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Phytostanol tablets reduce human LDL-cholesterol

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Abstract

The feasibility of using solid dosage forms containing stanol lecithin to lower human LDL-cholesterol was investigated. The particle size distribution of a coarse aqueous dispersion of a stanol lecithin mixture was determined at various weight ratios of the components. At a stanol-to-lecithin weight ratio of 1.00–1.50, dispersions could be spray dried and the solid reconstituted with water to produce a particle size distribution that was similar to that of the aqueous dispersion from which it was derived. Two solid dosage forms containing this spray-dried stanol lecithin preparation had different disintegration times – tablets less than 10 min and capsules greater than 45 min. Each delivery system was then tested for LDL-cholesterol reduction activity in a placebo-controlled, double-blind clinical trial containing a total of 52 subjects. After a six-week treatment period, the group that received rapidly disintegrating stanol lecithin tablets (1.26 g stanols daily) experienced a decrease in both LDL-cholesterol and the ratio of LDL-cholesterol to HDL-cholesterol by 10.4% ($P = 0.01$) and 11.5% ($P = 0.03$), respectively, relative to placebo. On the other hand, with slowly disintegrating capsules (1.01 g daily) there was no statistically significant difference in any lipid parameter between the active group and placebo group. Taken together, these studies demonstrate that for maximum LDL-cholesterol reduction activity the stanol lecithin formulation must be delivered in a rapidly dispersible form to reach the site of cholesterol absorption.

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Introduction

Elevated LDL-cholesterol is a significant risk factor for coronary artery disease and over the last two decades numerous strategies have been developed for its management (Lipid Research Clinics Program 1984). Currently, inhibition of hepatic cholesterol synthesis by statin drugs is the primary therapeutic option but recently new compounds have become available that function in the small intestine by blocking cholesterol absorption. There are currently two cholesterol absorption inhibitors and each is delivered using a different strategy. In the pharmaceutical approach, administration of 10 mg of ezetimibe lowers LDL-cholesterol by as much as 17.0% versus placebo (Dujovne et al 2002). Moreover, the reduction of LDL-cholesterol with 10 mg of ezetimibe and the lowest dose of simvastatin was the same as that found with the maximum dose of simvastatin alone (Goldberg et al 2004). On the other hand, cholesterol absorption inhibitors from plants, phytosterols or phytostanols, have properties that currently make them more suitable as food ingredients. Fatty acid esters of these water-insoluble compounds are dissolved in the oil phase of margarine or salad dressing to deliver a 1.0–3.0-g daily dose to produce a 7–11% reduction in LDL-cholesterol (Katan et al 2003). Like ezetimibe, these phytosterol-containing foods also provide an additional LDL-cholesterol lowering when ingested in combination with a statin drug (Blair et al 2000; Simons et al 2002). Because of their acknowledged safety, The National Cholesterol Education Program recommends phytosterol-containing foods as one of the Therapeutic Lifestyle Changes for those individuals at cardiovascular risk (Third Report of the NCEP 2001).

Many individuals prefer this non-pharmaceutical method for LDL-cholesterol management, but they would also prefer a more flexible dosing approach, such as that provided by a tablet or capsule. However, because of their low water and oil

solubility, free phytosterols are not effective when given as a solid, as shown by the erratic results found with Cytellin, an aqueous suspension of sitosterol marketed by Eli Lilly and now unavailable (Pollak 1985; Moreau et al 2002; Ostlund 2002). Recently, unesterified sterols and stanols were rendered water dispersible and bioavailable by the formation of complexes with lecithin (Ostlund et al 1999). In 26 mildly hypercholesterolaemic subjects, 6-week treatment with aqueous dispersions of stanol lecithin complex (SLC) lowered cholesterol absorption and LDL-cholesterol by 32.1% and 14.3%, respectively (Spilburg et al 2003). Moreover, this new lecithin delivery system was associated with very low rates of sterol and stanol absorption consistent with a good safety profile (Ostlund et al 2002).

