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(71) Applicant *(for all designated States except US)*: **SHASUN CHEMICALS AND DRUGS LIMITED** [IN/IN]; 60, VELACHARY ROAD, Velachary, Chennai 600042 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHIDAMBARAM, Tamilmaran** [IN/IN]; Jose & Jose House, 105, 12th Street, I Cross, Krishananagar, Pondicherry 605 001 (IN). **TAJ SHABBAR, Ali S** [IN/IN]; 13, Lukman Marg, Bohra Wadi, Udaipur 313001 (IN). **SIVASANKARAN, Narayanan** [IN/IN]; 926, 12th Central Cross Street, Mahakavi Bharathi Nagar, Vyasarpadi, Chennai 600039 (IN). **MARIKKANNU, Kannan** [IN/IN]; 175/2, Arasangudi, Thiruverumbur, Trichy 620013 (IN). **VENKATARAMAN, Swaminathan** [IN/IN]; Flat No. 10, Prasanth Enclave, 15, Rukmani Street, West Mambalam, Chennai 600033 (IN).

(74) Agents: **LAKSHMIKUMARAN, Varadhachari** et al.; LAKSHMIKUMARAN & SRIDHARAN, B 6/10, Safdarjung Enclave, New Delhi 110029 (IN).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** HIGH-BULK DENSITY CARISOPRODOL SUITABLE FOR DIRECT COMPRESSION

(57) **Abstract:** The invention discloses high bulk density carisoprodol having bulk density ranging from at least 400g/l to 700g/l; process for its preparation and directly compressible formulations manufactured using such high bulk density carisoprodol.

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HIGH-BULK DENSITY CARISOPRODOL SUITABLE FOR DIRECT COMPRESSION

TECHNICAL FIELD

The invention relates to high bulk density carisoprodol, process for its preparation by controlled crystallization of low density carisoprodol in an organic solvent, preferably utilizing seed crystal formation followed by addition of anti-solvent to obtain the product having desired physical characteristics essential for successful direct compression tablet formulation possessing desired hardness, disintegrating ability, acceptable dissolution characteristics and a process for the preparation of said formulation.

BACKGROUND OF THE INVENTION

Carisoprodol, also known as N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate, is a muscle-relaxant and is available as tablets, and marketed under the brand-name SOMA in the USA.

There are three common methods for tabletting. They are wet granulation method, dry granulation method and direct compression (DC) method. Pharmaceutical manufacturers would prefer to use direct compression techniques to wet / dry granulation methods because of quick processing time and cost advantages.

A solid dosage form containing a high dose drug (i.e. the drug itself comprises a substantial portion of the total compressed tablet weight), such as Carisoprodol, could only be directly compressed if the drug itself has desired physical characteristics (e.g. cohesiveness) for the ingredients to be directly compressed.

Most tablet formulations of Carisoprodol include a range of 60 to 70% by weight carisoprodol per tablet. This high dose drug, combined with lack of desired physical characteristics for direct compression, has not allowed pharmaceutical manufacturers to use direct compression as a method to prepare the final tablet.

For long it has been suggested that availability of granular, free-flowing carisoprodol material would advantageously enable making direct compressible tablets in relatively low dosages. However, the desire is still unmet as the active ingredient available in the market is of low-density (200-400g/l). Also, processes for the production of free-flowing Carisoprodol with a relatively high bulk density of about and above 400 grams per liter are not described in any prior art references.

Accordingly, it is an object of this invention to provide a high bulk density carisoprodol of bulk density ranging between 400-700g/l.

Another object of the invention is to provide a process for producing direct compressible carisoprodol tablets, which is suitable for mixing with various pharmaceutically acceptable excipients and compression into tablets by altering the crystalline surface of carisoprodol.

It is a further object of the invention to provide a directly compressed carisoprodol tablet in unit dosage form having an acceptable dissolution profile as well as acceptable degrees of hardness and resistance to chipping.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a Carisoprodol having bulk density ranging from 400 to -700g/l. its process of preparation by heating and dissolving low bulk density carisoprodol in an organic solvent preferably methanol, gradually adding water gradually to it, separating and drying the precipitated solid. The invention also relates to a tablet formulation obtained by direct compression of free-flowing high bulk density carisoprodol possessing desired hardness, disintegrating ability and an acceptable dissolution pattern.

The invention further relates to a carisoprodol tablet in unit dosage form obtained by a process that comprises mixing high bulk density carisoprodol particulate with selected pharmaceutically acceptable excipients and applying direct compression into tablets.

DETAILED DESCRIPTION OF THE INVENTION

In an embodiment of the invention, commercial grade, dry carisoprodol is converted from a flow inhibiting, easily caking, and raw product to a free-flowing, easily compressible high bulk density pharmaceutical grade material by precipitating low density carisoprodol from a solution comprising water and methanol.

