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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 38**SEÑOR****SUPERINTENDENTE DE INDUSTRIA Y COMERCIO****E. S. D.****REF: Expediente 09 068.966.****TÍTULO SOLICITADO: MÉTODO PARA FORMAR UNA TABLETA QUE
COMPRENDE EL PREMEZCLADO DE IBUPROFENO
Y SÍLICE.****PUBLICACIÓN: Gaceta 619 de 19/08/2010, número de publicación
600.****SOLICITANTE: SCOLR PHARMA, INC.****APODERADO: MAURICIO JARAMILLO CAMPUZANO.****TRÁMITE: SUSTENTACION DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 02 de Febrero de 2009, en los siguientes términos:

I. RATIFICACIÓN

Comendidamente me permito insistir en todos y cada uno de los argumentos planteados en la oposición referida, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia carece de los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 y que como tal, no merece recibir el beneficio patentario:

- Adicionar excipientes capaces de conferir a la formulación las características requeridas para la compresión directa¹ constituye la forma más fácil y habitual de conferir a un principio activo la capacidad de comprimir directamente, y obviamente corresponde a la estrategia utilizada por el formulador en la solicitud colombiana en trámite.
- Cualquier persona medianamente versada en la materia deber reconocer que la celulosa microcristalina silicificada es un producto co-procesado, que se realiza con 98% de celulosa microcristalina con dióxido de silicio coloidal al 2%. Los dos ingredientes son secados por aspersión para producir microcristales aglomerados que se forman como resultado de la fuerte asociación física entre los dos excipientes. Es así como se reconoce dicho excipiente como una opción adecuada para procesos de compresión directa². Lo mismo aplica para la sílice que se ha utilizado como excipiente en formulaciones para compresión directa con anterioridad³.
- La patente Española ES 2239119 publicada el 16 de Octubre de 2005 y manera la patente americana US 5191114 publicada el 02 de Marzo de 1993 revelan el uso del excipiente sílice (dióxido de silicio) en la elaboración de formulaciones sólidas que se pueden comprimir directamente.
- No tiene naturaleza inventiva elegir alguno de estos dos excipientes para lograr incluir Ibuprofeno (o cualquier otro principio activo) en formulaciones de compresión directa, puesto que no se debe determinar exclusivamente sobre la base de la documentación correspondiente al arte previo (si dichos excipientes habían sido mencionados con anterioridad, como además es el caso), sino teniendo en cuenta los conocimientos propios de una persona capacitada y experimentada en la formulación de productos farmacéuticos. Es así como dicha persona medianamente versada en la formulación, debe reconocer que la elección de excipientes con características inherentes a la compresión directa es una estrategia evidente, y por lo tanto dicha estrategia de selección

¹ Vila Jato, J.L. Tecnología Farmacéutica. Volumen II. Páginas 105 a 107.

² Mira Jivraja, Luigi G. Martini, b and Carol M. Thomson. An overview of the different excipients useful for the direct compression of tablets.

http://74.125.155.132/scholar?q=cache:Cwrb7IQgJHMJ:scholar.google.com/&hl=es&as_sdt=2000&as_vis=1

se evalúa de manera rutinaria a través de los respectivos ensayos de preformulación y formulación.

- Como regla general, las técnicas de formulación y el conjunto de compuestos que se pueden utilizar para desarrollar productos farmacéuticos viables en cualquiera de sus formas, son elementos que son claramente conocidos para una persona medianamente versada en la formulación de productos farmacéuticos, así que de ninguna manera puede ser inventivo escoger uno u otro excipiente para conseguir las características de eficacia, eficiencia, seguridad y estabilidad indispensables para todo medicamento.

II. COMPLEMENTO DE INFORMACIÓN

En complemento de los argumentos presentados oportunamente en la oposición correspondiente, se presentan nuevos argumentos relacionados a la tesis de falta de novedad y de nivel, veamos:

Existen documentos, como la patente americana US 6.103.219 publicada el 15 de agosto de 2000 y titulada "PHARMACEUTICAL EXCIPIENT HAVING IMPROVED COMPRESSIBILITY", que con anterioridad describen las aplicaciones técnicas de la celulosa microcristalina silisificada (entre estas la compresión directa) en composiciones tipo tableta para administración oral, tal y como se describe en las reivindicaciones 1 a 8, 11 y 15 a 17 de la solicitud colombiana en trámite, veamos:

A microcrystalline cellulose-based excipient having improved compressibility, whether utilized in direct compression, dry granulation or wet granulation formulations, is disclosed. The excipient is an agglomerate of microcrystalline cellulose particles and from about 0.1% to about 20% silicon dioxide particles, by weight of the microcrystalline cellulose, wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other. The silicon dioxide utilized in the novel excipient has a particle size from about 1 nanometer to about 100 microns. Most preferably, the silicon dioxide is a grade of colloidal silicon dioxide.

(...)

³ G. K. BOLHUIS 2, C. F. LERK 2 AND J. R. MOES 2 Comparative evaluation of excipients for direct compression. Pharmaceutisch . Weekblad.
<http://www.springerlink.com/content/170866223h374318/fulltext.pdf>

20. A method of preparing a solid dosage form, comprising:

- (a) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μ m, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight;
- (b) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide;
- (c) mixing an active ingredient with said excipient in a ratio from about 1:99 to about 99:1;
- (d) incorporating said mixture obtained in step (c) into a plurality of solid unit doses.

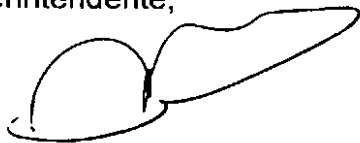
En conclusión, y en sustentación de los argumentos expuestos en la respectiva oposición presentada en su momento, se hace aun más evidente que la solicitud colombiana en trámite carece absolutamente de nivel inventivo, y que la formulación descrita en su capítulo reivindicatorio, corresponde al resultado de la aplicación de una estrategia tecnológica que deben ser reconocidas por cualquier persona medianamente versada en la formulación de productos farmacéuticos sólidos de compresión directa.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. ANEXOS

- La patente americana US 6.103.219 publicada el 15 de agosto de 2000 y titulada "PHARMACEUTICAL EXCIPIENT HAVING IMPROVED COMPRESSIBILITY".

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P. 44655 del C. S de la J.

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An overview of the different excipients useful for the direct compression of tablets

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Available online 14 February 2000.

Abstract

The humble **tablet** dosage form still accounts for more than 80% of all dosage forms administered to man. This review will outline the various excipients that have been used as fillers in **direct compression** formulations, with particular emphasis on what is expected from such excipients in terms of their functionality. It is intended that this overview (which is by no means exhaustive) will serve as an 'aide-memoire' to the formulation scientist.

Author Keywords: Excipients; Direct compression; Tableting; Compaction

Subject-index terms: Pharmacology

Article Outline

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- Microcrystalline cellulose
- Starch 1500
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- Dicalcium phosphate dihydrate
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- Other factors that influence excipient selection
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- Uncited reference (cited in box only)
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It is a remarkable fact that, in the new millennium, tablets still account for more than 80% of all dosage forms administered to man. The principal reasons for their continued popularity include their ease of manufacture, their convenience of dosing, and their stability compared with liquid and semi-solid presentations. One mode of tablet manufacture is that of direct compression of the active ingredient with other appropriate excipients to form a tablet, normally for medium- to high-potency compounds where the drug content is less than 30% of the formulation. The advantages of direct compression are well-known, the most important being fewer processing stages and the elimination of heat and moisture effects.

This review will outline the various excipients that have been used as fillers in direct compression formulations, with particular emphasis on what is expected from such excipients in terms of their functionality.

Direct compression (DC) manufacture

Direct compression is viewed as the technique of choice for the manufacture of tablets containing thermolabile and moisture-sensitive drugs[1], and although it affords many advantages it is still not as popular as wet granulation [1, 2 and 3].

The existing popularity of wet granulation can be understood when considering the compaction process. As a powder is compressed within a die, the various stages of the compaction process can be separated as follows[1]:

- rearrangement – where particles move within the die cavity to occupy void spaces that exist between particles;
- deformation – when particles can no longer rearrange themselves, the material will start to deform elastically;
- compaction – when the elastic limit of the material is exceeded, the material will deform either plastically or destructively (fragmentation or brittle fracture). Either mechanism can occur and is dependent upon the material characteristics, the compaction speed, compaction pressure and particle size. Plastic deformation will aid bonding because it increases the contact area between particles and fragmentation produces newer surfaces which also favours strong bonding.
- relaxation – once a compressional force has been withdrawn from a compressed mass (during punch withdrawal and ejection from the die cavity) the compact will undergo relaxation; if these elastic forces exceed the tensile strength of the tablet, then tablet integrity will fail.

Successful tablet production will depend upon achieving the right balance of brittle fracture and plastic behaviour within the compression mix, which, in turn, is dependent upon the compressional characteristics of the drug substance and the excipients. Theoretically, materials will compress by plastic deformation, such as microcrystalline cellulose, or brittle fracture, such as dicalcium phosphate dihydrate, but, in practice, most excipients and drugs will compact as a combination of these mechanisms. The most commonly employed excipients have been ranked in ascending order in terms of their brittleness: microcrystalline cellulose > spray-dried lactose > β -lactose > α -lactose > α -lactose monohydrate > dicalcium phosphate dihydrate.

The main advantage of wet granulation is that the poor compressional and flow properties exhibited by many drug substances can be masked as a result of their incorporation into a granule, allowing batch-to-batch differences to be ‘submerged in a sea of starch paste or povidone’[2]. However, with the judicious choice of excipients combined with an appropriate drug substance, the reward for establishing a direct compression process can be substantial.

A summary of the general advantages and disadvantages of direct compression have been outlined in [Box 1](#), although formulation-specific differences may manifest with different drug substances[3].

Box 1. Advantages and disadvantages of direct compression

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Advantages

- Requires fewer unit operations compared with wet granulation (shorter processing time and lower energy consumption)
- Fewer stability issues for actives that are sensitive to heat or moisture
- For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, norfloxacin⁴
- Fewer excipients may be needed in a direct compression formula

Disadvantages

- Issues with segregation – these can be reduced by matching the particle size and density of the active drug substance with

excipients

- In general, the drug content is limited to approximately 30% or approximately 50 mg
- May not be applicable for materials possessing a low bulk density because after compression the tablets produced may be too thin
- Not suited for poorly flowing drug compounds
- Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing

Direct compression excipients

Although the principles governing direct compression have been well known for many years, the technique has only recently become more established as a result of the introduction of excipients specifically designed for direct compression[5]. These excipients are not only directly compressible themselves, but can also be mixed with a large proportion of drug substance with no significant deterioration in tablet quality [6]. In addition to excipients possessing good flow and compression properties, they must also possess the following attributes:

- particle size distributions that are similar for most active drug substances, thus avoiding segregation during processing;
- a high bulk density;
- batch-to-batch quality must be reproducible.

These attributes are the most critical for direct compression functionality. The remaining attributes are required for all excipients, in that they should also be:

- physically and chemically stable when in contact with moisture, air and heat;
- chemically inert; that is, do not accelerate the degradation of active ingredients or other excipients;
- compatible with packaging components;
- available worldwide, and preferably from more than one supplier.

In addition, it is important to note that many excipients can possess multi-functionality, which is dependent upon the concentration at which they are employed. For example, microcrystalline cellulose (see below) can be used as an anti-adherent (5–20%), a disintegrant (5–15%) and as a diluent (20–90%)[7]. Materials that are currently available as direct compression vehicles can be classified according to their disintegration and flow properties, and these are summarized in Box 2.

Box 2. Materials used as direct compression vehicles classified according to their disintegration and flow properties

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- Materials that act as disintegration agents with poor flow characteristics, such as microcrystalline cellulose and directly compressible starch

- Free flowing materials that do not disintegrate, such as dibasic calcium phosphate dihydrate
- Free flowing powders that disintegrate by dissolution, such as lactose, mannitol and maltose
- Co-processed excipients – that is, excipients that have been combined together in a synergistic manner and which are more beneficial than simple physical admixtures, such as silicified microcrystalline cellulose

Disintegrants and poor flow

Microcrystalline cellulose

Microcrystalline cellulose is a purified, partially depolymerized cellulose, which is prepared by treating α -cellulose with mineral acids, producing bundles of needle-like microcrystals. In terms of appearance, this excipient is a white, crystalline powder composed of agglomerated porous particles[7]. In a survey conducted within the pharmaceutical industry, Shangraw and Demarest [8] concluded that many formulation scientists ranked microcrystalline cellulose as the most useful filler for direct compression. Its popularity can be ascribed to its excellent compactibility at low pressures, high dilution potential and superior disintegration properties. However, using paracetamol and potassium phenethicillin as model compounds, Khan *et al.*[9] found that the compactibility of microcrystalline cellulose decreased with a reduction in its moisture content.

However, when microcrystalline cellulose with high moisture levels were employed (>7.0%) the tablets formed were prone to capping. These workers postulated that moisture within the porous structure of microcrystalline cellulose facilitated the slippage of individual microcrystals, upon deformation, and that an optimum amount of moisture was needed to encourage hydrogen bonding between particles, thus preventing elastic recovery. Previous reports have shown that compacts of microcrystalline cellulose stored under high humidity tended to swell as a result of disruption of the hydrogen bonds that bind the cellulose fibres together[10].

Particle size has very little effect on compactibility[11 and 12] and, as a result of its low bulk density, microcrystalline cellulose has a high dilution potential. In addition, despite its plastic behaviour upon compression, Bolhuis *et al.*[13] found that microcrystalline cellulose compressed both with and without magnesium stearate (0.5%) still produced extremely hard compacts, although tablets are seldom manufactured without a lubricant and, as such, this is probably an academic point.