These previous acute and chronic studies were all performed by first dispersing SLC powder in water or a beverage before human administration, and they clearly indicated that properly formulated material can have a significant impact on cholesterol absorption and circulating levels of LDL-cholesterol. The aim of this study was to adapt this spray-dried formulation to a tablet or capsule dosage form to determine whether clinical effectiveness could be produced without first adding water. To that end, this study explored the aqueous particle size distribution at various weight ratios of stanol to lecithin and the behaviour of these spray-dried dispersions after rehydration. These spray-dried dispersions were then incorporated into two solid dosage forms that had different stanol compositions and different disintegration times to address two questions. First, does quick release or sustained release of stanol provide the better solid delivery strategy and, second, can a solid dosage form produce LDL-cholesterol reduction that is comparable with that found in previous beverage or margarine studies.

Materials and Methods

Materials

For small-scale experimental studies, reduced soy sterols (stanols) were purchased from AC Humko (Cordova, TN, USA) and Precept 8160, a mixture of lecithin and lysolecithin, was purchased from Solae (Fort Wayne, IN, USA). For clinical studies, soy lecithin (Ultralec P) and soy sterols were purchased from Archer Daniels Midland (Decatur, IL, USA) and the sterols were reduced to a mixture of campestanol and sitostanol (> 97.5% reduction) at Salsbury Chemical (Charles City, IA, USA).

Preparation and characterization of stanol lecithin dispersions

Stanol lecithin solutions were prepared at weight ratios of 0.0, 0.37, 1.0, 1.43 and 4.0 by adding increasing amounts of stanol to a stock 22 mg mL^{-1} solution of Precept 8160 in chloroform. The solvent was removed by incubating the solutions overnight in a 70 °C water bath. Water was added and, after a preliminary sonication, each mixture was microfluidized using an ice-cooled ceramic cartridge (75 μ) that produced a pressure drop of 17 000 psi (Model M110S; Microfluidics, Newton, MA, USA). The particle size distribution (volume % vs $\log_{10}$ particle size) of each coarse dispersion was determined in duplicate with a Zeta Sizer (Malvern Instruments, Southborough, MA, USA). In a typical analysis the residual was less than 1% and the obscuration was 10–30%.

Clinical materials

Capsules

An aqueous SLC solution was homogenized with a Gaulin dairy homogenizer operating at 500–4000 psi, and the emulsified mixture was spray dried with partially hydrolysed corn starch to give a free-flowing powder (University of Minnesota, St Paul, MN, USA or North Star Processing, Litchfield, MN, USA). Spray-dried SLC was blended with silicon dioxide (City Chemical, West Haven, CT, USA) and calcium carbonate (City Chemical) and filled into no. 0 opaque white gelatin capsules to a total weight of 0.342 g. Placebos were similarly prepared with lecithin, corn starch (City Chemical), silicon dioxide and calcium carbonate. Each placebo capsule contained the same amount of lecithin as that in the SLC-containing capsules and there was no visual difference between the two study materials.

Tablets

Spray-dried SLC was fluidized-bed granulated with polyvinylpyrrolidone (Spectrum Chemical, Gardena, CA, USA) at Fluid Air (Aurora, IL, USA). The granulation was blended with microcrystalline cellulose (FMC Biopolymer, Philadelphia, PA, USA), croscarmellose sodium (FMC), silicon dioxide (Professional Compounding Centers of America (PCCA), Houston, TX, USA) and magnesium stearate (PCCA). The blended material was compressed on a Korsch EK-0 single station tablet press to produce oval-shaped tablets to a weight of 1.01 g. Placebo tablets were prepared similarly to contain the same amount of lecithin as that in the SLC-containing tablets.