In a preferred embodiment, the high-bulk density carisoprodol is precipitated by

a) preparing a clear solution of carisoprodol in methanol by heating;
b) optionally cooling the solution to initiate precipitation;
c) adding water for completion of precipitation; and
d) recovery and drying of the precipitated solid

The low-density carisoprodol 200 – 400 g/l used in the invention can be obtained commercially or prepared by various methods known to one skilled in the art such as those mentioned in U.S. Patent No. 2,937,119.

The low-density carisoprodol is dissolved in sufficient quantity of methanol by heating to obtain a clear solution. While excess quantity of methanol can be used, lower quantities are preferred from a recovery point of view.

Precipitation can be done either by cooling the clear solution or by adding water to the clear solution. The addition of water to precipitate the product should be done in a gradual manner to enable the crystals to grow larger in size. The precipitation can take place at broad range of temperatures (0-50 ^{0}C), although it is preferable to be done at lower temperatures (0-50 °C) to enable complete precipitation. The rates of agitation should be lower to reduce shear impact on the crystals, which can cause reduction in the bulk density. Preferably the aqueous organic solvent solution can contain more amount of water to obtain higher yields.

Once the product has been completely precipitated, the desired product is recovered by known isolation techniques such as filtration or centrifugation. The separated, wet carisoprodol is then air-dried or oven dried

and screened by conventional techniques to produce a highly free-flowing, pharmaceutical grade carisoprodol, which is ready for tabletting by direct compression methodology.

In various experiments conducted by the Applicant, it has been determined that replacement of methanol with other water-miscible solvents such as ethanol, isopropanol, acetone, etc. that may facilitate such precipitation, does not lead to obtainment of the desired product profile.

Accordingly the invention also includes a pharmaceutical composition comprising of high-bulk density carisoprodol, as an active pharmaceutical ingredient associated with pharmaceutically acceptable excipients, wherein conventional direct compression techniques are used for the preparation of tablets.

For the first time, the present applicants have prepared a direct compressible formulation of carisoprodol. This formulation is prepared by blending the active pharmaceutical ingredient i.e. the high bulk density carisoprodol with appropriate excipients from a range of diluent, lubricant, disintegrant, and binder, and compressing this mixture. Tablets obtained using the free-flowing directly compressible carisoprodol of the present invention are characterized by the fact that they show very high hardness even when relatively low compression forces are used for tabletting whilst they are also capable of disintegrating in an aqueous medium at a high speed, and additionally exhibit a low friability pattern; thus exhibiting an ideal oral use tablet profile.

Diluents, or fillers, are added in order to increase the mass of an individual dose to a size suitable for tablet compression. Suitable diluents include powdered sugar, lactose, calcium phosphate, calcium sulfate, sodium starch glycollate, microcrystalline cellulose, lactose, mannitol, kaolin, sodium chloride, starch etc.

Lubricants are incorporated into a formulation for a variety of reasons. They reduce friction between the granulation and die wall during compression and ejection. This prevents granulate from sticking to the tablet punches,

facilitates its ejection from the tablet punches, etc. Examples of suitable lubricants include talc, stearic acid, vegetable oil, calcium stearate, zinc stearate, magnesium stearate, etc.

Glidant's are also typically incorporated into the formulation. A glidant improves the flow characteristics of the granulation. Examples of suitable glidant's include talc, silicon dioxide, sodium lauryl suplhate, colloidal silicon dioxide and cornstarch.

Binders may be incorporated into the formulation. Binders are typically utilized if the manufacture of the dosage form uses a granulation step. Examples of suitable binders include: povidone, polyvinylpyrrolidone, copolyvidone, polyvinyl pyrrolidone, xanthan gum, cellulose gums such as carboxymethylcellulose, methyl cellulose, hydroxypropylmethylcellulose, hydroxycellulose, gelatin, starch, and pregelatinized starch.

Other excipients including alginates, mineral oil, croscarmellose sodium, or calcium phosphate may be incorporated into the formulation. Also preservatives, antioxidants, or any other excipient commonly used in the pharmaceutical industry, etc may be included. Waxes and matrixing agents such as polymers can also be added to change the release profile of the formulation or binding profile. The finished composition of the invention is administered orally in the form of uncoated tablets. It can also be used as granulate loose filled into capsules.

The following examples are illustrative of the invention but not to be construed to limit the scope of the present invention. The present invention has been described in terms of its specific embodiments and certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of present invention.