Microcrystalline cellulose is regarded as being chemically inert and compatible with most drugs. The limitation of poor flow can be offset by mixing with another filler with good flowability, such as α -lactose monohydrate or dicalcium phosphate dihydrate. Experimental findings[14] showed that microcrystalline cellulose and extra fine lactose had the best overall properties when compared with eleven other microcrystalline cellulose–excipient combinations.

Starch 1500

Native starches possess good compression characteristics, but their poor flow properties and high lubricant sensitivity does make them less suitable for use in direct compression. They are particularly useful as a result of their good binding and disintegrant properties. Nevertheless, Starch 1500 continues to be widely regarded as the next choice excipient after lactose and microcrystalline cellulose[8].

Starch 1500 is a form of pregelatinized starch that has been modified to make it more compressible and flowable in character. In terms of appearance, it is a white to off-white powder of a moderately coarse-to-fine nature. It is odourless, but is reported to have a distinctive taste[7].

During the manufacturing process, some of the hydrogen bonding between amylose and amylopectin is partially ruptured, so that the product contains 5% free amylose, 15% free amylopectin and 80% unmodified starch. The free amylose is responsible for the disintegration properties and the free amylopectin provides cold water solubility and aids the binding properties[15].

Starch 1500 is extremely sensitive to the softening effects of alkaline stearate lubricants[16]. For this reason, the use of magnesium stearate should be avoided or kept at a level below 0.5% w/w [13] because higher concentrations can have adverse effects on tablet strength and dissolution. Consequently, stearic acid is usually preferred as the lubricant to be used with pregelatinized starch. Starch is a good disintegrant but this property may cause longer-term problems because the compacts formed may be friable. At high strain rates during compression a large proportion of the deformation is elastic and hence, elastic recovery occurs during the act of ejection, inducing capping [16 and 17].

Free-flowing materials that do not disintegrate

Dicalcium phosphate dihydrate

Dicalcium phosphate (dihydrate) is a commonly used directly compressible filler produced by a complicated process using phosphoric acid and slaked lime. Although predominantly used in vitamin and mineral supplements because of the high calcium and phosphorus content, the use of dicalcium phosphate is increasing in pharmaceutical preparations as a result of its low cost and desirable flow and compression characteristics[7].

The addition of a lubricant is necessary as non-lubricated tablets made with dicalcium phosphate are difficult to eject from dies. One of the main advantages of using dicalcium phosphate as a filler or binder is that alkaline lubricants such as magnesium stearate have practically no effect on its binding properties[18]. This insensitivity to magnesium stearate has been attributed to the fact that clean, lubricated surfaces are created by crystal fragmentation during the process of consolidation and compaction.

When placed in water, dicalcium phosphate tablets are rapidly and completely penetrated by the liquid[19]. This rapid penetration is caused by the hydrophilic nature of the material [20] and the high porosity of the tablets. Despite the fast and complete water penetration, dicalcium phosphate tablets do not disintegrate because the excipient is relatively insoluble in water and no disintegration force is developed [21]. Therefore, it is important to include a disintegrant with an active mechanism such as swelling, for example starch, povidone and sodium starch glycolate, to induce the disintegration forces necessary to break up the tablet.

Dicalcium phosphate is best used in direct compression when combined with microcrystalline cellulose or starch[22 and 23]. Good compression characteristics can be obtained with 10–33% dicalcium phosphate and 66–90% microcrystalline cellulose with 0.5% magnesium stearate and as little as 0.1% sodium starch glycolate. This combination of excipients can convert up to 20% of a poorly compressible drug substance into a directly compressible formulation [24].

Free-flowing powders that disintegrate by dissolution

Lactoses

Lactose is widely used as a filler or diluent in tablets and several grades are commercially available with

differing physical properties. Spray-dried lactose was developed 30 years ago and is a form of lactose designed specifically for direct compression. It comprises mainly α -lactose monohydrate microcrystals bound into spherical aggregates by small amounts of amorphous lactose. Other types used for direct compression are agglomerated lactose produced by fluid bed drying, anhydrous α -lactose and anhydrous β -lactose. Anhydrous α -lactose has the significant drawback of relatively slow disintegration, and is not discussed further here. Hydrous lactose monohydrate is not directly compressible and is therefore used in wet granulation formulations. The characteristics of some commonly employed lactoses have been summarized in Boxes 3 and 4.

Box 3. Features of α -lactose monohydrate (crystalline)

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- Good flow characteristics¹⁴
- Unreactive, except for discoloration when formulated with amines (Maillard reaction) and alkaline materials²²⁵
- Contains approximately 5% moisture but only 0.2% is free moisture. The residue is water of crystallization, which is unavailable to react with moisture-sensitive drugs
- Commonly used in combination with microcrystalline cellulose with synergistic effects on disintegration time and improved crushing strength²⁴
- Inexpensive

Box 4. Features of anhydrous β -lactose and spray-dried lactose

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Anhydrous β -lactose

- Poor flowability
- Can pick up moisture at elevated humidities, causing a change in tablet dimension

Spray-dried lactose

- Requires high compression pressures to produce hard tablets
- Compressibility is affected if it is allowed to dry below a level of 3% moisture
- Has high dilution capacity
- A disintegrant is required
- Requires a lubricant, but the lubricant does not affect binding

A comparative evaluation of the use of six lactose-based excipients as direct compression excipients gave the following rank order in terms of effectiveness: anhydrous β -lactose, followed closely by spray-dried lactose and Ludipress (see co-processed excipients section)[26].

Sorbitol

- Sorbitol is a common tablet excipient suitable for direct compression and is widely used in the manufacture of chewable and sublingual tablets. It is a white, crystalline and odourless solid with a pleasant, cooling, sweet taste[7], and is a hygroscopic isomer of mannitol, produced on a commercial scale by high-pressure catalytic hydrogenation of glucose in the presence of copper or nickel.

There are four different types (α , β , γ , and δ) as well as an amorphous form that is known to exist. The γ form is the most stable and has the best compaction properties. It does, however, require longer than other excipients, such as lactose, for disintegration and dissolution to occur. The tableting properties of sorbitol are dependent upon particle structure, particle-size distribution and bulk density[27 and 28]. The addition of up to 2% magnesium stearate to a sorbitol tablet formulation produced no deteriorative effects on tablet hardness [28]. One limitation of sorbitol is that its hygroscopic nature can accelerate the degradation of moisture-sensitive compounds [7]. Other issues include the hardening of tablets upon ageing, caused by the recrystallization of sorbitol. However, the inclusion of pregelatinized starch within the formulation has been shown to prevent recrystallization [29].

Mannitol

Mannitol is commonly used in pharmaceutical formulations and for food products. It occurs as a white, odourless, crystalline powder or as free-flowing granules. It has a sweet taste and a cooling sensation in the mouth (negative heat of solution), making it a useful excipient for lozenges and chewable tablets[7]. Because mannitol is non-hygroscopic, it is possible to use it with moisture-sensitive drugs. In addition, unlike sorbitol, the metabolism of mannitol does not cause increases in blood sugar levels, making it a viable filler for the formulation of diabetic medications [30]. Previous studies have identified several polymorphic forms for mannitol, including the α , β , and γ forms. Their performance under compression differed markedly, suggesting that wet granulation of the α form prior to direct compression improved its poor flowability and binding properties [30].

Granulated lactitol

Lactitol is a direct compression filler derived from the catalytic hydrogenation of lactose. It is a wet granulated product composed of microcrystalline agglomerates, and is chemically more stable than related disaccharide-based fillers as it is not a mediator for the Maillard reaction[31]. This form of lactose is freely soluble in water, has reasonably good flow properties, and formulations containing granulated lactitol do not require a glidant [31].

Crystalline maltose

Crystalline maltose is a disaccharide carbohydrate used in the food and pharmaceutical industry. It has a pleasant taste and can be used for both chewable and non-chewable tablets. This excipient is produced by a spray-drying process, creating spherical, highly compressible and flowable particles. A study revealed that when crystalline maltose (25%) was incorporated into a 75% microcrystalline cellulose-based formulation and then tableted, there was an improvement in the powder flow, the disintegration times and the friability[32].

Co-processed excipients

Ludipress

Ludipress is a co-processed product consisting of three components: a filler, a binder and a disintegrant. The exact concentrations of its constituents are stated below: 93.4% α -lactose monohydrate, 3.2%

polyvinylpyrrolidone and 3.4% croscopovidone. Ludipress has excellent flowability because the material consists of spherical particles made up of a large number of small crystals with smooth surfaces[33 and 34]. Good tablets can be prepared at low compression forces and when Ludipress was compared with six other lactose-based excipients, including agglomerated lactose and the anhydrous β form, it gave the second best performance in terms of physical strength.

Initial studies showed the need for a glidant to be incorporated within a formulation because of the build up of friction upon compression[33 and 34]. Of the two glidants used, 2% stearyl fumarate showed the better improvement in friability, crushing strength and disintegration time compared with magnesium stearate, which appeared to increase both the friability and the disintegration time. In general, the disintegration time of formulations containing Ludipress is much longer than those containing lactose, as a result of the presence of PVP. This limitation can be overcome by the addition of microcrystalline cellulose in the formula, promoting disintegration by a capillary and wicking action. Alternatively, experiments have shown that powerful disintegrants such as sodium starch glycolate may also be of some value [35].

Silicified microcrystalline cellulose

Silicified microcrystalline cellulose is a co-processed product, which is made of 98% microcrystalline cellulose that is silicified with 2% colloidal silicon dioxide. The two ingredients are spray-dried together to produce agglomerated microcrystals which are formed as a result of the strong physical association between the two excipients (although no covalent bonds are produced that classify it as a new chemical entity). Silicified microcrystalline cellulose is claimed to have superior flow properties compared with conventional grades of microcrystalline cellulose and a low lubricant sensitivity when blended with magnesium stearate, producing tablets of an acceptable hardness even after prolonged mixing. Results from experiments also show that there is no difference in disintegration time, friability and dissolution rate[36 and 37].

Other factors that influence excipient selection

This overview has focused on the physicochemical properties required from excipients; the assumption being that excipients are 'inert' and unreactive entities. It is imperative that a comprehensive drug–excipient compatibility screening procedure is initiated before a dosage form development programme commences. Often drug–excipient compatibility testing will identify incompatibilities, such as lactoses and amines[25], but sometimes a positive interaction may be desired [38]. In addition, the nature of the interaction testing may itself yield false positives if the ratio of the drug to excipient is not appropriate; the reader is referred to a recent publication that elegantly describes the main issues involved in excipient compatibility and selection for solid dosage forms [39].

Summary

In conclusion, an overview of the main excipients used for direct compression has shown that alternatives to lactose and microcrystalline cellulose are available, and a summary of their properties has been presented. It is up to the formulator to test each potential excipient with each new chemical entity, bearing in mind the physicochemical properties of each component of the formulation.

Uncited reference (cited in box only)

[4]

Acknowledgements

The authors wish to thank Karrar Khan for his help with this review.

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OTHER ORIGINAL ARTICLES

Comparative evaluation of excipients for direct compression

III. The formulation of a low and a medium dosage range drug

G. K. Bolhuis, C. F. Lerk, J. R. Moes and C. W. A. Mulder

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Two drugs which are used in a low and a medium dosage range, respectively, have been formulated with directly compressible excipients and compressed into tablets.

Of the prepared blends, the flow and lubrication properties were investigated. The tablets, containing 5 mg prednisone and 50 mg phenobarbitone, respectively, were investigated for content uniformity, crushing strength, friability, disintegration time, dissolution rate of the drug and stability after storage for 8 weeks at 20±C and 50% or 85% relative humidity.

The results show that with a knowledge of properties and interactions of drugs, directly compressible excipients and other tablet vehicles, formulations can be composed from which tablets with good properties can be prepared.

See for Part I: *Pharm. Weekblad* (1973)108, 469 and for Part II: *Pharm. Weekblad* (1974)109, 945.

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OTHER ORIGINAL ARTICLES

Comparative evaluation of excipients for direct compression

III. The formulation of a low and a medium dosage range drug¹

G. K. BOLHUIS², C. F. LERE^{2,3}, J. R. MOES² AND G. W. A. MULDER²

ABSTRACT

Two drugs which are used in a low and a medium dosage range, respectively, have been formulated with directly compressible excipients and compressed into tablets.

Of the prepared blends, the flow and lubrication properties were investigated. The tablets, containing 5 mg prednisone and 30 mg phenobarbitone, respectively, were investigated for content uniformity, crushing strength, friability, disintegration time, dissolution rate of the drug and stability after storage for 8 weeks at 20°C and 50% or 85% relative humidity.

The results show that with a knowledge of properties and interactions of drugs, directly compressible excipients and other tablet vehicles, formulations can be composed from which tablets with good properties can be prepared. (Pharm. Weekblad Sci. Ed. 1, 203-213.)

1. INTRODUCTION

Although a number of useful reports have been published dealing with the properties of excipients for direct compression, the literature contains very few studies where a drug has been incorporated in the formulation. For this reason little attention has been paid to factors like distribution, dissolution and stability of the drug and the mutual effects of drug and excipients on tablet quality. Some investigators (MANUDHANE *et al.* 1969; KHAN and RHODES 1971; SEXSMITH 1977) have used 1% amaranth tracer to simulate dissolution from placebo tablets. Most of the ready-made formulations for direct compression have originated from the research laboratories of the manufacturers of directly compressible tablet excipients.