Characterization of clinical materials

The stanol content of tablets and capsules was measured using a variation of the colorimetric cholesterol oxidase test for the measurement of free cholesterol (Moreau et al 2002). Disintegration was assessed using the apparatus and method defined in Chapter 701 of the United States Pharmacopeia 26 (2003), with 0.1 M HCl at 37°C as the immersion fluid.

Subjects

Healthy subjects were recruited by word of mouth and by e-mail advertising throughout the campus of Washington University School of Medicine to achieve an enrollment of 25 subjects for the tablet study and 27 for the capsule study. In a preliminary visit, subjects were screened to ensure that they were free of active medical or surgical illnesses and that they did not take prescription medicines except for oral contraceptives, analgesics, noncyclic

Table 1 Characteristics of study subjects

Characteristic	Tablet study[a]	Capsule study[a]
Women/men	14/11	18/9
Age (years)	46.5 ± 8.1	50.7 ± 12.5
Body mass index ($kg\,m^{-2}$)	26.0 ± 3.4	27.8 ± 5.3
Total cholesterol ($mg\,dL^{-1}$)	200.5 ± 34.8	207.6 ± 35.6
LDL-cholesterol ($mg\,dL^{-1}$)	130.3 ± 31.3	136.4 ± 32.2
HDL-cholesterol ($mg\,dL^{-1}$)	47.8 ± 11.7	50.1 ± 13.2
Triglycerides ($mg\,dL^{-1}$)	112.5 ± 53.6	105.8 ± 47.9

[a]Except for gender, each value is given as the mean $\pm$ s.d.

hormone replacement preparations, antihypertensives and antidepressants. Only those subjects with LDL-cholesterol between $70\,mg\,dL^{-1}$ and $190\,mg\,dL^{-1}$ and triglycerides $< 300\,mg\,dL^{-1}$ were enrolled. As shown in Table 1, the mean entry LDL-cholesterol values for subjects in both studies were similar: $130.3 \pm 31.3\,mg\,dL^{-1}$ (tablet study) and $136.4 \pm 32.2\,mg\,dL^{-1}$ (capsule study).

Study design

Two placebo-controlled, double-blind studies were approved by the Washington University Human Studies Committee. For 14 weeks, all subjects followed the American Heart Association Heart Healthy Diet, which restricts cholesterol consumption to less than 300 mg daily and total fat to less than 30% of total calories, of which no more than one-third is saturated fat. To monitor dietary compliance, subjects completed a diet diary that described food consumption for the three-day period before each visit. For the first six weeks of the study, subjects were counselled weekly by a dietitian to assist them in maintaining the diet, based on the information that was contained in the diet diary. For the last eight weeks of the Study, subjects were counselled every other week and they continued to maintain a diet diary for a 3-day period each week.

Each study consisted of three parts (Table 2). During the initial 6 weeks (dietary lead-in phase), all subjects received lecithin placebo, and they were instructed to consume a dose consisting of either 3 tablets or 4 capsules before their breakfast meal and before their evening meal. Subjects returned to the clinic for a fasted blood draw after four, five and six weeks of diet control. Participants who maintained a stable LDL-cholesterol value over this three-week time period were admitted to the dosing phase and randomly assigned to receive either active stanol or to continue to receive placebo. Fasted blood samples were taken two, four and six weeks after randomization. After completion of the dosing phase, all subjects in the active group were returned to placebo and individuals in the placebo group continued their dosing regimen. The purpose of this final two-week period (recovery phase) was to monitor the overall health of the subjects.

Lipid and lipoprotein measurement

Blood samples were taken from fasted, seated subjects. All lipid measurements, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, were performed in the Core Laboratory for Clinical Studies at Washington University School of Medicine. LDL-cholesterol was calculated using the Friedewald formula.

