,

(c) about 17 mg polyvinyl pyrrolidone as said granulation binder, and

(d) about 7 mg stearic acid as said lubricant.

19. A formulation as set forth in claim 16, wherein said oral sustained release tablet contains

(a) about 750 mg nicotinic acid,

(b) about 205 mg hydroxypropyl methylcellulose as said total amount of the swelling agent,

(c) about 26 mg polyvinyl pyrrolidone as said granulation binder, and

(d) about 10 mg stearic acid as said lubricant.

20. A formulation as set forth in claim 16, wherein said oral sustained release tablet contains

(a) about 30% to about 90% by weight nicotinic acid,

(b) about 5% to about 50% by weight hydroxypropyl methylcellulose as said total amount of the swelling agent,

(c) about 1% to about 5% by weight polyvinyl pyrrolidone as said granulation binder, and

(d) about 0.5% to about 2% by weight stearic acid as said lubricant.

21. A formulation as set forth in claim 16, wherein said oral sustained release tablet contains

(a) about 30% to about 90% parts by weight nicotinic acid, and

(b) about 5% to about 50% parts by weight hydroxypropyl methylcellulose as said total amount of the swelling agent.

22. Use of a formulation as set forth in any one of claims 1 to 21 for treating hyperlipidemia in a patient without inducing treatment-limiting (i) hepatotoxicity and (ii) abnormalities in uric acid levels or glucose levels or both to an extent which would require the use of said formulation to be discontinued.

23. A sustained release formulation of nicotinic acid for oral administration to a patient once per day during the evening or at night, or before bedtime, for providing an effective antihyperlipidemic amount of nicotinic acid to the patient to induce at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream, without causing abnormalities in uric acid levels or glucose levels or both to an extent which would require the use of said sustained release formulation by the patient to be discontinued, said sustained release formulation comprising a blend of:

(a) milled agglomerates of:

(i) an effective antihyperlipidemic amount of nicotinic acid,

(ii) an excipient to provide sustained release of the nicotinic acid, said excipient comprising a portion of a total amount of a swelling agent, and

(iii) a granulation binder,

the milled agglomerates having a uniform particle size distribution, and

(b) the remaining portion of the total amount of swelling agent, and

(c) an external lubricant,

said total amount of swelling agent functioning as a controlled release agent.

24. A sustained release formulation of claim 23, wherein the excipient further comprises a processing aid.

25. A sustained release formulation of claim 24, wherein the swelling agent is selected from group consisting of a polymer, a wax, a natural material selected from the group consisting of gums and gelatins, and mixtures thereof.

26. A sustained release formulation of claim 25, wherein the polymer is selected from the group consisting of hydroxypropyl methylcellulose, sodium carboxymethylcellulose and ethylcellulose.

27. A sustained release formulation of claim 25, wherein the wax is bees wax.

28. A sustained release formulation of claim 25, wherein the natural material is a gum.

29. A sustained release formulation of claim 24, wherein the granulation binder is povidone.

30. A sustained release formulation of claim 24, wherein the processing aid is a lubricant.

31. A sustained release formulation of claim 30, wherein the lubricant is stearic acid.

32. A sustained release formulation of claim 26, wherein the polymer is hydroxypropyl methylcellulose in an amount ranging from about 5% to about 50% parts by weight per 100 parts by weight of the sustained release formulation.

33. A sustained release formulation of claim 24, wherein the granulation binder is in an amount ranging from about 1% to about 5% parts by weight per 100 parts by weight of the sustained release formulation.

34. A sustained release formulation of claim 24, wherein the processing aid is in an amount ranging from about 0.5% to about 2% parts by weight per 100 parts by weight of the sustained release formulation.

35. A sustained release formulation of claim 23, wherein the sustained release formulation consists essentially of nicotinic acid, hydroxypropyl methylcellulose, povidone and stearic acid.

36. A sustained release formulation of claim 23, wherein the sustained release formulation consists essentially of

nicotinic acid	375.0 mg,
hydroxypropyl methylcellulose	188.7 mg,
povidone	12.9 mg, and
stearic acid	5.8 mg.