There are few studies in which one or more drugs have been tableted: by means of direct compression, using different excipients, which

was then followed by a comparative evaluation of the tablets made. FOX *et al.* (1963) compared the properties of amphetamine sulphate tablets with different proportions of microcrystalline cellulose (Avicel PH 101) and spray-dried lactose. Acceptable tablets were produced if at least 60-70% Avicel was present in the formulation. DUVALL *et al.* (1965) found few differences in the properties of phenobarbitone tablets, compressed with dextrose monohydrate (Celerose® hydrous) and spray-dried lactose, respectively. SCHWARTZ and BAVITZ (1976) incorporated low dosage range water soluble and water insoluble drugs in tablets, formulated with various excipient combinations. The authors concluded that the choice of excipients was more critical when insoluble drugs were incorporated.

The most extensive study in this field was from STANN and MATHIS (1974). In a comparative evaluation, propyromazine was formulated with several directly compressible tablet vehicles. The authors reported large differences in tablet properties, including dissolution rate. A rapid drug release was found from tablets, containing cellulose products, a slow release from tablets with mannitol, sorbitol or spray-dried maltose-dextrose (Eindex®). SEBERT *et al.* (1976) studied eight tablet formulations with 79% disulfiram. Tablets from seven formulations did not disintegrate within 30 minutes, whereas tablets from one formulation had a disintegration time less than one minute.

A disadvantage of the foregoing studies is

¹ See for Part I: Pharm. Weekblad (1973) 108, 469 and for Part II: Pharm. Weekblad (1974) 109, 945.

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³ Reprints.

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US006103219A

United States Patent [19]
Sherwood et al.

[11] **Patent Number:** **6,103,219**
[45] **Date of Patent:** **Aug. 15, 2000**

[54] **PHARMACEUTICAL EXCIPIENT HAVING IMPROVED COMPRESSIBILITY**
[75] **Inventors:** **Bob E. Sherwood**, Amenia, N.Y.; **John H. Staniforth**, Bath, United Kingdom; **Edward A. Hunter**, Glenham, N.Y.
[73] **Assignee:** **Edward Mendell Co., Inc.**, Patterson, N.Y.

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[21] **Appl. No.:** **08/992,073**
[22] **Filed:** **Dec. 17, 1997**

Related U.S. Application Data

[60] Continuation of application No. 08/724,613, Sep. 30, 1996, Pat. No. 5,725,884, which is a division of application No. 08/370,576, Jan. 9, 1995, Pat. No. 5,585,115.
[51] **Int. Cl.⁷** **A61K 7/16; A61K 9/26; A61K 9/32; A61K 9/16**
[52] **U.S. Cl.** **424/49; 424/464; 424/489; 424/494; 424/495; 424/496; 424/497; 106/154.51**
[58] **Field of Search** **424/489, 494, 424/468, 490, 487, 486, 78.1, 461, 49, 495-497, 464; 106/154.51**

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Assistant Examiner—W. Benston
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[57] **ABSTRACT**

A microcrystalline cellulose-based excipient having improved compressibility, whether utilized in direct compression, dry granulation or wet granulation formulations, is disclosed. The excipient is an agglomerate of microcrystalline cellulose particles and from about 0.1% to about 20% silicon dioxide particles, by weight of the microcrystalline cellulose, wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other. The silicon dioxide utilized in the novel excipient has a particle size from about 1 nanometer to about 100 microns. Most preferably, the silicon dioxide is a grade of colloidal silicon dioxide.