Statistical analysis

The primary endpoint of the solid dosage studies was difference in LDL-cholesterol and total serum cholesterol after a 6-week treatment period. Secondary endpoints were changes in HDL-cholesterol, serum triglycerides and the ratio of LDL-cholesterol to HDL-cholesterol. The baseline lipid value was the mean of the value at randomization and that from either one or two weeks before randomization. For each subject, the change in lipid values after the 6-week treatment period was expressed either as a percentage of the baseline level or as the absolute change in $mg\,dL^{-1}$ between the treatment value and the baseline value.

In both studies, values were analysed by repeated measures analysis of variance using Statistical Analysis System software (SAS Institute, Cary, NC). Comparisons of active and treatment groups were performed using a general linear model.

Results

Characterization of stanol lecithin dispersions

The effect of each SLC weight ratio on the $\log_{10}$ particle size distribution of its aqueous dispersion is shown in Figure 1. The initial microfluidized lecithin dispersion consisted of two distributions, the major one centered at

Table 2 Summary of the study design

Phase	Entry	Dietary lead in – placebo					Dosing period – placebo or active				Recovery
Week	−6	−5	−4	−3	−2	−1	0[a]	2	4	6	8
Visit	1	2	3	4	5	6	7	8	9	10	11
Diet counseling	X	X	X	X	X	X	X	X	X	X	X
Lipid panel					X	X	X	X	X	X	X

[a]Randomized to placebo or active.

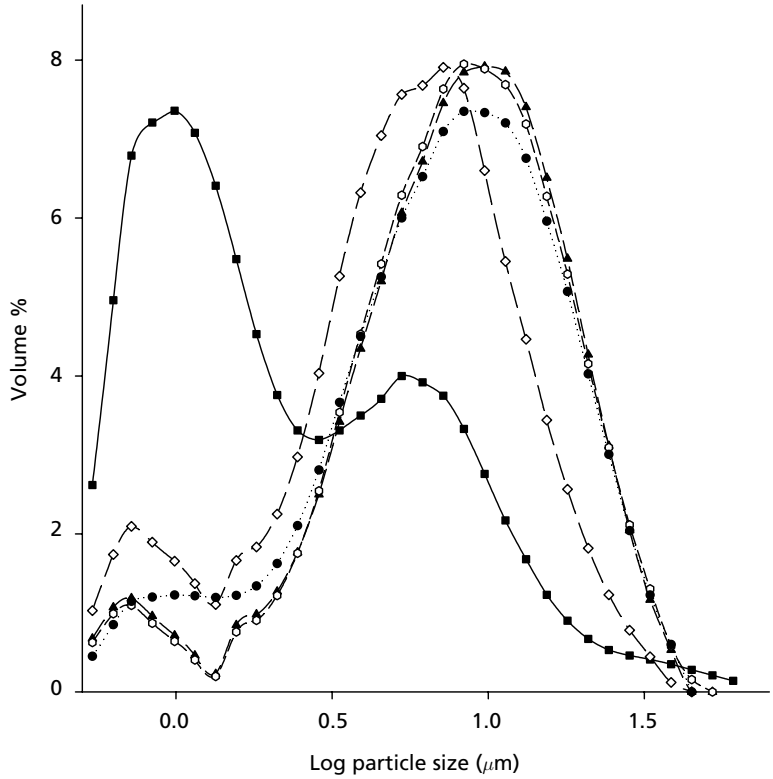

Figure 1 Effect of the weight ratio of stanol to lecithin on the particle size distribution ($\log_{10}\mu$m) of each aqueous coarse dispersion. Stanol and lecithin were mixed in solvent at ratios 0.0 (■), 0.37 (◇), 1.00 (▲), 1.43 (○) and 4.00 (●). After solvent removal, the solids were dispersed in water, microfluidized and the particle size distribution determined.

1.0 μm and a second one at about 5.0 μm. Addition of increasing amounts of stanol to lecithin changed the particle size distribution. A new distribution centered at about 10.0 μm was generated that changed little when the stanol lecithin weight ratio increased from 1.0 to 4.0. Since no further changes were observed in the particle size distribution above a 1.0:1.0 stanol-to-lecithin weight ratio, a weight ratio of stanol to lecithin of 1.00 to 1.50 was used for all clinical work.