37. A sustained release formulation of claim 23, wherein the sustained release formulation consists essentially of

nicotinic acid	500.0 mg,
hydroxypropyl methylcellulose	203.0 mg,
povidone	17.2 mg, and
stearic acid	7.3 mg.

38. A sustained release formulation of claim 23, wherein the sustained release formulation consists essentially of

nicotinic acid	750.0 mg,
hydroxypropyl methylcellulose	204.7 mg,
povidone	25.9 mg, and
stearic acid	9.9 mg.

39. Use of a sustained release formulation of any one of claims 23 to 38 for daily treating hyperlipidemia in a patient without inducing treatment-limiting elevations in uric acid levels or glucose levels or both in the patient, said formulation being in a form for orally dosing the patient with an effective antihyperlipidemic amount of nicotinic acid once per day during the evening or at night, or before bedtime, as a single dose, wherein said single dose treatment induces at least some (i) decrease in levels of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and (ii) some elevation in HDL cholesterol in the patient.

40. Use of a sustained release formulation of any one of claims 23 to 38 for treating hyperlipidemia in a patient without inducing treatment-limiting (i) hepatotoxicity and (ii) abnormalities in uric acid levels or glucose levels or both, said formulation being in a form for orally dosing the patient with an

effective antihyperlipidemic amount of nicotinic acid once per day during the evening or at night, or before bedtime, as a single dose, wherein the oral sustained release solid dosage form is effective in reducing a serum lipid without causing treatment-limiting (a) hepatotoxicity and (b) elevations in uric acid levels or glucose levels or both in the patient to a level which would require said treatment to be discontinued by the patient when it is ingested by the patient once per day during the evening or at night as the single dose in accordance with said single dose treatment.

41. Use of a sustained release formulation of any one of claims 23 to 38 for daily treating hyperlipidemia in a patient, said formulation being in a form for orally administering to the patient once per day during the evening or night, or before bedtime, for providing an effective antihyperlipidemic amount of nicotinic acid to the patient during times of peak lipid production or synthesis by the patient to induce at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream, without causing abnormalities in liver function tests and uric acid levels or glucose levels to an extent which would require said daily treatment to be discontinued by the patient.

42. A sustained release formulation of nicotinic acid for oral administration to a patient once per day during the evening or night , or before bedtime, or as the patient lies down to go to sleep for providing an effective antihyperlipidemic amount of nicotinic acid to the patient during times of peak lipid production or synthesis by the patient to induce at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream, without causing abnormalities in liver function tests and uric acid levels or glucose levels or both to an extent which would require the use of said sustained release formulation by the patient to be discontinued, the sustained release formulation comprising a blend of:

(a) mixed agglomerates of:

(i) an effective antihyperlipidemic amount of nicotinic acid,

(ii) an excipient to provide sustained release of the nicotinic acid, said excipient comprising a portion of a total amount of a swelling agent, and

(iii) a granulation binder,

the milled agglomerates having a uniform particle size distribution, and

(b) the remaining portion of the total amount of swelling agent and an external lubricant,

wherein said total amount of swelling agent functions as a controlled release agent.

43. A pharmaceutical formulation for treating hyperlipidemia in a hyperlipidemic comprising an effective antihyperlipidemic amount of a compound which is metabolized to nicotinic acid by the hyperlipidemic to produce (i) a reduction in total and LDL cholesterol, triglycerides and Lp(a), and (ii) an increase in HDL cholesterol, wherein the compound is combined with at least one pharmaceutically acceptable carrier comprising a swelling agent in a total amount which functions as a controlled release agent, to form an oral solid dosage form, and wherein the compound is selected from the group consisting of d-glucitol hexanicotinate, aluminum nicotinate and d,l-alpha-tocopheryl nicotinate, said formulation comprising a blend of:

(a) milled agglomerates of said compound, a portion of the total amount of swelling agent, and a granulation binder, the milled agglomerates having a uniform particle size distribution, and

(b) the remaining portion of the total amount of swelling agent and an external lubricant.