83 Claims, 5 Drawing Sheets

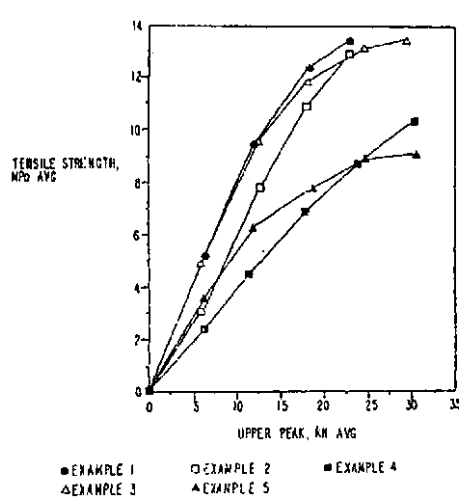


FIG. 1

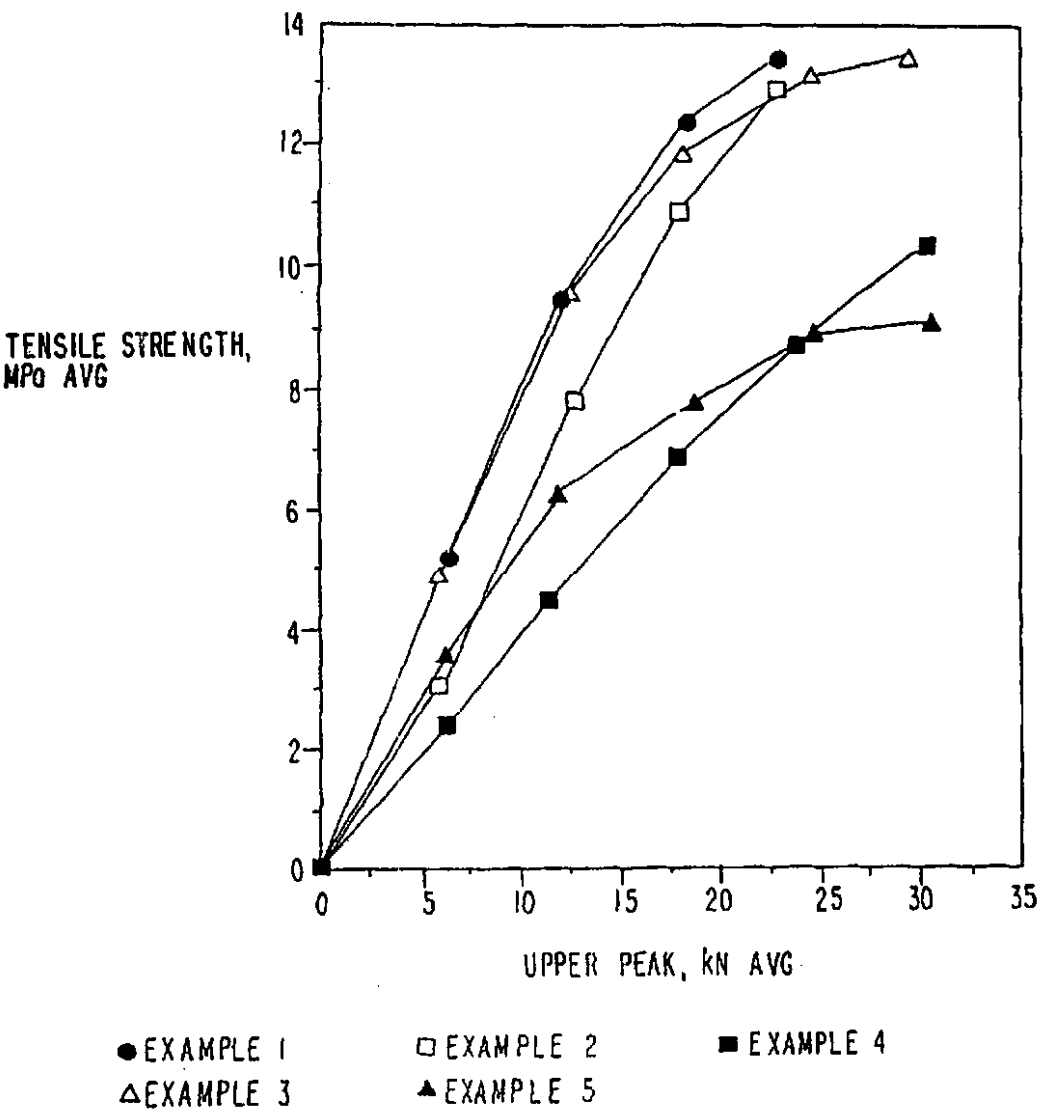


FIG. 2

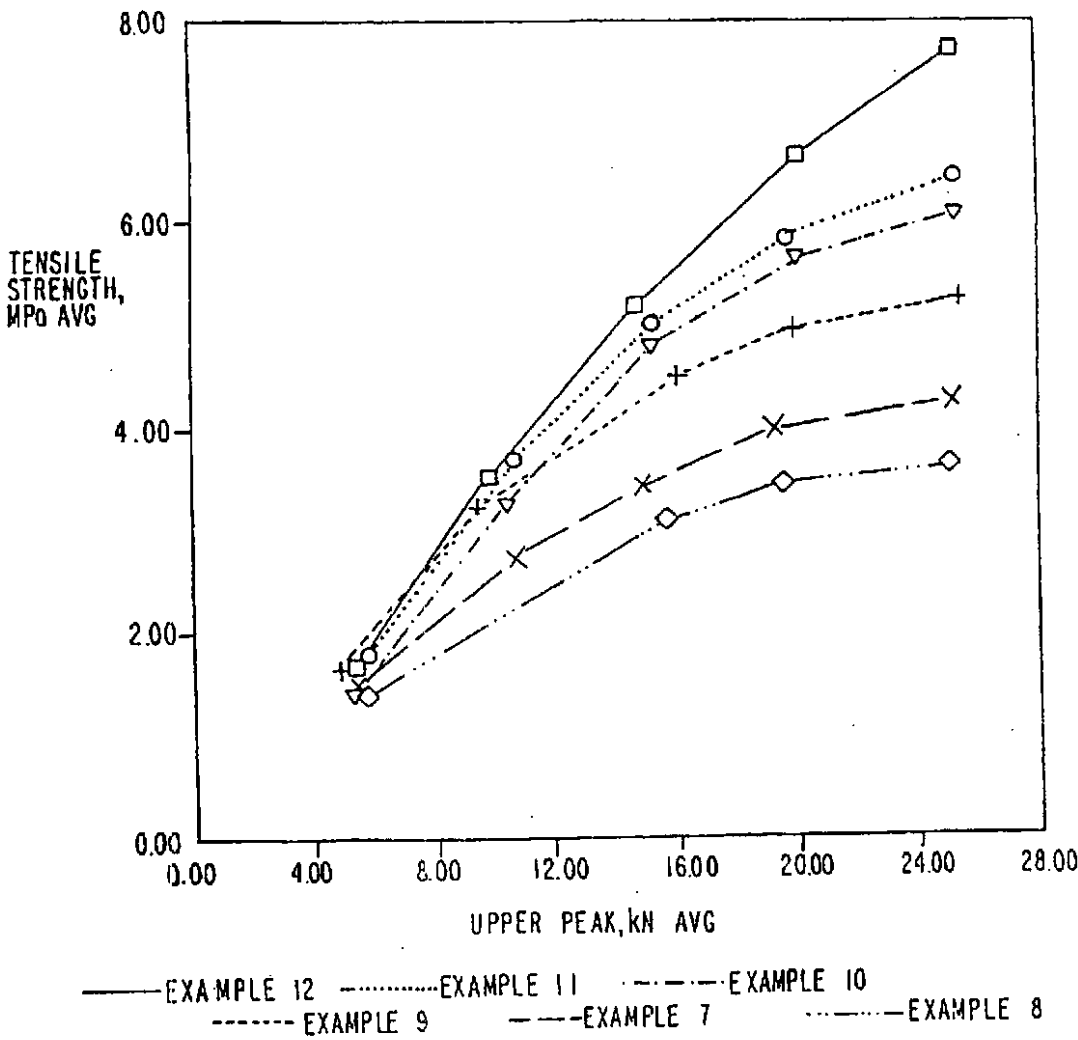
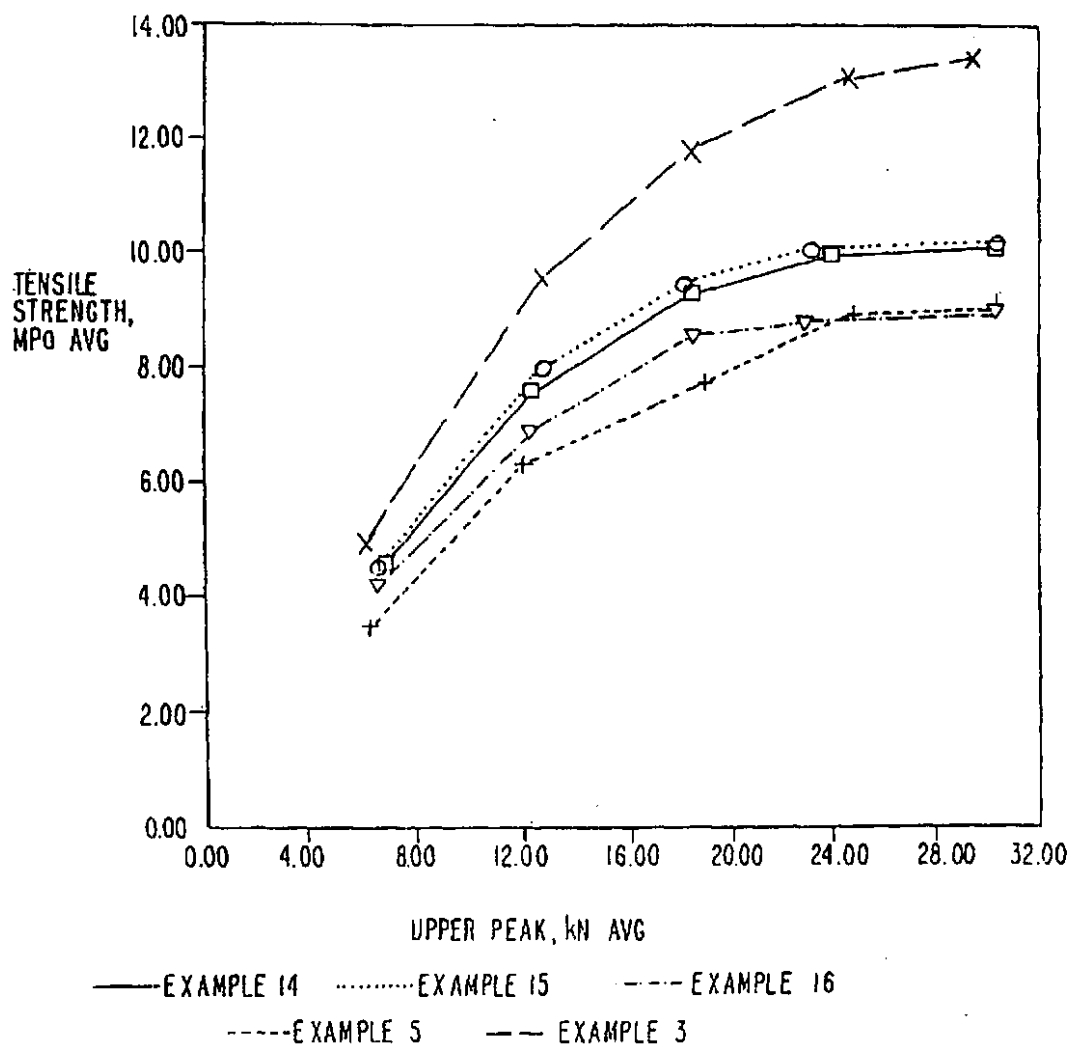
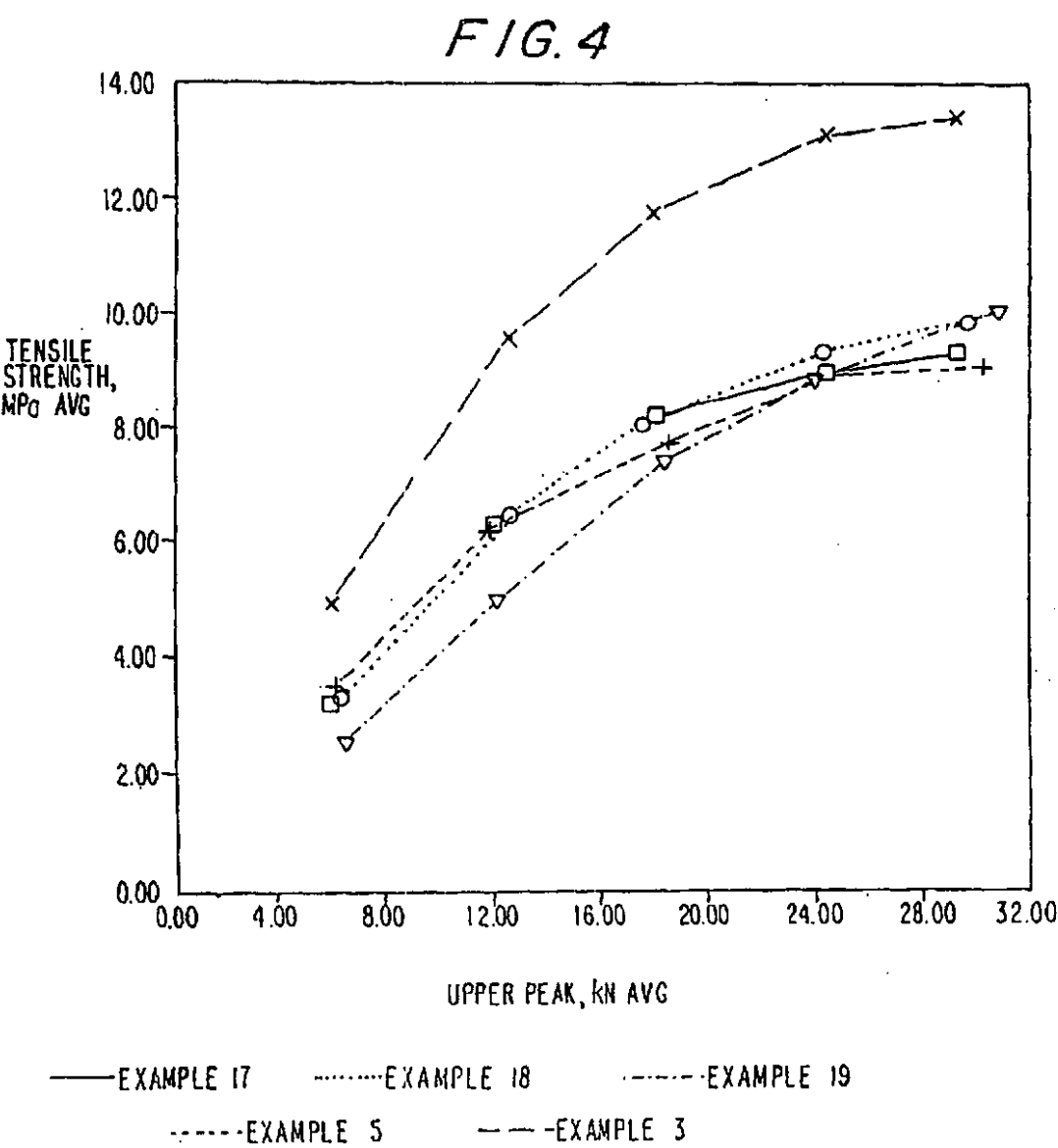
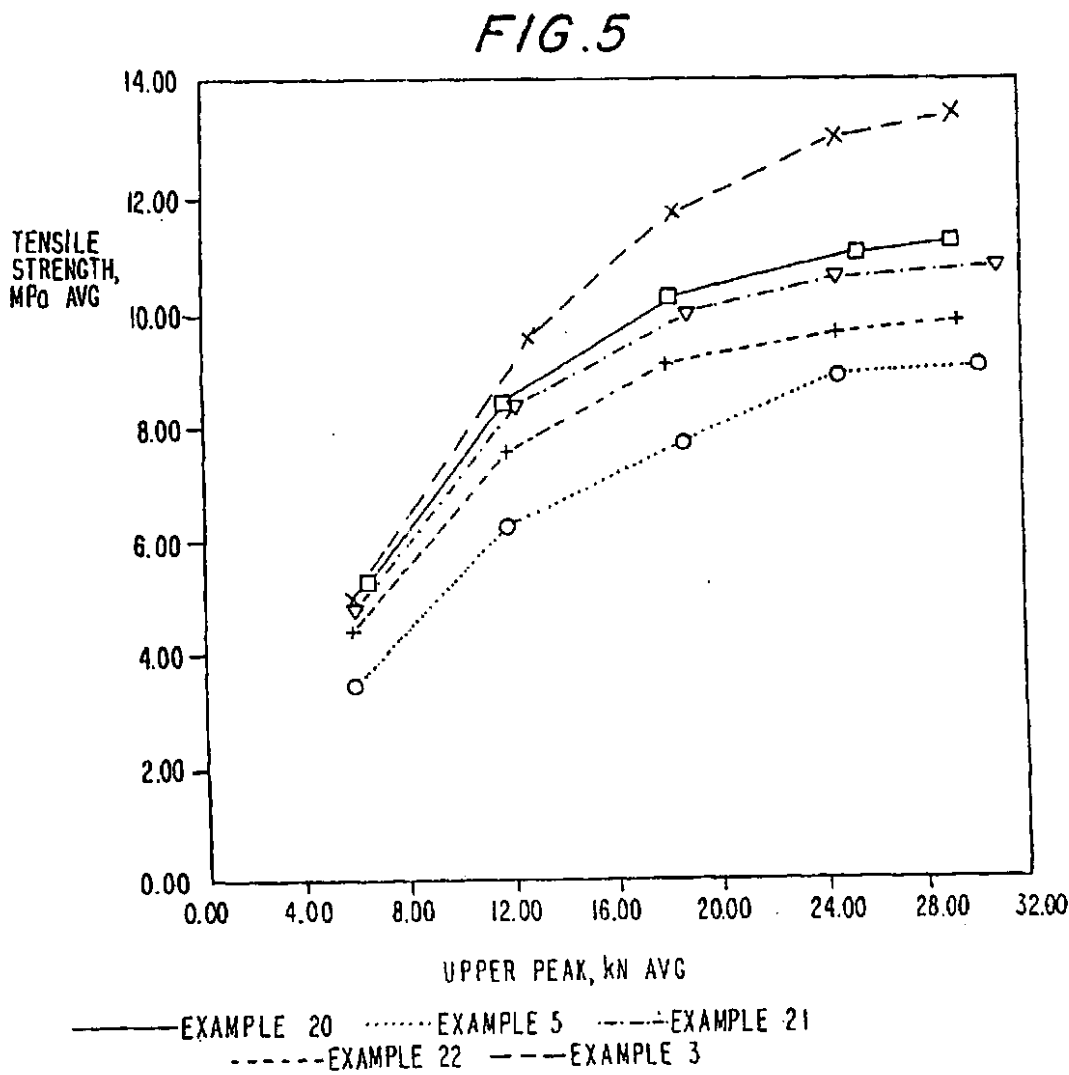


FIG. 3







**PHARMACEUTICAL EXCIPIENT HAVING
IMPROVED COMPRESSIBILITY**

This application is a continuation of application Ser. No. 08/724,613, filed on Sep. 30, 1996, now U.S. Pat. No. 5,725,884 which is a division of application Ser. No. 08/370,576, filed on Jan. 9, 1995, now U.S. Pat. No. 5,585,115.

BACKGROUND OF THE INVENTION

The present invention relates to a novel excipient for use in the manufacture of pharmaceuticals, and in particular, solid dosage forms such as tablets which include one or more active ingredients.

In order to prepare a solid dosage form containing one or more active ingredients (such as drugs); it is necessary that the material to be compressed into the dosage form possess certain physical characteristics which lend themselves to processing in such a manner. Among other things, the material to be compressed must be free-flowing, must be lubricated, and, importantly, must possess sufficient cohesiveness to insure that the solid dosage form remains intact after compression.

In the case of tablets, the tablet is formed by pressure being applied to the material to be tableted on a tablet press. A tablet press includes a lower punch which fits into a die from the bottom and a upper punch having a corresponding shape and dimension which enters the die cavity from the top after the tableting material fills the die cavity. The tablet is formed by pressure applied on the lower and upper punches. The ability of the material to flow freely into the die is important in order to insure that there is a uniform filling of the die and a continuous movement of the material from the source of the material, e.g. a feeder hopper. The lubricity of the material is crucial in the preparation of the solid dosage forms since the compressed material must be readily ejected from the punch faces.

Since most drugs have none or only some of these properties, methods of tablet formulation have been developed in order to impart these desirable characteristics to the material(s) which is to be compressed into a solid dosage form. Typically, the material to be compressed into a solid dosage form includes one or more excipients which impart the free-flowing, lubrication, and cohesive properties to the drug(s) which is being formulated into a dosage form.

Lubricants are typically added to avoid the material(s) being tableted from sticking to the punches, commonly used lubricants include magnesium stearate and calcium stearate. Such lubricants are commonly included in the final tableted product in amounts of less than 1% by weight.

In addition to lubricants, solid dosage forms often contain diluents. Diluents are frequently added in order to increase the bulk weight of the material to be tableted in order to make the tablet a practical size for compression. This is often necessary where the dose of the drug is relatively small.

Another commonly used class of excipients in solid dosage forms are binders. Binders are agents which impart cohesive qualities to the powdered material(s). Commonly used binders include starch, and sugars such as sucrose, glucose, dextrose, and lactose.

Disintegrants are often included in order to ensure that the ultimately prepared compressed solid dosage form has an acceptable disintegration rate in an environment of use (such as the gastrointestinal tract). Typical disintegrants include starch derivatives and salts of carboxymethylcellulose.

There are three general methods of preparation of the materials to be included in the solid dosage form prior to

compression: (1) dry granulation; (2) direct compression; and (3) wet granulation.

Dry granulation procedures may be utilized where one of the constituents, either the drug or the diluent, has sufficient cohesive properties to be tableted. The method includes mixing the ingredients, slugging the ingredients, dry screening, lubricating and finally compressing the ingredients.

In direct compression, the powdered material(s) to be included in the solid dosage form is compressed directly without modifying the physical nature of the material itself.

The wet granulation procedure includes mixing the powders to be incorporated into the dosage form in, e.g., a twin shell blender or double-cone blender and thereafter adding solutions of a binding agent to the mixed powders to obtain a granulation. Thereafter, the damp mass is screened, e.g., in a 6- or 8-mesh screen and then dried, e.g., via tray drying, the use of a fluid-bed dryer, spray-dryer, radio-frequency dryer, microwave, vacuum, or infra-red dryer.

The use of direct compression is limited to those situations where the drug or active ingredient has a requisite crystalline structure and physical characteristics required for formation of a pharmaceutically acceptable tablet. On the other hand, it is well known in the art to include one or more excipients which make the direct compression method applicable to drugs or active ingredients which do not possess the requisite physical properties. For solid dosage forms wherein the drug itself is to be administered in a relatively high dose (e.g., the drug itself comprises a substantial portion of the total tablet weight), it is necessary that the drug(s) itself have sufficient physical characteristics (e.g., cohesiveness) for the ingredients to be directly compressed.

Typically, however, excipients are added to the formulation which impart good flow and compression characteristics to the material as a whole which is to be compressed. Such properties are typically imparted to these excipients via a pre-processing step such as wet granulation, slugging, spray drying, spheronization, or crystallization. Useful direct compression excipients include processed forms of cellulose, sugars, and dicalcium phosphate dihydrate, among others.

A processed cellulose, microcrystalline cellulose, has been utilized extensively in the pharmaceutical industry as a direct compression vehicle for solid dosage forms. Microcrystalline cellulose is commercially available under the tradename EMCOCEL® from Edward Mendell Co., Inc. and as Avicel® from FMC Corp. Compared to other directly compressible excipients, microcrystalline cellulose is generally considered to exhibit superior compressibility and disintegration properties.

