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COMMUNICATION

Physico-Mechanical Characterization of Policosanol, a Novel Hypocholesterolemic Drug

E. Uribarri,[1] A. Laguna,[2,*] R. Sierra,[2] and Y. Ricardo[2]

[1]*Laboratorios MedSol, Ave 23 and 266, P.O. Box 4444, Lisa, Havana, Cuba*
[2]*Center of Natural Products, C.N.I.C., P.O. Box 6990, Playa, Havana, Cuba*

ABSTRACT

As part of the formulation studies of policosanol, a new hypocholesterolemic drug, a physico-mechanical characterization was developed. Thermal analysis, using differential scanning calorimetry was used to evaluate the purity of policosanol from batch to batch and, also, the particle size distribution. The degree of wettability of policosanol was studied by measuring the contact angle and solubility in different solvents. The compressibility and cohesion of particles were evaluated using a profile of compression forces, ranging between 6.5 kN and 39.0 kN. Also, other properties such as flow properties, true density, and tapped and bulk density were measured. The industrial batches of policosanol that were studied show an adequate purity and a uniform distribution of the particle sizes. Policosanol shows good flow properties, compressibility, and cohesion as well as a low solubility in the majority of the solvents used in the pharmaceutical industry, and its solubility in water or in aqueous solutions was, mainly, null. The wettability of policosanol in the different solvents shows the following order: methylene chloride > ethanol > acetone ≫ water.

*Corresponding author. Fax: (537) 33 6837; E-mail: dalmer@ip.etecsa.cu

INTRODUCTION

The development of any new drug requires extensive marketing studies, which include the pharmaceutical chemistry research of the product and the development of the pharmaceutical dosage form. For such an aim, formulation (1) studies represent an obligatory step in which the determination of the physico-mechanical properties of the active principle is the basis for the development of a formulation of a new drug dossified as tablets. The knowledge of these properties defines the strategy to be used in the development of the formulation.

Policosanol is a new cholesterol-lowering drug indicated for patients with type II hypercholesterolemia that effectively reduces serum total cholesterol and low-density lipoprotein cholesterol (LDL-C); these effects were demonstrated in experimental models (2,3) as well as in clinical trials (4–6). Policosanol is a mixture of eight primary fatty alcohols of high molecular weight obtained from sugar cane (*Saccharum officinarum L*) wax as a light-cream powder (7). Its composition is highly reproducible from batch to batch and this study takes into account if different batches reproduce the properties that are measured in order to ensure the same technological response in the future formulation.

The thermal study of policosanol using differential scanning calorimetry (DSC) as the first parameter to be considered in order to define its purity (8) and its thermal behavior. Other properties, such as particle size distribution, flow properties, true density, bulk density, tapped density, the property of policosanol to diminish its volume under compression, and its cohesion, were evaluated using a profile of applied forces between 6.5 to 39.0 kN (9). Also, the angle of contact, the solubility of policosanol in different solvents, and wettability of the active principal are important properties to be considered in the development of solid formulation.

MATERIALS AND PROCEDURES

Batches of policosanol (# 5792, # 12792, # 250493, and # 30821197), produced on the industrial scale, were supplied by Laboratories DALMER (Havana, Cuba).

Thermal Analysis

The DSC studies were carried out using a Mettler DSC-4 (Greifensee, Switzerland). A quantity of 5–7 mg of each sample was placed in an aluminum pan, with a range of temperature scanned from 30 to 160°C, at scan rate of 10°C/min and 30 ml/min of nitrogen flux. Thermograms were obtained in the following way: first, melted at 85°C and, later on, dried in a vacuum oven for several hours. Finally, the temperature was decreased slowly up to room temperature. In each case, the analysis was performed in triplicate.

Particle Size Analysis

This was performed using wet granulometry; ethanol was used as solvent and suspensions were prepared at 1.0% of policosanol by weight. Sieves of 0.125 mm, 0.045 mm, 0.032 mm, 0.020 mm and a fast filter paper were used, situated in a decreasing pore diameter sieve set; a collector was situated under the filter paper. The quantity of policosanol retained in each sieve, as well as in the filter paper, was calculated by weight difference; the results were expressed in percent of the total weight. The analysis was done in triplicate and the final result was obtained considering the mean of the three values for each particle size. The mean size diameter of particle (d) was determined using the following formula:

$$d = \frac{\text{Mean pore size} \times \text{Retained\%}}{100}$$

True Density

Three samples of 450 mg of policosanol are punched using a flat punch of 13 mm in an hydraulic press (SPECA, Model 15,011), with a pressure of 130 kN for 30 s. These pressed compacts were weighed in an analytical balance (with 0.0001 g of sensitivity) and also, the height of the compacts was measured: the true density was calculated, according to the ratio between mass and volume of the obtained compacts, and expressed in g/cm^3. The analyses were done in triplicate and the final result was obtained as the mean of the three values.