44. A method of manufacturing a sustained release nicotinic acid solid dosage form, said method comprising:

(a) forming a wet granulation which consists essentially of nicotinic acid, a portion of a total amount of a swelling agent which functions as a controlled release agent, and a granulation binder;

(b) drying the wet granulation to form dry granules;

(c) milling the dry granules to obtain a substantially uniform particle size distribution;

(d) dry blending the milled dry granules, the remaining portion of the total amount of swelling agent, and an external lubricant to form a final dosage blend; and

(e) forming the sustained release nicotinic acid solid dosage form from the final dosage blend.

45. A method as set forth in claim 44, wherein step (a) comprises:

forming a dry mix which consists essentially of said nicotinic acid, said portion of said total amount of a swelling agent and said granulation binder; and

forming said wet granulation from the dry mix.

46. A method as set forth in claim 44 or 45, wherein the sustained release nicotinic acid solid dosage form is a sustained release nicotinic acid tablet.

47. A method as set forth in claim 44, 45 or 46, wherein said oral sustained release solid dosage form comprises from about 250 mg to about 3000 mg of nicotinic acid.

48. A method as set forth in claim 46, wherein said oral sustained released tablet contains nicotinic acid in an amount selected from the group consisting of about 375 mg, about 500 mg and about 750 mg.

49. A method as set forth in claim 44, 45, 46, 47 or 48, wherein the swelling agent which functions as the controlled-release agent is selected from the group consisting of a polymer, a wax, a natural material selected from the group consisting of gums and gelatins, and mixtures thereof.

50. A method as set forth in claim 49, wherein the polymer is selected from the group consisting of hydroxypropyl methylcellulose, sodium carboxymethylcellulose and ethylcellulose.

51. A method as set forth in claim 49, wherein the wax is bees wax.

52. A method as set forth in claim 51, wherein the natural material is a gelatin.

53. A method as set forth in any one of claims 44 to 52, wherein the granulation binder is povidone.

54. A method as set forth in any one of claims 44 to 53, wherein the lubricant is stearic acid.

55. A method as set forth in any one of claims 44 to 50, wherein the swelling agent which functions as the controlled-release agent is

hydroxypropyl methylcellulose which is in an amount ranging from about 5% to about 50% parts by weight per 100 parts by weight of the sustained release formulation.

56. A method as set forth in any one of claims 44 to 55, wherein the granulation binder is in an amount ranging from about 1% to about 5% parts by weight per 100 parts by weight of the sustained release nicotinic acid solid dosage.

57. A method as set forth in any one of claims 44 to 56, wherein the external lubricant is in an amount ranging from about 0.5% to about 2% parts by weight per 100 parts by weight of the sustained release nicotinic acid solid dosage.

58. A method as set forth in any one of claims 44 to 48, wherein the sustained release nicotinic acid solid dosage consists essentially of nicotinic acid, hydroxypropyl methylcellulose, povidone and stearic acid.

59. A formulation as set forth in claim 16, wherein said oral sustained release tablet contains:

(a) about 500 mg nicotinic acid,

(b) about 185 mg hydroxypropyl methylcellulose as said swelling agent,

(c) about 17 mg polyvinyl pyrrolidone as said granulation binder, and

(d) about 7 mg of stearic acid as said lubricant.

60. A formulation as set forth in claim 16, wherein said oral sustained release tablet contains:

(a) about 750 mg nicotinic acid,

(b) about 183 mg hydroxypropyl methylcellulose as said swelling agent,

(c) about 26 mg polyvinyl pyrrolidone as said granulation binder, and

(d) about 9.7 mg stearic acid as said lubricant.

61. A formulation as set forth in claim 12, wherein said oral sustained release dosage form is an oral sustained release tablet which contains:

(a) about 1000 mg nicotinic acid,

(b) about 156 mg hydroxypropyl methylcellulose as said swelling agent,

(c) about 35 mg polyvinyl pyrrolidone as said granulation binder, and

(d) about 12 mg stearic acid as said lubricant.

62. A sustained release formulation of any one of claims 23 to 35, wherein said effective amount of nicotinic acid is 1000 mg.