EXAMPLE 1

Synthesis of high bulk density carisoprodol: 100 g of low bulk density carisoprodol is dissolved in 70 ml methanol by heating to 50°C. The solution is cooled slowly to 5-10°C over a period of 4-6 hours. The agitation speed during cooling is maintained about 50-60 rpm. 100 ml of ice-cold water is added to

the thick slurry of the product in about 20 minutes. The slurry is stirred at 5-10 °C for about 30 minutes. The precipitated white crystals are filtered off and washed with 100 ml of water. Wet product is dried at 50°C under high vacuum. The high bulk density carisoprodol is obtained in about 97% yield.

Bulk density: 0.49 g/ml; tap density: 0.64 g/ml.

EXAMPLE 2

Synthesis of high bulk density carisoprodol: 50 g of low bulk density carisoprodol is dissolved in 80 ml methanol by heating it to 50°C. 120 ml water is added to the hot solution over a period of 30 minutes under slow agitation. The slurry is stirred for 1 hour at 50°C. The precipitated crystals are filtered off and washed with 50 ml water. Wet product is dried at 50°C under high vacuum. The high bulk density carisoprodol is obtained in about 90% yield.

Bulk density: 0.45 g/ml; tap density: 0.57 g/ml.

EXAMPLE 3

Synthesis of high bulk density carisoprodol: 100 g of low bulk density carisoprodol is dissolved in 40 ml methanol by heating it to 50-55°C. The product started crystallizing out after 15 minutes from methanol solution. The slurry is stirred slowly at 50°C for about 2 hours. A mixture of methanol/water (300 ml) in the ratio of 1:5 is added over a period of 15 minutes. The slurry is stirred slowly at 50°C for about 30 minutes. The precipitated crystals are filtered off and washed with 100 ml water. Wet product is dried at 50 °C under high vacuum. The high bulk density carisoprodol is obtained in about 96% yield.

Bulk density: 0.50 g/ml; tap density: 0.60 g/ml.

EXAMPLE 4

Tablet production by direct compression process

Table 1

	Per 500 mg tablet
High bulk-density carisoprodol	350 mg
Microcrystalline cellulose	120 mg
Sodium starch glycollate	10 mg
Polyvinyl pyrrolidone	10 mg
Sodium lauryl sulphate	5 mg
Stearic acid	3 mg
Talc	2 mg

All ingredients, except talc, are passed through a 40-mesh (420 microns) sieve, and blended together for about 10 minutes. Talc is then added, and blending is continued for an additional 5 minutes. Tablets are now manufactured by direct compression by application of a low compression force using a rotary tablet machine. Friability: 0.2% w/w. The uncoated carisoprodol tablets, thus formed are described in table 1. Bulk density of 0.49 g of carisoprodol used in the above formulation was 0.47g/ml and tap density was 0.6 g/ml.

EXAMPLE 5

Tablet production by direct compression process

Table 2

	Per 450 mg tablet
High bulk-density carisoprodol	350 mg
Microcrystalline cellulose	80 mg
Sodium starch glycollate	5 mg
Povidone	6 mg
Sodium lauryl sulphate	3 mg
Colloidal silicon dioxide	2 mg
Stearic acid	2 mg
Talc	2 mg

a) High bulk density Carisoprodol was passed through #20 mesh (840 microns). Povidone was passed through #40 mesh (420 microns).

b) Microcrystalline cellulose, sodium starch glycollate, colloidal silicon dioxide and sodium lauryl sulphate was passed through #40 mesh (420 microns).

c) Talc and stearic acid was passed through #60 mesh (250 microns).

Carisoprodol and povidone were mixed for three minutes. The carisoprodol + povidone mixture was added to the mixture of microcrystalline cellulose, sodium starch glycollate, colloidal silicon dioxide and sodium lauryl sulphate and mixed for 5 minutes. Now purified talc and stearic acid mixture is added to the above mixture and blended for 2 minutes.

This blend is now pre-compressed followed by final compression using 10 mm SC punches with a punch force: 1 - 2 KN.

Physical parameters observed	
Hardness	70 N
Disintegration Time	31 seconds
Friability	0.02%

I / We claim:

1. Carisoprodol having bulk density ranging from 400 to -700g/l.
2. A process for producing carisoprodol having a high bulk density ranging from 400 to -700g/l, said process comprising:
   a. precipitating carisoprodol from a solution of low bulk density carisoprodol in an organic solvent; and
   b. recovering the precipitated solid as crystals.
3. A process according to claim 2, wherein the low bulk density carisoprodol used has a bulk density of about 150 g/l to about 350 g/l.
4. A process according to claim 2, wherein the organic solvent used is methanol.
5. A process according to claim 2, wherein precipitation is performed by addition of water.
6. A process according to claim 2, wherein larger crystals is obtained by growing the size of the crystals by gradual addition of water at a temperature in the range of about 0-50 °C.
7. A pharmaceutical composition comprising therapeutically effective amount of carisoprodol having bulk density ranging from 400g/l to 700g/l in association with at least one or more pharmaceutically acceptable excipients.
8. The pharmaceutical composition as claimed in claim 7, wherein the excipient is selected from a group consisting of diluents, carriers, binders, lubricants and disintegrants.
9. A pharmaceutical composition according to claim 7 consisting of high bulk density carisoprodol, micro crystalline cellulose, sodium lauryl sulphate, sodium starch glycollate, colloidal silicon dioxide, povidone, purified talc and stearic acid.
10. A process for the preparation of high bulk density carisoprodol tablets, said process comprising blending a pharmaceutical composition consisting therapeutically effective amount of carisoprodol having bulk density ranging from 400g/l to 700g/l with appropriate excipients selected from diluents, carriers, binders, lubricants and disintegrants