Flow Properties

The flow properties of policosanol were calculated by determining the angle of repose, the Carr's index, and the Hausner's index (1).

Angle of Repose

There are different methods for measuring the angle of repose, but we used the one reported by Jones and Pilpel (10). The final result for the angle of repose was obtained after the analysis of three samples, as the mean of the three values.

Bulk and Tapped Density

To a glass cylinder of 250 cm^3 were added 50 g of policosanol, weighed in a balance to 0.001 g accuracy; the volume that was occupied by this quantity of policosanol was measured to determine the bulk density. Then, the cylinder is dropped from a constant height 50 times over a soft surface; the volume occupied by policosanol is determined and the tapped density calculated. Both are determined using the ratio between the mass of policosanol and the volume occupied by it in each case, expressed in g/cm^3. The analyses were done in triplicate and the final results were obtained by considering the mean of the three values.

Compressibility and Compactibility

Policosanol was mixed for 5 min. with 0.5 % magnesium stearate and different tablets were produced using a 13 mm flat punch press (SPECAC Model 15.011) compressed for 2 s applying the following compression force: 6.5, 13.0, 19.5, 26.0, 32.5 and 39.0 kN. It was determined the strength and volume of the compacts. The analyses were done by triplicate and the final result was obtained considering the mean of the three values.

Contact Angle

Compacts of policosanol were prepared by compressing about 450 mg powder in a 13-mm diameter flat punch press (SPECA Model 15.011) at appropriate pressure and time. The contact angles between solid and liquid were measured with a wettability tester, in which small drops of water, ethanol, chloroform, methylene chloride, and acetone were placed on the surface of the sample, previously compacted, by means of a microsyringe. The assay was carried out five times and the final result is the mean of these determinations.

Solubility in Organic Solvents and Water

Approximately 5 mg of policosanol were accurately weighed and transferred to a 100 ml Erlenmeyer flask. Solvents were added dropwise, using a burette, until the product was completely dissolved. The solubility (in mg/l) was calculated considering the volume of solvent added to dissolve that quantity of policosanol. The solvents used in this experiment were chloroform, 1,2-dichloroethane, acetone, hexane, methanol, diethyl ether, and water. For the study of the solubility in water 1 mg of policosanol was used; it was accurately weighed, and transferred to a 2 l Erlenmeyer flask, adding de-ionized water dropwise, using a burette, to dissolve the product. The solubility (in mg/l) was calculated from the volume of water added to dissolve the policosanol. Also, the solubility of policosanol in the same solvents was determined at 40°C in the same way, temperature was controlled using a water bath. These assays were done in triplicate in each solvent and the mean of the results was considered as the final value.

RESULTS AND DISCUSSION

In Table 1 are shown the thermal properties of three batches of policosanol. Also, thermogravimetric analysis of policosanol was performed and it was demonstrated that policosanol melts without decomposition and is stable at temperatures as high at 185°C; above this temperature, it starts to decompose.

Table 1

Melting Temperature of Different Batches of Policosanol

Batch #	T (°C)
5792	81.2
12792	81.0
50493	81.8

Table 2

Particle Size Distribution of Policosanol

Particle Size (μm)	Batch			Mean (%)	SD	CV (%)
	5792	12792	250493			
<45	18.0	18.1	18.5	18.2	0.3	1.6
45–125	45.2	45.4	45.1	45.2	0.2	—
125–250	33.7	33.4	33.3	33.5	0.2	0.6
>250	3.1	3.1	3.1	3.1	—	—
Mean diameter	117.3	116.9	116.6	116.9	0.4	0.3

The particle size distribution of three batches of policosanol is shown in Table 2, where it is possible to observe a lower coefficient of variation in each analyzed fraction. This indicates homogeneity of the particle size distribution between batches, an aspect of great importance in the development of the formulation.