Two requirements had to be met for the preparation of adequate amounts of clinical material. First, the small-scale method described above had to be adapted to the kilogram scale to produce coarse dispersions with a particle size distribution centered at 10 μm, which could be subsequently spray dried. Second, rehydration of this spray-dried material needed to produce a particle size distribution that was similar to that of the coarse dispersion from which it was derived. Therefore, the gram-scale method described above was repeated with 3.8 kg of SLC at a stanol-to-lecithin weight ratio of 1.50. The particle size distribution of this coarse dispersion was centered at 10 μm, similar to that found in small-scale preparations. The dispersion was then spray dried and when the powder was added to water with vigorous shaking, its particle size distribution was similar to that of the starting, microfluidized dispersion from which it was derived (data not shown). Taken together, these results indicate that a coarse dispersion of SLC can be processed on a large scale to produce a powder that can serve as the active dispersible ingredient for a tablet or capsule delivery system.

Tablet and capsule properties

The capsules contained 37% by weight of stanol, or 126.5 mg/capsule. Subjects consumed eight capsules per day, for a total daily stanol dose of 1.01 g. The disintegration time for the capsules was greater than 60 min. After the shell dissolved, the powder inside the capsule formed a plug with a viscous gel, formed by the hydrated SLC.

The tablets contained 21% by weight of stanol, or 212.1 mg/tablet. Subjects consumed six tablets per day, for a daily stanol dose of 1.26 g. The disintegration time for the tablets was 5.3 ± 2.5 min. The disintegration process proceeded as water penetrated the tablet core and released the active granulation. There was no viscous shell formed as found with the capsules.

The effect of different delivery properties on LDL-cholesterol reduction was determined with capsules containing a higher percent of stanol and a longer disintegration time. For this delivery system, no disintegrant was added and the powder contained a higher percentage of stanol, 37%, than that used in the tablets, 21%. Collectively, these changes produced a capsule that had a much longer disintegration time than 60 min. Moreover, after the capsule shell dissolved, the powdered SLC

Table 3 Summary of 6-week treatment-induced changes in serum lipid values[a]

Lipid parameter	Tablet dosage form Treatment group		Difference	*P*-value	Capsule dosage form Treatment group		Difference	*P*-value
	Placebo	Active			Placebo	Active		
LDL at baseline	121.3 ± 9.7	117.3 ± 8.2		0.76	123.1 ± 8.3	135.4 ± 6.0		0.25
Change (mg dL^{-1})	6.8 ± 3.4	−5.5 ± 3.1	−12.3	0.01	1.3 ± 3.2	−3.9 ± 3.8	−5.2	0.30
Percent change	6.5 ± 2.6	−3.9 ± 2.6	−10.4%	0.01	0.3 ± 2.8	−2.2 ± 2.7	−2.5%	0.52
Cholesterol at baseline	195.3 ± 10.0	186.3 ± 10.5		0.54	198.2 ± 9.6	203.1 ± 7.5		0.46
Change (mg dL^{-1})	5.4 ± 4.4	−4.2 ± 2.9	−9.6	0.07	0.2 ± 3.2	−4.1 ± 5.0	−4.3	0.47
Percent change	3.0 ± 2.3	−1.8 ± 1.5	−4.8%	0.09	0.1 ± 1.6	−1.8 ± 2.3	−1.9%	0.52
HDL at baseline	47.4 ± 3.4	45.2 ± 3.7		0.66	52.2 ± 4.4	46.5 ± 3.4		0.32
Change (mg dL^{-1})	0.4 ± 1.7	0.8 ± 1.6	0.4	0.87	1.0 ± 1.4	1.4 ± 1.4	0.4	0.88
Percent change	−0.2 ± 3.1	1.4 ± 3.1	1.6%	0.73	3.5 ± 2.7	2.8 ± 2.9	−0.7%	0.85
Triglycerides at baseline	136.6 ± 27.0	118.6 ± 18.2		0.58	115.0 ± 22.6	118.5 ± 13.0		0.67
Change (mg dL^{-1})	−12.3 ± 11.7	3.3 ± 5.9	15.6	0.23	−10.9 ± 9.4	−8.6 ± 11.2	2.3	0.88
Percent change	−3.6 ± 7.9	1.7 ± 5.2	5.3%	0.58	−2.2 ± 6.1	−2.7 ± 7.5	−0.5%	0.96
LDL/HDL at baseline	2.74 ± 0.29	2.73 ± 0.21		0.98	2.66 ± 0.32	3.12 ± 0.28		
Change	0.21 ± 0.08	−0.11 ± 0.10	−0.32	0.03	−0.03 ± 0.07	−0.14 ± 0.11	0.11	0.39
Percent change	7.3 ± 2.9	−4.2 ± 3.8	11.5%	0.03	−2.7 ± 2.7	−3.9 ± 4.0	−1.2%	0.80