Another limitation of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active ingredient is high, a pharmaceutical formulator may choose to wet granulate the active with other excipients to attain an acceptably sized tablet with the desired compact strength. Usually the amount of filler/binder or excipients needed in wet granulation is less than that required for direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet. Thus, despite the advantages of direct compression (such as reduced processing times and costs), wet granulation is widely used in the industry in the preparation of solid dosage forms. Many of those skilled in the art prefer wet granulation as compared to direct compression because this method has a greater probability of overcoming any problems associated with the physical characteristics of the various ingredients in the formulation, thereby providing a

material which has the requisite flow and cohesive characteristics necessary to obtain an acceptable solid dosage form.

The popularity of the wet granulation process as compared to the direct compression process is based on at least three advantages. First, wet granulation provides the material to be compressed with better wetting properties, particularly in the case of hydrophobic drug substances. The addition of a hydrophilic excipient makes the surface of a hydrophobic drug more hydrophilic, easing disintegration and dissolution. Second, the content uniformity of the solid dosage forms is generally improved. Via the wet granulation method, all of the granules thereby obtained should contain approximately the same amount of drug. Thus, segregation of the different ingredients of the material to be compressed (due to different physical characteristics such as density) is avoided. Segregation is a potential problem with the direct compression method. Finally, the particle size and shape of the particles comprising the granulate to be compressed are optimized via the wet granulation process. This is due to the fact that when a dry solid is wet granulated, the binder "glues" particles together, so that they agglomerate in the granules which are more or less spherical.

Due to the popularity of microcrystalline cellulose, pharmaceutical formulators have deemed it desirable to include this excipient in a formulation which is wet granulated prior to tableting. Unfortunately, currently-available microcrystalline cellulose does not hold to the typical principle that the amount of filler/binder needed in wet granulation is less than that in direct compression. It is known that the exposure of the microcrystalline cellulose to moisture in the wet granulation process severely reduces the compressibility of this excipient. The loss of compressibility of microcrystalline cellulose is particularly problematic where the formulation dictates that the final product will be relatively large in the environment of use. For example, if a pharmaceutical formulator desires to prepare a solid oral dosage form of a high dose drug, and the use of the wet granulation technique is deemed necessary, the loss of compressibility of the microcrystalline cellulose dictates that a larger amount of this material may be needed to obtain an acceptably compressed final product. The additional amount of microcrystalline cellulose needed adds cost to the preparation, but more importantly adds bulk, making the product more difficult to swallow.

The loss of compressibility of microcrystalline cellulose when exposed to wet granulation has long been considered a problem in the art for which there has been no satisfactory solution.

Attempts have been made to provide an excipient having high compressibility, a small bulk (high apparent density), and good flowability, while being capable of providing satisfactory disintegration of the solid dosage form, which is applicable to wet granulation as well as to dry granulation and direct compression methods for preparation of solid dosage forms.

For example, U.S. Pat. No. 4,159,345 (Iakco, et al.) describes an excipient which consists essentially of a microcrystalline cellulose having an average degree of polymerization of 60 to 375 and obtained through acid hydrolysis or alkaline oxidative degradation of a cellulosic substance selected from linters, pulps and regenerated fibers. The microcrystalline cellulose is said to be a white cellulosic powder having an apparent specific volume of 1.6-3.1 cc/g, a repose angle of 35° to 42°, a 200-mesh sieve residue of 2 to 80% by weight and a tapping apparent specific volume of at least 1.4 cc/g.

In U.S. Pat. No. 4,744,987 (Mehra, et al.), a particulate co-processed microcrystalline cellulose and calcium carbonate composition is described wherein the respective components are present in a weight ratio of 75:25 to 35:65. The co-processed composition is said to be prepared by forming a well-dispersed aqueous slurry of microcrystalline cellulose and calcium carbonate and then drying the slurry to yield a particulate product. The combination of these two ingredients is said to provide a lower cost excipient which has tableting characteristics similar to those of microcrystalline cellulose and which would satisfy a need for an economical excipient with good performance that is desired by the vitamin market.

European Patent Application EP 0609976A1 (assigned to Asahi Kasei Kabushiki Kaisha) describes an excipient comprising white powdery microcrystalline cellulose having an average degree of polymerization of from 100 to 375, preferably from 190 to 210, and an acetic acid holding capacity of 280% or more, preferably from 290 to 370%. The excipient is said to exhibit high compactability and a high rate of disintegration and is said to be obtained by heat-treating an aqueous dispersion of purified cellulose particles, which has a solids content of 40% or less by weight, at 100° C. or more, followed by drying, or by subjecting an aqueous dispersion of purified cellulose particles having a solids content of 23% or less by weight to thin film-forming treatment and drying the resultant thin film. The excipient is said to possess a high compressibility, and a good balance of compactability and rate of disintegration.

There still remains a need in the industry for a pharmaceutical excipient which possesses excellent compressibility whether utilized in a direct compression or wet granulation procedure.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide an excipient which is useful in a variety of applications, and which may be utilized in direct compression or wet granulation methods.

It is a further object of the present invention to provide an excipient useful in direct compression methods which has improved compressibility relative to microcrystalline cellulose.

It is a further object of the present invention to provide an excipient useful in wet granulation methods which has improved compressibility relative to microcrystalline cellulose.

It is a further object of the present invention to provide a free-flowing excipient which has excellent compressibility properties when utilized in direct compression or wet granulation methods, and which furthermore possesses pharmaceutically acceptable disintegration properties.

It is a further object of the present invention to provide an improved microcrystalline cellulose excipient in which the microcrystalline cellulose has not been chemically altered, and which has improved compressibility relative to "off-the-shelf" commercially available microcrystalline cellulose.

It is a further object of the present invention to provide a solid dosage form which includes one or more active ingredients and the improved microcrystalline cellulose excipient of the present invention.

It is a further object of the present invention to provide an oral solid dosage form for one or more drugs which is

economical to manufacture, which maintains its integrity during storage, and which possesses excellent disintegration and dissolution properties when exposed, e.g., to gastrointestinal fluid.

In accordance with the above objects and others which will be obvious to those skilled in the art, the present invention is directed to an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, and the silicon dioxide portion of the agglomerate being derived from a silicon dioxide having a particle size from about 1 nanometer (nm) to about 100 microns (μm), based on average primary particle size.

In preferred embodiments, the silicon dioxide comprises from about 0.5% to about 10% of the excipient, and most preferably from about 1.25% to about 5% by weight relative to the microcrystalline cellulose.

In additional preferred embodiments of the invention, the silicon dioxide has a particle size from about 5 nm to about 40 μm , and most preferably from about 5 nm to about 50 μm .

In preferred embodiments of the present invention, the silicon dioxide is further characterized by a surface area from about 10 m^2/g to about 500 m^2/g , preferably from about 50 m^2/g to about 500 m^2/g , and more preferably from about 175 m^2/g to about 350 m^2/g .

The present invention is further directed to an aqueous slurry useful in the preparation of a compressible excipient useful in dry and wet granulation formulation methods, comprising a mixture of microcrystalline cellulose and from about 0.1% to about 20% silicon dioxide, by weight relative to the microcrystalline cellulose, the silicon dioxide having a particle size from about 1 nm to about 100 μm . The solids content of the aqueous slurry is from about 0.5% to about 25%, by weight, preferably from about 15% to about 20% by weight, and most preferably from about 17% to about 19% by weight.

The present invention is further directed to a mixture of an active ingredient(s) and an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, and the silicon dioxide having a particle size from about 1 nm to about 100 μm . The ratio of active ingredient to excipient is from about 1:99 to about 99:1, by weight.

The present invention is further directed to a granulate of an active ingredient(s) and the novel excipient described herein, wherein the active ingredient(s) and excipient have been subjected to a wet granulation procedure.

The present invention is further directed to a compressed solid dosage form comprising an active ingredient(s) and the novel excipient described herein, wherein the active ingredient(s) and excipient have been directly compressed into the solid dosage form or have been subjected to a wet granulation procedure and thereafter compressed into the solid dosage form. The compressed solid dosage form provides a suitable immediate release dissolution profile of the active ingredient(s) when exposed to aqueous solutions during invitro dissolution testing, and provides a release of drug in an environment of use which is considered bioavailable. In further embodiments of the invention, the dissolution profile of the solid dosage form is modified to provide a controlled or sustained release dissolution profile.

The present invention is further directed to a method of maintaining and/or enhancing the compressibility of microcrystalline cellulose. The method includes forming an aqueous slurry containing a mixture of microcrystalline cellulose and silicon dioxide having a particle size from about 1 nm to about 100 μm , and drying the slurry to obtain microcrystalline cellulose-based excipient particles in which the silicon dioxide particles have been integrated with the microcrystalline cellulose particles. Within this aspect of the invention, the slurry contains from about 0.5% to about 25% by weight microcrystalline cellulose, with amounts of from about 15% to about 20% being preferred. Furthermore, the slurry contains from about 0.25% to about 5% by weight silicon dioxide.

The novel excipient described herein is free-flowing, possesses excellent disintegration properties, and importantly, in certain embodiments possesses improved compressibility relative to normal "off-the-shelf" commercially available microcrystalline cellulose when directly compressed. The advantages of the novel excipient described herein are especially realized in pharmaceutical formulations prepared using wet granulation techniques. When utilized in wet granulation techniques, the novel excipient surprisingly provides a compressibility which is substantially improved in preferred embodiments in comparison to the compressibility of normal "off-the-shelf" commercially available microcrystalline cellulose used in wet granulation and is even comparable to "off-the-shelf" microcrystalline cellulose used in direct compression techniques. In other embodiments, the novel excipient surprisingly provides a compressibility which is substantially superior to the compressibility of normal "off-the-shelf" commercially available microcrystalline cellulose used in direct compression techniques.

The term "environmental fluid" is meant for purposes of the invention to encompass, e.g., an aqueous solution, or gastrointestinal fluid.

By "sustained release" it is meant for purposes of the invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 12 hour or a 24 hour dosage form.

By "bioavailable" it is meant for purposes of the invention that the therapeutically active medicament is absorbed from the sustained release formulation and becomes available in the body at the intended site of drug action.

By "primary particle size" it is meant for purposes of the invention that the particles are not agglomerated. Agglomeration is common with respect to silicon dioxide particles, resulting in a comparatively average large agglomerated particle size.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. 1 graphically shows a comparison of the tensile strength of tablets prepared in accordance with the invention and prior art tablets.

FIG. 2 graphically shows a comparison of the tensile strength of APAP containing tablets prepared in accordance with the invention and prior art APAP containing tablets.

FIG. 3 graphically shows a comparison of the tensile strength of tablets prepared in accordance with the invention

to contain MCC coprocessed with diatomaceous earth, tablets containing MCC coprocessed with 2% w/w SiO₂ and prior art tablets prepared to contain only unmodified MCC.

FIG. 4 graphically illustrates a comparison of the tensile strength of tablets prepared using MCC coprocessed with silica gel, tablets prepared with the novel coprocessed MCC and tablets prepared with MCC alone.

FIG. 5 graphically illustrates a comparison of the tensile strength of tablets prepared using MCC coprocessed with HS 5 grade SiO₂, tablets prepared using coprocessed MCC-SiO₂ and prior art tablets prepared to contain only unmodified MCC.

DETAILED DESCRIPTION OF THE INVENTION

Microcrystalline cellulose is a well-known tablet diluent and disintegrant. Its chief advantage over other excipients is that it can be directly compressed into self-binding tablets which disintegrate rapidly when placed into water. This widely-used ingredient is prepared by partially depolymerizing cellulose obtained as a pulp from fibrous plant material with dilute mineral acid solutions. Following hydrolysis, the hydrocellulose thereby obtained is purified via filtration and the aqueous slurry is spray dried to form dry, white odorless, tasteless crystalline powder of porous particles of a broad size distribution. Another method of preparing microcrystalline cellulose is disclosed in U.S. Pat. No. 3,141,875. This reference discloses subjecting cellulose to the hydrolytic action of hydrochloric acid at boiling temperatures so that amorphous cellulosic material can be removed and aggregates of crystalline cellulose are formed. The aggregates are collected by filtration, washed with water and aqueous ammonia and disintegrated into small fragments, often called cellulose crystallites by vigorous mechanical means such as a blender. Microcrystalline cellulose is commercially available in several grades which range in average particle size from 20 to 200 microns.

Microcrystalline cellulose is water-insoluble, but the material has the ability to draw fluid into a tablet by capillary action. The tablets then swell on contact and the microcrystalline cellulose thus acts as a disintegrating agent. The material has sufficient self-lubricating qualities so as to allow a lower level of lubricant as compared to other excipients.

Typically, microcrystalline cellulose has an apparent density of about 0.28 g/cm³ and a tap density of about 0.43 g/cm³. *Handbook of Pharmaceutical Excipients*, pages 53-55.

When utilized in pharmaceutical applications, microcrystalline cellulose is typically used as a tablet binder/diluent in wet granulation and direct compression formulations in amounts of 5-30% of the formulation, or more. However, it is known to use more or less microcrystalline cellulose in pharmaceutical products, depending upon the requirements of the formulation.

Silicon dioxide is obtained by insolubilizing dissolved silica in sodium silicate solution. When obtained by the addition of sodium silicate to a mineral acid, the product is termed silica gel. When obtained by the destabilization of a solution of sodium silicate in such a manner as to yield very fine particles, the product is termed precipitated silica. Silicon dioxide is insoluble in water. Prior to the present invention, silicon dioxide, and in particular colloidal silicon dioxide, was used mainly as a glidant and anti-adherent in tabletting processes and encapsulation, promoting the flowability of the granulation. The amount of silicon dioxide

included in such tablets for those applications is very limited, 0.1-0.5% by weight. *Handbook of Pharmaceutical Excipients*, ©1986 American Pharmaceutical Association, page 255. This is due in part to the fact that increasing the amount of silicon dioxide in the mixture to be tabletted causes the mixture to flow too well, causing a phenomena known to those skilled in the tabletting art as "flooding". If the mixture flows too well, a varying tablet weight with uneven content uniformity can result.