In Table 3 are shown the bulk density, the tapped density, and the true density of policosanol, demonstrating that it is a powder with a very low bulk density. This property should be taken into account by a formulator, because the homogeneity of the powder mixture will depend, to a large of the similarity between the powder's bulk density and its particle size distribution. In accordance with the scale previously established for Carr's and Hausner's indexes, the values obtained for policosanol powder are in the limit of acceptance for good flow properties of the powder. The value obtained for the angle of repose of policosanol is quite good, considering the parameters previously established for the powder's flow (1).

When the response of policosanol to compression was studied, it was observed (Figs 1 and 2) that increasing compression forces produce a decrease of the volume up to 26 kN. After that, no changes in the volume of the product were observed; it can be considered that policosanol is a compressible powder at low pressures. On the other hand, policosanol shows good cohesion, because the compacts obtained with it shows high values of strength, moving from 12.5 kgf Monsanto with 6.5 kN up to 15.5 kgf Monsanto with 39 kN. It can be considered that policosanol shows good compression

Table 3

Values Obtained for Different Properties of Policosanol

Parameter	Value
Bulk density	0.217 g/cm^3
Tapped density	0.272 g/cm^3
True density	0.944 g/cm^3
Angle of repose	26.6°
Carr's index	20.2%
Hausner's index	1.25

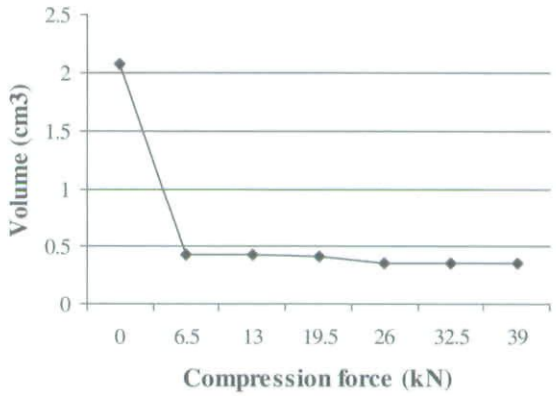

Figure 1. Compressibility of policosanol.

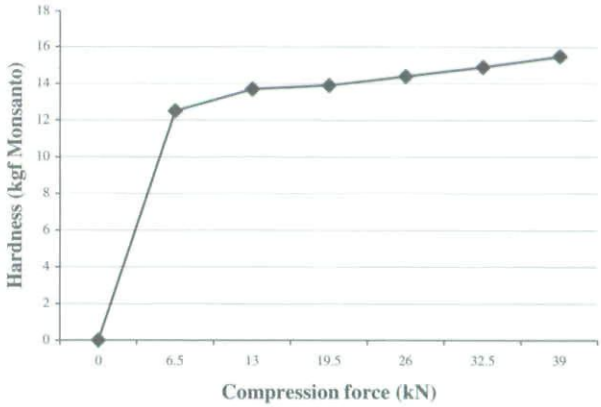

Figure 2. Compactibility of policosanol.

Table 4

Angle of Contact of Policosanol in Organic Solvents and Water

Solvent	Angle of Contact
Water	$73° \pm 1.2°$
Ethanol	$14° \pm 0.9°$
Methylene chloride	$6° \pm 0.6°$
Acetone	$17° \pm 0.6°$

Table 5

Solubility of Policosanol in Organic Solvents and Water at Two Temperatures

	Solubility (mg/ml)	
Solvent	25°C	40°C
Chloroform	1.25	2.5
1,2-Dichloroethane	0.01	0.36
Acetone	0.0025	0.083
Diethyl ether	0.055	—
Hexane	0.0033	0.015
Methanol	0.0025	0.02
Water	1.7×10^{-15} [a]	2.5×10^{-15} [a]

[a]Theoretically calculated.

properties. During the compressibility studies as well as in the determination of the true density was observed the adherence of it to the punch.

Considering the angle of contact values (Table 4), policosanol is a material with a very low wettability in water and aqueous solutions. This property has a great effect in the process of forming granulates and must be considered in order to establish the composition of the coating suspension. Also, in Table 5 is reported the solubility of policosanol in organic solvents and water at two different temperatures. As can be seen from the results of this table, the solubility of policosanol is extremely low in the solvents that are usually used in the pharmaceutical industry and its solubility in water or in aqueous solutions is almost null.

CONCLUSIONS

The industrial batches of policosanol show good purity and uniformity in the particle size distribution. Policosanol shows good flow properties, compressibility and compactibility, as well as very low solubility in many of the solvents that are used in the pharmaceutical industry, especially in water, where it is almost insoluble. The wettability of policosanol in the different solvents tested is, methylene chloride > ethanol > acetone ≫ water.

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