[a]Mean ± s.e.m.

became trapped in a core that was surrounded by a gummy, slowly dissolving exterior. This provided a longer, sustained delivery time, providing a steady stanol supply over the digestion period.

Human studies

To determine the effect of these two dosage forms on circulating lipid levels, two studies were performed in which subjects first received lecithin placebo for six weeks before their breakfast and evening meals, while complying with the American Heart Association Heart Healthy Diet. The diet placebo combination lowered circulating lipids. For example, the entry level LDL-cholesterol for the tablet group was 130.3 ± 31.3 mg dL^{-1} (Table 1), which decreased after 6 weeks of diet control to 119.3 ± 31.0 mg dL^{-1}. Similarly, in the capsule study, diet control lowered LDL-cholesterol from 136.4 ± 32.2 mg dL^{-1} (Table 1) to 129.0 ± 27.2 mg dL^{-1}. These diet-induced changes were expected and they have been observed in other studies (Spilburg et al 2003). Importantly, a subject was randomized only if the LDL-cholesterol value was constant for at least two weeks before randomization, allowing for a baseline lipid value to be determined from the mean of these values. This study design permits a more realistic assessment of treatment effects for subjects who are not sequestered in a lipid clinic but who are free to follow their daily routine.

In the tablet study, subjects received a total daily dose of 1.26 g stanol, while in the capsule study they received 1.01 g stanol daily, dose levels that are in the mid-range of the dose–response curve observed for plant sterols and LDL-reduction (Katan et al 2003). After the six-week treatment period, subjects who received SLC in the quick-release tablet experienced a statistically significant reduction in the primary endpoint, change in LDL-cholesterol (−12.3 mg dL^{-1}, $P = 0.01$) and in the secondary endpoint, the change in the ratio of LDL-cholesterol to HDL-cholesterol (−11.5%, $P = 0.03$, Table 3, left panel). Individual changes in LDL-cholesterol are shown in Figure 2, and nine of thirteen subjects experienced a significant decrease in LDL-cholesterol. The absence of an effect in the other subjects was most likely due to poorly controlled diet, a drawback for studies that use a free-living subject population. There were no statistically significant changes in the other lipid values.

Subjects who consumed SLC in slow-release capsules for six weeks experienced no statistical changes in any of their lipid values (Table 3, right panel). However, when the mean LDL-cholesterol values from weeks 4 and 6 were compared with baseline, a 6.3% reduction ($P = 0.04$) was found, a value that is at the limit of the power of the study (data not shown).