Those skilled in the art will appreciate that the name and/or method of preparation of the silicon dioxide utilized in the present invention is not determinative of the usefulness of the product. Rather, as previously mentioned, it has been surprisingly discovered that it is the physical characteristics of the silicon dioxide which are critical. In particular, it has been discovered that silicon dioxide having a relatively large particle size (and correspondingly small surface area), such as silica gel, is not useful in the preparation of the improved microcrystalline cellulose products of the invention. The appended claims are deemed to encompass all forms of silicon dioxide having an average primary particle size from about 1 nm to about 100 μ m, and/or a surface area from about 10 m²/g to about 500 m²/g.

The silicon dioxide utilized in the invention is of the very fine particle size variety. In the most preferred embodiments of the invention, the silicon dioxide utilized is a colloidal silicon dioxide. Colloidal silicon dioxide is a submicron fumed silica prepared by the vapor-phase hydrolysis (e.g., at 1110° C.) of a silicon compound, such as silicon tetrachloride. The product itself is a submicron, fluffy, light, loose, bluish-white, odorless and tasteless amorphous powder which is commercially available from a number of sources, including Cabot Corporation (under the tradename Cab-O-Sil); Degussa, Inc. (under the tradename Aerosil); E.I. DuPont & Co.; and W.R. Grace & Co. Colloidal silicon dioxide is also known as colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, and silicon dioxide fumed, among others. A variety of commercial grades of colloidal silicon dioxide are produced by varying the manufacturing process. These modifications do not affect the silica content, specific gravity, refractive index, color or amorphous form. However, these modifications are known to change the particle size, surface areas, and bulk densities of the colloidal silicon dioxide products.

The surface area of the preferred class of silicon dioxides utilized in the invention ranges from about 50 m²/gm to about 500 m²/gm. The average primary particle diameter of the preferred class of silicon dioxides utilized in the invention ranges from about 5 nm to about 50 nm. However, in commercial colloidal silicon dioxide products, these particles are agglomerated or aggregated to varying extents. The bulk density of the preferred class of silicon dioxides utilized in the invention ranges from about 20 g/l to about 100 g/l.

Commercially available colloidal silicon dioxide products have, for example, a BET surface area ranging from about 50±15 m²/gm (Aerosil OX50) to about 400±20 (Cab-O-Sil S-17) or 390±40 m²/gm (Cab-O-Sil EH-5). Commercially available particle sizes range from a nominal particle diameter of 7 nm, (e.g., Cab-O-Sil S-17 or Cab-O-Sil EH-5) to an average primary particle size of 40 nm (Aerosil OX50). The density of these products range from 72.0±8 g/l (Cab-O-Sil S-17) to 36.8 g/l (e.g., Cab-O-Sil M-5). The pH of these products at 4% aqueous dispersion ranges from pH 3.5-4.5. These commercially available products are described for exemplification purposes of acceptable properties of the preferred class of silicon dioxides only, and this description is not meant to limit the scope of the invention in any manner whatsoever.

When the novel excipient of the invention utilizes a colloidal silicon dioxide, it has been found that the resultant excipient product surprisingly provides a compressibility which is substantially improved in preferred embodiments even in comparison to the compressibility of normal "off-the-shelf" commercially available microcrystalline cellulose used in direct compression techniques.

In other embodiments of the present invention, it has been discovered that the compressibility of microcrystalline cellulose which is wet granulated is significantly improved by a wider range of silicon dioxide products. Thus, in embodiments of the present invention where an improvement in overall compressibility of the microcrystalline cellulose (whether utilized in wet granulation or dry granulation) is not important, and the microcrystalline cellulose product is to be subjected to wet granulation, it has been discovered that the surface area of the silicon dioxide can be as low as about 50 m²/gm and the average primary particle diameter can be as large as about 100 μ m. Such silicon dioxide products are also deemed to be encompassed within the scope of the invention.

Both microcrystalline cellulose and silicon dioxide are substantially water insoluble. Therefore, the particle size of these ingredients as present in the well-dispersed aqueous slurry is directly related to the particle size of these two ingredients as they were introduced into the aqueous solution. There is no appreciable dissolution of either ingredient in the aqueous slurry.

After a uniform mixture of the ingredients is obtained in the suspension, the suspension is dried to provide a plurality of microcrystalline cellulose-based excipient particles having enhanced compressibility.

In the spray-drying process, the aqueous dispersion of microcrystalline cellulose and silicon dioxide is brought together with a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The highly dispersed slurry of microcrystalline cellulose and silicon dioxide is pumpable and capable of being atomized. It is sprayed into a current of warm filtered air, which supplies the heat for evaporation and conveys a dried product to a collecting device. The air is then exhausted with the removed moisture. The resultant spray-dried powder particles are approximately spherical in shape and are relatively uniform in size, thereby possessing excellent flowability. The coprocessed product consists of microcrystalline cellulose and silicon dioxide in intimate association with each other. Magnifications of the resultant particles indicate that the silicon dioxide is integrated with, or partially coats, the surfaces of the microcrystalline cellulose particles. When the amount of silicon dioxide including in the excipient is greater than about 20% by weight relative to the microcrystalline cellulose, the silicon dioxide appears to substantially coat the surfaces of the microcrystalline cellulose particles. The exact relationship of the two ingredients of the excipients after coprocessing is not presently understood; however, for purposes of description the coprocessed particles are described herein as including an agglomerate of microcrystalline cellulose and silicon dioxide in intimate association with each other. By "intimate associate", it is meant that the silicon dioxide has in some manner been integrated with the microcrystalline cellulose particles, e.g., via a partial coating of the microcrystalline particles, as opposed to a chemical interaction of the two ingredients. The term "intimate association" is therefore deemed for purposes of the present description as being synonymous with "integrated" or "united". The coprocessed particles are not necessarily uniform or homogeneous. Rather, under

magnification, e.g., scanning electron microscope at 500 $\times$, the silicon dioxide at the preferred percent inclusion appears to be an "edgecoating".

It is most preferred in the present invention that the microcrystalline cellulose and silicon dioxide are coprocessed, resulting in an intimate association of these ingredients, rather than being combined, e.g., as a dry mixture. In preferred embodiments of the present invention, the aqueous slurry of the microcrystalline cellulose and silicon dioxide are introduced into the spray dryer as a single aqueous medium. However, it is possible to separately introduce each ingredient into separate aqueous medium which are then combined. Other procedures for combining the microcrystalline cellulose and silicon dioxide known to those skilled in the art are deemed to be equivalent to the spray-drying technique described above, and are further deemed to be encompassed by the appended claims.

In certain preferred embodiments of the present invention, the coprocessing of the microcrystalline cellulose and silicon dioxide is accomplished by forming a well-dispersed aqueous slurry of microcrystalline cellulose and silicon dioxide, and thereafter drying the slurry and forming a plurality of microcrystalline cellulose-based excipient particles. Typically, microcrystalline cellulose is first added to an aqueous solution so that a slurry or suspension containing from about 0.5% to about 25% microcrystalline cellulose in the form of solids is obtained. Preferably, the slurry or suspension contains from about 15% to 20% microcrystalline cellulose and most preferably from about 17% to about 19% microcrystalline cellulose. At this stage, it is often desirable to adjust the pH of the slurry to about neutral with ammonium hydroxide, sodium hydroxide, and mixtures thereof or the like. The suspension is kept under constant agitation for a sufficient time to assure a uniform distribution of the solids prior to being combined with the silicon dioxide.

At this point, the silicon dioxide is added to the suspension or slurry in amounts ranging from 0.1% to about 20% by weight, based on the amount of microcrystalline cellulose, amounts from about 0.5% to about 10% are preferred while amounts of from about 1.25% to about 5% by weight are especially preferred. The silicon dioxide is preferably in colloidal form prior to addition to the MCC slurry. The microcrystalline cellulose and colloidal silicon dioxide are well-dispersed in the slurry or suspension prior drying and forming the novel particles.

It is preferred that the suspension be dried using spray-drying techniques, as they are known in the art. Other drying techniques, however, such as flash drying, ring drying, micron drying, tray drying, vacuum drying, radio-frequency drying, and possibly microwave drying, can also be used. The exact manner in which the suspension is dried is not believed to be critical for the microcrystalline cellulose/silicon dioxide particles to demonstrate enhanced compressibility after wet granulating.

Depending upon the amount and type of drying, the concentration of the microcrystalline cellulose and silicon dioxide in the suspension, the novel compressible particles will have different particle sizes, densities, pH, moisture content, etc.

The particulate coprocessed product of the present invention possesses desirable performance attributes that are not present when the combination of microcrystalline cellulose and silicon dioxide are combined as a dry mixture. It is believed that the beneficial result obtained by the combination of these two materials is due to the fact that the two materials are intimately associated with each other.

The average particle size of the integrated excipient of the present invention ranges from about 10 microns to about 1000 microns. Particle sizes of about 10–500 microns are preferred, particle sizes of about 30–250 microns are more preferred and particle sizes of about 40–200 microns are most preferred. It will be appreciated by those of ordinary skill in the art that the drying of the microcrystalline cellulose-silicon dioxide suspension results in a random size distribution of the novel excipient excipient particles being produced. For example if spray drying techniques are used, droplet size, temperatures, agitation, dispersion, air flow, atomizer wheel speed, etc. will effect final particle size. Furthermore, it is within the scope of the invention to sort or mechanically alter the dried particles according to ranges of particle sizes depending upon end uses. The particle size of the integrated excipient is not narrowly critical, the important parameter being that the average size of the particle must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets.

The novel excipient has a bulk (loose) density ranging from about 0.2 g/ml to about 0.6 g/ml, and most preferably from about 0.35 g/ml to about 0.55 g/ml. The novel excipient has a tapped density ranging from about 0.2 g/ml to about 0.6 g/ml, and most preferably from about 0.35 g/ml to about 0.55 g/ml. The pH of the particles is most preferably about neutral, although granulates having a pH of from about 3.0 to about 8.5 are possible. The moisture content of the excipient particles will broadly range from about 0.5% to about 15%, preferably from about 2.5% to about 6%, and most preferably from about 3.0% to about 5% by weight.

The angle of repose is a measurement used to determine the flow characteristics of a powder. The angle of repose is subject to experiment and experimenter, but in a comparative test, the novel excipient is superior.

The novel excipient of the invention is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with an active agent and optional lubricant (dry granulation), and then directly compressed into solid dosage forms. In preferred embodiments of the present invention wherein the silicon dioxide is colloidal silicon dioxide, the novel excipient comprising the coprocessed microcrystalline cellulose and colloidal silicon dioxide integrated together represents an augmented microcrystalline cellulose having improved compressibility as compared to standard commercially available grades of microcrystalline cellulose.

Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient. A representative wet granulation includes loading the novel excipient particles into a suitable granulator, such as those available from Baker-Perkins, and granulating the particles together with the active ingredient, preferably using an aqueous granulating liquid. The granulating liquid is added to the mixture with stirring until the powdery mass has the consistency of damp snow and then wet screened through a desired mesh screen, for example, having a mesh from about 12 to about 16. The screened granulate is then dried, using standard drying apparatus such as a convection oven before undergoing a final screening. Additional dry screening of this material is possible, such as by using screens of from about 40 to about 200 mesh. Those materials flowing through 40 and 60 mesh screens may be further ground prior to ultimate tablet formulation. The thus obtained wet granulate containing novel excipient is now capable of undergoing tableting or otherwise placed into a unit dosage form.

In certain preferred embodiments, a portion of the total amount of the novel excipient is wet granulated with the

active ingredient, and thereafter the additional portion of the novel excipient is added to the granulate. In yet other embodiments, the additional portion of the novel excipient to be added to the excipient/active ingredient granulate may be substituted with conventional microcrystalline cellulose, or other excipients commonly used by those skilled in the art, depending of course upon the requirements of the particular formulation.

By virtue of the novel excipient of the present invention, the amount of the novel excipient compared to the amount of microcrystalline cellulose which must be used in a wet granulation technique to obtain an acceptable solid dosage form is substantially reduced.

In other embodiments of the invention, a further material is added to the slurry of microcrystalline cellulose and silicon dioxide. Such additional materials include non-silicon metal oxides, starches, starch derivatives, surfactants, polyalkylene oxides, cellulose ethers, celluloses esters and mixtures thereof. These additives may be included in desired amounts which will be apparent to those skilled in the art.

In addition to one or more active ingredients, additional pharmaceutically acceptable excipients (in the case of pharmaceuticals) or other additives known to those skilled in the art (for non-pharmaceutical applications) can be added to the novel excipient prior to preparation of the final product. For example, if desired, any generally accepted soluble or insoluble inert pharmaceutical filler (diluent) material can be included in the final product (e.g., a solid dosage form). Preferably, the inert pharmaceutical filler comprises a monosaccharide, a disaccharide, a polyhydric alcohol, inorganic phosphates, sulfates or carbonates, and/or mixtures thereof. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, xylitol, fructose, sorbitol, calcium phosphate, calcium sulfate, calcium carbonate, "off-the-shelf" microcrystalline cellulose, mixtures thereof, and the like.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may optionally be added to the novel excipient at the time the medicament is added, or in any event prior to compression into a solid dosage form. The lubricant may comprise, for example, magnesium stearate in any amount of about 0.5–3% by weight of the solid dosage form.