and directly compressing the blend using pre-compression and final compression phases.

11. A formulation comprising high bulk density carisoprodol and pharmaceutically acceptable excipients as substantially described herein above.

AMENDED CLAIMS

received by the International Bureau on 06 June 2006 (06.06.06)

1. A granular free flowing easily compressible high bulk density carisoprodol characterized by its bulk density which is in the range of about 400 to about 700 g/l.
2. A process for producing Carisoprodol having a high bulk density in the range of about 400 to about 700 g/l, said process comprising:
    a. precipitating carisoprodol from a of solution of low bulk density carisoprodol in methanol, and
    b. recovering the precipitate as crystals.
3. The process according to claim 2, wherein the precipitation is performed by addition of water.
4. A pharmaceutical composition comprising therapeutically effective amount of carisoprodol as defined in claim 1 in association with at least one or more pharmaceutically acceptable excipients.
5. A process for the preparation of carisoprodol tablets, said process comprising;
    a. blending a pharmaceutical composition consisting therapeutically effective amount of carisoprodol as defined in claim 1 with appropriate excipients selected from diluents, carriers, binders, lubricants and disintegrants, and
    b. directly compressing the blend.

Statement under Article 19 (1)

The present invention relates to a granular, free flowing, easily compressible and high bulk density carisoprodol having bulk density in the range of about 400 to about 700 g/l and its process of preparation.

ISR acknowledges novelty and inventive step in respect of claim 4.

Document D1, D2 and D4 teaches a process of preparation of N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (Carisoprodol) by an ester interchange reaction between N-isopropyl-2-methyl-2-propyl-3hydroxy propyl carbamate and ethyl urethane. The carisoprodol obtained was recrystallized from either aqueous isopropanol solvent or leaving the carisoprodol in water leading to its crystallization.

The present application is different from the cited documents.

The present application relates to a process of obtaining high bulk density carisoprodol (400-700 g/l) from a low bulk density carisoprodol (150-350 g/l). In the present invention, the low bulk density carisoprodol (150-350 g/l) is dissolved in methanol and precipitated using water. This results in production of high bulk density carisoprodol having bulk density of 400-700 g/l which is granular, free flowing and easily compressible into a tablet. With increase in compressibility property, it has given the flexibility to choose between creating smaller tablets while maintaining the carisoprodol content or keeping tablet sizes constant while increasing the carisoprodol claim on the label.

The high bulk density and free-flowing carisoprodol obtained in the present invention, imparts a high degree of fluidity to the pharmaceutical composition, which is essential for high-speed compaction and tablet filling. Use of low bulk density carisoprodol, resulting there were two problems: low weight and low flowability. During wet or dry granulation using low bulk density material, both bulk density and flowability should be maximized. Furthermore, drugs with low bulk density are difficult to compress directly due to air entrapment. They are also sensitive to over-lubrication and there is a limit to color variation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2005/000446

A. CLASSIFICATION OF SUBJECT MATTER
C07C271/12 A61K31/325 A61P21/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 937 119 A (BERGER FRANK M ET AL) 17 May 1960 (1960-05-17) cited in the application Example 2 (column 10). Paragraph 1 (column 14).	1-3,5-11
X	GB 873 908 A (CARTER PRODUCTS, INC) 2 August 1961 (1961-08-02) Example 2 (page 8). Line 82, right-hand column (page 9)- line 10, left-hand column (page 10).	1-3,5-11
X	DE 10 68 242 B (CARTER PRODUCTS, INC) 5 November 1959 (1959-11-05) Beispiel 2 (column 7), Beispiel 9 (column 9-10). Lines 47-57 (column 9).	1-3,5-11

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2006	06/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menchaca, R

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 022 641 A (ORGAMOL S.A) 16 March 1966 (1966-03-16) Example III (page 5)	1-3,5,6

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2005/000446

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2937119 A	17-05-1960	DK 102958 C ES 252741 A2	01-11-1965 01-04-1960
GB 873908 A	02-08-1961	NONE	
DE 1068242 B		NONE	
GB 1022641 A	16-03-1966	NONE	