Discussion

Plant sterols and stanols are recognized as safe and effective agents for the reduction of LDL-cholesterol (St-Onge & Jones 2003). Their incorporation into foods, especially margarine, is accepted by regulatory agencies throughout the world, and they provide a non-pharmaceutical, long-term approach to cholesterol management. For example, in a one year study in which subjects consumed 1.6 g of plant sterols per day, there was a statistically significant 6% decrease in LDL-cholesterol, and the accompanying slight 15–20% decrease in serum carotenoids was the only change in clinical chemical or haematological blood values (Hendriks et al 2003). Maintenance of this lipid-lowering

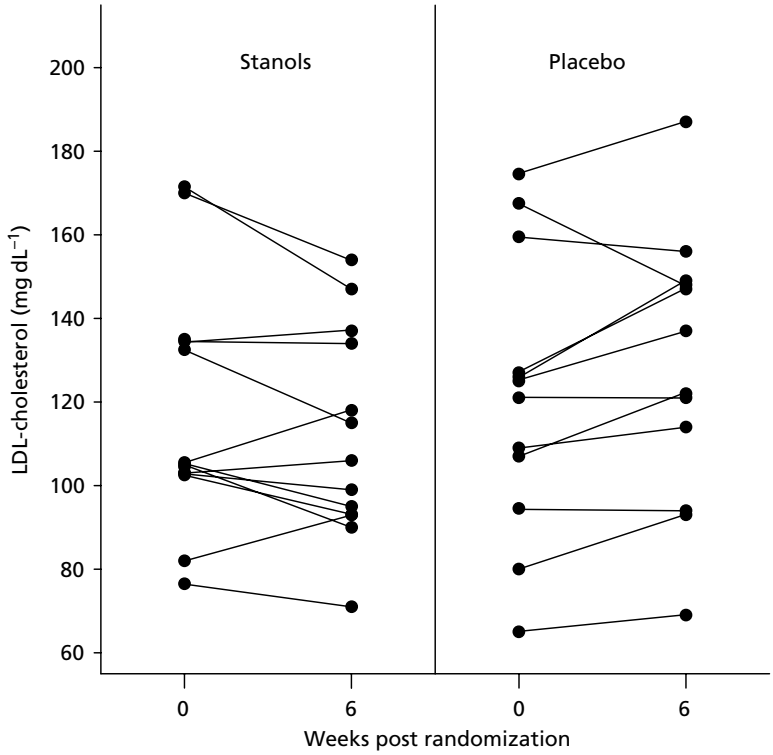

Figure 2 Subject by subject change in LDL-cholesterol when stanol (left) or placebo (right) was delivered in rapidly disintegrating tablets.

strategy for at least two years, and preferably for five years, might reduce the mortality associated with heart disease and stroke (Law et al 1994, 2003). Because the maximum health benefit requires long-term use, stanol- or sterol-containing margarines may not be the best delivery vehicle for some consumers because of objections to taste or to inconvenience. Therefore, a solid dosage form that is portable, fat-free and tasteless provides an important alternative, especially for long-term use.

Previous attempts to lower LDL-cholesterol by administration of aqueous or oil-based suspensions of solid sterols have been unsuccessful. For example, the daily consumption of capsules containing 3 g of stanol powder dispersed in safflower oil produced no change in LDL-cholesterol (Denke 1995). Similarly, when 1.8 g of unesterified sterol was dispersed in either a low- or non-fat beverage, there was no effect on LDL-cholesterol after 21 days of dosing (Jones et al 2003). Finally, consumption of 1.0 g of finely divided sitostanol in two capsules, followed by a beverage containing micellar lecithin, had no effect on blocking cholesterol absorption (Ostlund et al 1999). There is currently speculation that the crystal form of free sterols may be an important factor in determining their solubility in intestinal fluid and their subsequent ability to inhibit cholesterol absorption (Christiansen et al 2001; Christiansen 2002). In the SLC described here, lecithin may serve to disrupt the crystalline nature of plant sterols when they are mixed together in solvent and this disruption may be maintained even after solvent removal. Thus, after the solvent-free mixture was homogenized in water and spray dried, the powder readily dispersed when it was added back to water. Importantly, this coarse dispersion differed little from the dispersion from which it was derived, evidence that the solid SLC is in a physical-chemical state that is more easily dispersible in an aqueous environment than that found with micronized crystalline stanol.