The complete mixture, in an amount sufficient to make a uniform batch of tablets, may then be subjected to tableting in a conventional production scale tableting machine at normal compression pressures for that machine, e.g., about 1500–10,000 lbs/sq in. The mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

The average tablet size for round tablets is preferably about 50 mg to 500 mg and for capsule-shaped tablets about 200 mg to 2000 mg. However, other formulations prepared in accordance with the present invention may be suitably shaped for other uses or locations, such as other body cavities, e.g., periodontal pockets, surgical wounds, vaginally. It is contemplated that for certain uses, e.g., antacid tablets, vaginal tablets and possibly implants, that the tablet will be larger.

In certain embodiments of the invention, the tablet is coated with a sufficient amount of a hydrophobic polymer to render the formulation capable of providing a release of the medicament such that a 12 or 24 hour formulation is obtained. The hydrophobic polymer which included in the tablet coating may be the same or different material as

compared to the hydrophobic polymeric material which is optionally granulated with the sustained release excipient. In other embodiments of the present invention, the tablet coating may comprise an enteric coating material in addition to or instead of the hydrophobic polymer coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100-555.

In further embodiments, the dosage form may be coated with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.).

The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60–70° C. for about 3–4 hours in a coating pan. The solvent for the hydrophobic polymer or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

The coatings which may be optionally applied to the compressed solid dosage form of the invention may comprise from about 0.5% to about 30% by weight of the final solid dosage form.

In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Pat. No. 4,839,177, hereby incorporated by reference.

In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the polymeric materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10 μ m if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic polymer or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1% to about 20%, and in certain embodiments preferably from about 5% to about 10%.

Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as

a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

The active agent(s) which may be incorporated with the novel excipient described herein into solid dosage forms invention include systemically active therapeutic agents, locally active therapeutic agents, disinfecting agents, chemical impregnants, cleansing agents, deodorants, fragrances, dyes, animal repellents, insect repellents, a fertilizing agents, pesticides, herbicides, fungicides, and plant growth stimulants, and the like.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g. pharmaceutical agents) which may be used in the compositions of the present invention include both water soluble and water insoluble drugs. Examples of such therapeutically active agents include anti-histamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardipine), anti-tussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g. clonidine, methyl dopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

A wide variety of locally active agents can be used in conjunction with the novel excipient described herein, and include both water soluble and water insoluble agents. The locally active agent(s) which may be included in the controlled release formulation of the present invention is intended to exert its effect in the environment of use, e.g., the oral cavity, although in some instances the active agent may also have systemic activity via absorption into the blood via the surrounding mucosa.

The locally active agent(s) include antifungal agents (e.g., amphotericin B, clotrimazole, nystatin, ketoconazole, miconazol, etc.), antibiotic agents (penicillins, cephalosporins, erythromycin, tetracycline, aminoglycosides, etc.), antiviral agents (e.g. acyclovir, idoxuridine, etc.), breath fresheners (e.g. chlorophyll), anti-tussive agents (e.g., dextromethorphan hydrochloride), anti-cariogenic compounds (e.g., metallic salts of fluoride, sodium monofluorophosphate, stannous fluoride, amine fluorides), analgesic agents (e.g., methylsalicylate, salicylic acid, etc.), local anesthetics (e.g., benzocaine), oral antiseptics (e.g., chlorhexidine and salts thereof, hexylresorcinol, decaaluminum chloride, cetylpyridinium chloride), anti-inflammatory agents (e.g., dexamethasone, betamethasone,

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prednisone, prednisolone, triamcinolone, hydrocortisone, etc.), hormonal agents (oestriol), antiplaque agents (e.g., chlorhexidine and salts thereof, octenidine, and mixtures of thymol, menthol, methysalicylate, eucalyptol), acidity reducing agents (e.g., buffering agents such as potassium phosphate dibasic, calcium carbonate, sodium bicarbonate, sodium and potassium hydroxide, etc.), and tooth desensitizers (e.g., potassium nitrate). This list is not meant to be exclusive. The solid formulations of the invention may also include other locally active agents, such as flavorants and sweeteners. Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing*, pub 1274 by the National Academy of Sciences, pages 63-258 may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857-884, hereby incorporated by reference), stabilizers, binders, odor controlling agents, and preservatives.

Alternatively, the novel excipient can be utilized in other applications wherein it is not compressed. For example, the granulate can be admixed with an active ingredient and the mixture then filled into capsules. The granulate can further be molded into shapes other than those typically associated with tablets. For example, the granulate together with active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

DETAILED DESCRIPTION OF THE
PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

The examples set forth the preparation of various microcrystalline cellulose/silicon dioxide compositions. Tablets were prepared using each of the compositions and each of tablet preparations was tested for tensile strength.

EXAMPLES 1-3

PREPARATION OF COPROCESSED MCC-SiO₂
COMPOSITIONS AND GRANULATIONS
THEREOF

Example 1

MCC-SiO₂ Product—5% w/w SiO₂

A. EXCIPIENT PARTICLES

In this example, about 6.2 kilograms of microcrystalline cellulose (MCC), (Mendell Co., Inc. Patterson, N.Y.) in the form of a wet cake was combined with 5.2 kilograms of water in a mix tank to form a slurry containing about 15% solids. The pH was adjusted to about neutral with about 3 ml of ammonium hydroxide. The slurry was allowed to mix for about 15 minutes before being combined with 5% w/w silicon dioxide (SiO₂), 200 m²/g (CaboSil, PTG grade, available from Cabot Corpo., Tuscola, Ill.) After allowing the materials to become intimately combined, the slurry was spray dried using a Niro Production Minor (Nira, Columbia, Md.), inlet temperature-215° C., outlet temperature-125° C., atomizer wheel speed 22,300 rpm, to provide MCC-SiO₂ having an average particle size of 40-60 microns.

B. GRANULATION OF EXCIPIENT PARTICLES

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The MCC-SiO₂ particles obtained as a result of step 1 A. were wet granulated in a Baker-Perkins 10 liter high-shear granulator for 3 minutes using water as the granulating fluid. The resultant product was wet screened through a 12 mesh screen, tray dried in a convection oven for about 2-3 hours until a moisture content of less than 5% was obtained, dry screened and sieved to obtain an average particle size of from about 55 to about 70 microns.

Example 2

MCC-SiO₂ Product—20% w/w SiO₂

The processes of Example 1A and B were repeated except that 20% w/w silicon dioxide was used to form the product.

Example 3

MCC-SiO₂ Product—2% w/w SiO₂

In this example, the processes of Example 1A and B were repeated except that 2% w/w silicon dioxide was used to form the product.

Example 4

Dry Blend Mix of MCC and SiO₂ (5% w/w)—
Comparative

As a control, EMCOCEL® grade 50 M microcrystalline cellulose (Mendell Co., Inc.) and 5% w/w silicon dioxide, 200 m²/g (CaboSil, PTG grade) were dry blended. No spray drying or other treatment of the mixture was undertaken. The method of Example 1B, however, was repeated.

Example 5

Processed MCC without SiO₂

As a second control, the process described in Example 1B was repeated except that no SiO₂ was added.

Example 6

In this example, batches of compressed tablets were prepared using each of the products obtained as a result of Examples 1-5. The tablets were prepared using a Korsch tablet press having a punch size of 3/8" and an aim weight of about 245 mg. The granulations were included in five separate tableting runs using compression forces of 6, 12, 18, 24 and 30 kN respectively. Ten tablets from each run were weighed, measured for diameter and tested for thickness and hardness on the Erweka TBH 30 tablet hardness tester to determine the compressibility of the microcrystalline cellulose as measured by tensile strength. The results of the analysis are graphically illustrated in FIG. 1 as a comparison of tensile strength versus compression force.

As can be seen from the graph, substantial benefits are obtained by coprocessing MCC with SiO₂. The tablets prepared using the products of comparative examples 4 and 5 demonstrated poor tensile strength. The novel excipient is superior and demonstrates approximately the same relative improvement across the entire range of compression forces. Furthermore, the graph also illustrates that tablets prepared with a mere dry admixture of MCC and SiO₂ (example 4 formulation) failed to demonstrate acceptable tensile strengths. Thus, the coprocessed MCC-SiO₂ described herein provides significant retention of MCC compressibility.

EXAMPLES 7-12

In these examples, compressed tablet products containing 70% by weight MCC and 30% acetaminophen (APAP

herein) were prepared. The products of examples 7-9 were controls and prepared without the coprocessed MCC-SiO₂ of the present invention. The products of examples 10-12, on the other hand, included 70% by weight of the novel coprocessed MCC-SiO₂ and 30% APAP. Details concerning the preparation of each granulation product is set forth below. A graphical comparison of the tensile strength versus compression force for each tableted product is provided in FIG. 2.

Example 7

Intragranulation and Extragranulation of APAP with MCC

In this example, tablets were prepared using off-the-shelf MCC (EMCOCEL® 50 M) according to the following formula:

INGREDIENTS	WEIGHT (GRAMS)
MCC	267.9
APAP	114.3
Deionized water	165.8

One half of the MCC was added to a Baker-Perkins 10 liter blender and combined with all of the APAP. The blender impeller was adjusted to 200 rpm and the chopper was set at 1000 rpm. After one minute, the water was added over 90 seconds using a rinse bottle. Thereafter, mixing was continued for an additional 90 seconds. The granulation was removed from the blender, wet screened through a 12 screen mesh and dried in a convection oven for 2-3 hours at 60° C. until a moisture content of less than 5% was obtained. The granulation was then dry screened through a 16 mesh screen before being blended for 10 minutes with the remaining portion of the MCC in a 2 quart V-blender. The granulation was removed from the blender and tableted in accordance with the method described below.

Tablet Strength Testing

In order to prepare tablets for the formulations of examples 7, 8, 10 and 11, the following procedure was used: the wet granulation products were weighed and mixed in a 2 quart V-blender for 5 minutes with 0.2% Pruv™ (sodiumstearyl fumarate, available from Mendell Co., Inc.).

Five separate tableting runs were undertaken with compression forces of 5, 10, 15, 20 and 25 kN respectively using a Korsch tablet press having a punch size of 3/8" and an aim weight of about 245 mg. Ten tablets from each compression force were selected and used in the experiment set forth in Example 13.

Example 8

Wet Granulation of APAP with MCC

In this example, only wet granulation or the intragranulation step as described above was undertaken. The formulation was prepared according to the following formula using off-the-shelf EMCOCEL® 50 M MCC:

INGREDIENTS	WEIGHT (GRAMS)
MCC	178.6
APAP	76.5
Deionized water	170.1

The MCC was added to a Baker-Perkins 10 liter blender and combined with the APAP. The blender impeller was adjusted to 200 rpm and the chopper was set at 1000 rpm. After one minute, the water was added over 90 seconds using a rinse bottle. Thereafter, mixing was continued for an additional 90 seconds. The granulation was removed from the blender, wet screened through a 12 screen mesh and then dried in a convection oven at 60° C. for 2-3 hours, until a moisture content of less than 5% was achieved. The granulation was then dry screened through a 16 mesh screen and tableted in accordance with the method described in example 7.

Example 9

Direct Compression Formulation of APAP with MCC

A direct compression formulation for tablets was prepared to contain 70% off-the-shelf EMCOCEL® 50 M MCC and 30% APAP by weight. The tablets were prepared according to the following formula:

INGREDIENTS	WEIGHT (GRAMS)
MCC	175.0
APAP	74.5
PRUV	0.5

The MCC and APAP were combined in a V-blender and mixed for 15 minutes. Thereafter, the Pruv was added and mixing was continued for another 5 minutes. The granulation was removed and five separate tableting runs were undertaken using compression forces of 5, 10, 15, 20 and 25 kN respectively on a Korsch tablet press. The tablet press had a punch size of 3/8" and an aim weight of about 245 mg. Ten tablets from each compression force were used in the experiment set forth in Example 13.

Example 10

Wet Granulation of APAP with Coprocessed MCC-SiO₂ (5% w/w)

In this example, tablets were prepared by wet granulation with the coprocessed MCC (5% w/w SiO₂) of Example 1A. The tablet granulation was prepared according to the following formula:

INGREDIENTS	WEIGHT (GRAMS)
MCC-SiO ₂	178.6
APAP	76.5
Deionized water	170.1

The MCC-SiO₂ was added to a Baker-Perkins 10 liter blender and combined with the APAP. The blender impeller

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was adjusted to 200 rpm and the chopper was set at 1000 rpm. After one minute, the water was added over 90 seconds using a rinse bottle. Thereafter, mixing was continued for an additional 90 seconds. The granulation was removed from the blender, wet screened through a 12 screen mesh and then dried in a convection oven for 2-3 hours at 60° C. until a moisture content of less than 5% was achieved. The granulation was then dry screened through a 16 mesh screen and tabletted according to the method set forth in Example 7.

Example 11

Intra- and Extragranulation of APAP with MCC-SiO₂ (5% w/w)

A granulation for compressed tablets was prepared according to the following formula:

INGREDIENTS	WEIGHT (GRAMS)
MCC-SiO ₂	267.9
APAP	114.8
Deionized water	165.8

One half of the coprocessed MCC-SiO₂ (prepared as in Example 1A) was added to a Baker-Perkins 10 liter blender and combined with all of the APAP. The blender impeller was adjusted to 200 rpm and the chopper was set at 1000 rpm. After one minute, the water was added over 90 seconds using a rinse bottle. Thereafter, mixing was continued for an additional 90 seconds. The granulation was removed from the blender, wet screened through a 12 screen mesh and then dried in a convection oven for 2-3 hours at 60° C. until a moisture content is less than 5% was achieved. The granulation was then dry screened through a 16 mesh screen before being blended for 10 minutes with the remaining portion of the coprocessed MCC-SiO₂ in a 2 quart V-blender, removed from the blender, and tabletted according to the method of Example 7.