The SLC powder is a flexible formulation system and by incorporating appropriate tablet additives, it is possible to explore properties that favour maximum stanol-associated LDL-cholesterol-lowering activity. For example, the tablet used in this work was designed to disintegrate rapidly within 10 min so as to deliver a 625-mg stanol bolus before the morning and evening meals. However, a slower release rate may improve efficacy by gradually delivering stanol throughout the course of the digestive process. To test this possibility, a capsule formulation was developed to disintegrate over a 60-min period to deliver a total dose of 1.0 g of stanol (2×500 mg). Using this delivery system, there was no statistically significant reduction in LDL-cholesterol after 6 weeks of dosing. Collectively, these two solid dosing studies indicate that the optimum stanol effect is most likely achieved by rapid disintegration and mixing in the stomach or the duodenum, the site of cholesterol absorption.

These observations may pertain to the mechanism of action of cholesterol absorption inhibitors. Previously, it was thought that plant sterols exerted their effect by preferential inclusion in the bile salt micelle, forcing cholesterol into solution where it was precipitated and excreted (Armstrong & Carey 1987). The discovery that cholesterol and plant sterol absorption are under genetic control indicated that uptake may be controlled by protein receptors or transporters, pointing to a cellular receptor ligand interaction as the key

absorptive step rather than a physical-chemical phenomenon in the intestinal lumen (Sehayek 2003). This specific kind of interaction is consistent with the observed uptake of plant sterols by the small intestinal cell and also with the discovery that ezetimibe is found throughout the intestinal villus (Bhattacharyya 1981; van Heek et al 2000). Efficient blockade of the putative cholesterol receptor by a concentrated bolus of plant stanol may provide a partial explanation for the greater efficacy of the tablet delivery system.

To our knowledge, the rapidly disintegrating stanol lecithin tablet described here is the first report of a solid dosage form that produces a meaningful reduction in LDL-cholesterol at a dose level that can be easily incorporated into a daily routine. After six-week consumption of 625 mg of tabletted soy stanol before the morning and dinner meals (1.25 g total daily dose), subjects experienced a statistically significant decrease in LDL-cholesterol of 12.3 mg dL^{-1} or 10.4%. The magnitude of this reduction at this dose level compares favourably with that found when sterol- or stanol-ester is delivered in margarine type foods. Using a meta-analysis of 41 trials, two dose ranges, 0.7–1.1 g daily and 1.5–1.9 g daily, were found to reduce LDL-cholesterol by 6.7% and 8.5%, respectively (Katan et al 2003). This same analysis showed that consumption of 2.5 g daily lowered LDL-cholesterol by 11.3% with no additional benefit from higher doses.

Conclusion

Spray-dried coarse dispersions of plant stanol and lecithin produce a powder that can serve as the starting material for a number of delivery systems for the reduction of LDL-cholesterol. Previous work showed its utility as a food ingredient in beverages (Spilburg et al 2003) and here we show that, when properly granulated, the powder can be compressed into a tablet that maintains its ability to lower LDL-cholesterol. The clinically effective tablet delivery system described here can be easily integrated into currently accepted therapeutic lifestyle changes recommended by the National Cholesterol Education Program and can provide another choice for subjects who need to lower LDL-cholesterol, but who are not ready for drug therapy (Maki et al 2001; Third Report of the NCEP 2001). Moreover, this fat-free tablet delivery system can be easily adapted as complementary therapy to currently available LDL-cholesterol reduction strategies. Future clinical studies will examine the effect of tablets containing SLC on further LDL lowering for subjects who are already on stable doses of statin drugs or bile-salt-sequestering agents.

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