Example 12

Direct Compression Formulation of APAP with MCC-SiO₂ (5% w/w)

A direct compression formulation similar to that set forth in example 9 was undertaken except that the tablets were prepared to contain the coprocessed MCC-SiO₂ of Example 1A. The tablet granulation was prepared according to the following formula:

INGREDIENTS	WEIGHT (GRAMS)
MCC-SiO ₂	175.0
APAP	74.5
PRUV	0.5

As was the case in example 9, five separate tableting runs were undertaken using compression forces of 5, 10, 15, 20 and 25 kN respectively on a Korsch tablet press, (punch size: 3/8" and aim weight—about 245 mg). Ten tablets from each compression force were used to carry out the experiment set forth in Example 13.

Example 13

Tablet Strength Testing

Ten tablets from each compression force run for each formulation prepared in Examples 7-12 were weighed,

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measured for diameter and tested for thickness and hardness on the Erweka TBH 30 tablet hardness tester to determine the compressibility of the microcrystalline cellulose. The results are graphically illustrated in FIG. 2 as a comparison of tensile strength versus compression force.

Referring now to FIG. 2, it can be seen that compressed tablets made with the inventive coprocessed MCC-SiO₂ have relatively high tensile strengths when compared to those made with off-the-shelf MCC. The advantages of the coprocessed MCC-SiO₂ are clearly seen in both direct compression and wet granulation formulations and especially in wet granulation products.

EXAMPLES 14-16

Diatomaceous Earth

In these examples, the coprocessing method described in Example 1A was repeated except that diatomaceous earth of about 40 micron particle size (J. T. Baker, Phillipsburg, N.J. was used as the source of SiO₂).

Example	Diatomaceous Earth (wt %)
14	2.0
15	1.0
16	0.5

The resultant granulates prepared according to Example 1B were tabletted according to the same method described in Example 6 and evaluated for tensile strength. The products of inventive Example 3 (MCC-SiO₂ 2% w/w) and Example 5 (MCC alone) were included in FIG. 3 for comparison purposes.

Referring now to FIG. 3, it can be seen that although the retention of compressibility afforded by coprocessing diatomaceous earth is not as great as that provided by colloidal SiO₂ having surface areas of about 200 m²/g, the coprocessed MCC-diatomaceous earth nonetheless demonstrates improved compressibility in wet granulation formulations.

EXAMPLES 17-19

Silica Gel

In these examples, the coprocessing method described in Example 1A was repeated using silica gel 200 micron particle size (VWR Corp., Piscataway, N.J. as the source of SiO₂).

Example	Silica Gel (wt %)
17	1
18	2
19	5

The resultant granulates prepared according to Example 1B were tabletted according to the same method described in Example 6 and evaluated for tensile strength. The products of inventive Example 3 (MCC-SiO₂ 2% w/w) and Example 5 (MCC alone) were included in FIG. 4 for comparison purposes.

Referring now to FIG. 4, it can be seen that the retention of compressibility afforded by coprocessing with silica gel is

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well below that provided by colloidal SiO₂ having surface areas of about 200 m²/g. In fact, MCC coprocessed with silica gel demonstrates compressibility properties about the same as off-the-shelf MCC in wet granulation formulations.

EXAMPLES 20-22

HS-5 Grade Silicon Dioxide

In these examples, the coprocessing method described in example 1 was repeated using HS-5 grade SiO₂ surface area 325 m²/g (Cabot Corp., Tuscola, Ill.).

Example	Silica Gel (wt %)
20	2
21	1
22	0.5

The resultant granulates prepared according to Example 1B were tableted according to the same method described in Example 6 and evaluated for tensile strength. The products of inventive Example 3 (MCC-SiO₂ 2% w/w) and Example 5 (off-the-shelf MCC) were included in FIG. 5 for comparison purposes.

Referring now to FIG. 5, the retention of compressibility afforded by coprocessing with HS-5 is comparable to that obtained using SiO₂ having surface areas of about 200 m²/g.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention. It is intended to claim all such changes and modifications that fall within the true scope of the invention.

What is claimed is:

1. An aqueous slurry useful in the preparation of a compressible pharmaceutical excipient, comprising a mixture of microcrystalline cellulose in the form of a wet cake and from about 0.1 % to about 20% by weight silicon dioxide based on the weight of said microcrystalline cellulose, said silicon dioxide having an average primary particle size from about 1 nm to about 100 μm, the solids content of said aqueous slurry being from about 0.5% to about 25% by weight, said silicon dioxide being present in an amount from about 0.5% to about 10%, by weight, based on the weight of said microcrystalline cellulose.

2. The slurry of claim 1, wherein said silicon dioxide is present in an amount from about 1.25% to about 5%, by weight, based on the weight of said microcrystalline cellulose.

3. The slurry of claim 1, which has a solid content from about 15% to about 20%.

4. The slurry of claim 3, which has a solid content from about 17% to about 19%.

5. The Slurry of claim 1, which has been pH-adjusted with a member of the group consisting of ammonium hydroxide, sodium hydroxide and mixtures thereof.

6. The slurry of claim 1, further comprising a member of the group consisting of non-silicon metal oxides, starches, starch derivatives, surfactants, polyalkylene oxides, celluloses, cellulose ethers, cellulose esters and mixtures thereof.

7. A method of enhancing the compressibility of microcrystalline cellulose in wet granulation products, comprising:

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(i) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having an average primary particle size from about 1 nm to about 100 μm, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight, wherein said slurry comprises from about 0.5% to about 25% by weight microcrystalline cellulose; and

(ii) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide.

8. The method of claim 7, wherein said slurry contains from about 15% to about 20% microcrystalline cellulose.

9. The method of claim 7, wherein said slurry contains from about 17% to about 19% microcrystalline cellulose.

10. The method of claim 7, wherein said silicon dioxide is colloidal silicon dioxide.

11. The method of claim 7, further comprising drying said slurry of microcrystalline cellulose and silicon dioxide by a method selected from the group consisting of flash drying, ring drying, spray drying, and micron drying.

12. The method of claim 7, further comprising drying said slurry of microcrystalline cellulose and silicon dioxide by spray drying.

13. The method of claim 7, further comprising drying said slurry such that the resultant excipient particles have an average particle size from about 10 μm to about 1,000 μm.

14. The method of claim 7, further comprising drying said slurry such that the resultant excipient particles have a particle size of from about 10 μm to about 500 μm.

15. The method of claim 12, further comprising drying said slurry such that the resultant excipient particles have a particle size of from about 30 μm to about 250 μm.

16. The method of claim 7, further comprising drying said slurry such that the resultant excipient particles have a moisture content of from about 0.5 to about 15%.

17. The method of claim 7, wherein said slurry further comprises a member of the group consisting of non-silicon metal oxides, starches, starch derivatives, surfactants, polyalkylene oxides, cellulose, celluloses, celluloses ethers, and mixtures thereof.

18. The microcrystalline cellulose-based excipient particles prepared by the process of claim 7.

19. The microcrystalline cellulose-based excipient particles prepared by the process of claim 15.

20. A method of preparing a solid dosage form, comprising:

(a) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μm, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight;

(b) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide;

(c) mixing an active ingredient with said excipient in a ratio from about 1:99 to about 99:1;

(d) incorporating said mixture obtained in step (c) into a plurality of solid unit doses.

21. The method of claim 20, wherein said silicon dioxide is colloidal silicon dioxide, further comprising wet granulating said mixture obtained in step (c) prior to incorporating said mixture into said solid unit doses.

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22. The method of claim 22, wherein said aqueous slurry prepared in step (a) comprises from about 0.5% to about 25% by weight microcrystalline cellulose.

23. The method of claim 20, wherein said drying of step (b) is accomplished by spray drying such that the resultant excipient particles have an average particle size from about 10 μm to about 1,000 μm .

24. The method of claim 20, wherein said drying of step (b) is accomplished by spray drying such that the resultant excipient particles have an average particle size from about 30 μm to about 250 μm .

25. The method of claim 20, wherein the resultant excipient particles have a bulk density from about 0.2 g/ml to about 0.6 g/ml.

26. The method of claim 21, wherein the resultant excipient particles have a bulk density of from about 0.35 g/ml to about 0.55 g/ml.

27. The method of claim 21, further comprising wet granulating the mixture of step (c), adding a further amount of excipient obtained in step (b) to said granulation, and thereafter incorporating the mixture into a solid dosage form.

28. The method of claim 21, further comprising wet granulating the mixture of step (b) prior to mixing said excipient with said active ingredient in step (c).

29. The method of claim 28, further comprising adding a further amount of excipient obtained in step (b) to the mixture of said granulation and said active ingredient, and thereafter compressing the mixture into a solid dosage form.

30. The method of claim 21, further comprising wet granulating the mixture of step (c), adding a further amount of a pharmaceutically acceptable excipient to said granulation, and thereafter compressing the mixture into a solid dosage form.

31. The method of claim 28, further comprising adding a further amount of pharmaceutically acceptable excipient to the mixture of said granulation and said active ingredient, and thereafter compressing the mixture into a solid dosage form.

32. A solid dosage form of a compressed mixture of from about 1% to about 99% of an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% by weight silicon dioxide, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, said silicon dioxide portion of said agglomerate being derived from a silicon dioxide having an average primary particle size from about 1 nm to about 100 μm , and from about 99% to about 1% of a systemically active therapeutic agent.

33. The solid dosage form of claim 32, wherein the active agent is an antihistamine.

34. The solid dosage form of claim 33, wherein the antihistamine is selected from the group consisting of dimenhydrinate, dimenhydramine, chlorpheniramine, and dexchlorpheniramine.

35. The solid dosage form of claim 32, wherein the active agent is an analgesic.

36. The solid dosage form of claim 32, wherein the analgesic is selected from the group consisting of aspirin, codene, morphine, dihydromorphine, and oxycodone.

37. The solid dosage form of claim 32, wherein the active agent is a non-steroidal anti-inflammatory agent.

38. The solid dosage form of claim 37, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of naproxyn, diclofenac, indomethacin, ibuprofen, and sulindac.

39. The solid dosage form of claim 32, wherein the active agent is an anti-emetic.

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40. The solid dosage form of claim 39, wherein the anti-emetic is metoclopramide.

41. The solid dosage form of claim 32, wherein the active agent is an anti-epileptic.

42. The solid dosage form of claim 41, wherein the anti-epileptic is selected from the group consisting of phenytoin, meprobamate and nitrazepam.

43. The solid dosage form of claim 32, wherein the active agent is a vasodilator.

44. The solid dosage form of claim 43, wherein the vasodilator is selected from the group consisting of nifedipine, papaverine, diltiazem and nicardipine.

45. The solid dosage form of claim 32, wherein the active agent is an anti-tussive agent.

46. The solid dosage form of claim 32, wherein the active agent is an expectorant.

47. The solid dosage form of claim 32, wherein the active agent is an anti-asthmatic.

48. The solid dosage form of claim 32, wherein the active agent is an antacid.

49. The solid dosage form of claim 32, wherein the active agent is an anti-spasmodic.

50. The solid dosage form of claim 32, wherein the active agent is an antidiabetic.

51. The solid dosage form of claim 32, wherein the active agent is a diuretic.

52. The solid dosage form of claim 32, wherein the active agent is an antihypotensive.

53. The solid dosage form of claim 32, wherein the active agent is an antihypertensive.

54. The solid dosage form of claim 32, wherein the active agent is a bronchodilator.

55. The solid dosage form of claim 32, wherein the active agent is a steroid.

56. The solid dosage form of claim 55, wherein the steroid is selected from the group consisting of hydrocortisone, triamcinolone, and prednisone.

57. The solid dosage form of claim 32, wherein the active agent is an antibiotic.

58. The solid dosage form of claim 32, wherein the active agent is selected from the group consisting of antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, and stimulants.

59. The solid dosage form of claim 32, prepared by a process comprising the steps of

(a) forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μm , the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight;

(b) drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide;

(c) mixing the active agent with said excipient in a ratio from about 1:99 to about 99:1;

(d) incorporating said mixture obtained in step (c) into a plurality of solid dosage forms.

60. The solid dosage form of claim 32, wherein the solid dosage form provides a sustained-release of the systemically active therapeutic agent.

61. The solid dosage form of claim 32, the solid dosage form provides a sustained-release of the systemically active therapeutic agent over a period of at least 12 hours.

62. The solid dosage form of claim 32, wherein the solid dosage form provides an immediate release of the systemically active therapeutic agent.

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63. The solid dosage form of claim 32, further comprising a coating of a hydrophobic polymer.
64. The solid dosage form of claim 63, wherein the solid dosage form includes a sufficient amount of the hydrophobic polymer coating to provide a sustained release of the active agent over a predetermined period.
65. The solid dosage form of claim 63, wherein the coating further includes an enteric coating material.
66. The solid dosage form of claim 32, further comprising a coating of an enteric coating material.
67. The solid dosage form of claim 66, wherein the enteric coating material is selected from a group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures thereof.
68. The solid dosage form of claim 63, wherein the coating further includes a hydrophilic material.
69. The solid dosage form of claim 32, further comprising a coating of a hydrophilic material.
70. The solid dosage form of claim 66, wherein the solid dosage form includes a sufficient amount of the coating to provide a sustained release of the active agent over a predetermined period.
71. The solid dosage form of claim 64, wherein the predetermined period is 12 hours.
72. The solid dosage form of claim 64, wherein the predetermined period is 24 hours.
73. The solid dosage form of claim 69, wherein the hydrophilic material is hydroxypropylmethylcellulose.
74. The solid dosage form of claims 32, further comprising a coating of an additional amount of the active agent.
75. The solid dosage form of claim 63, wherein the coating further includes an additional amount of the active agent.

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76. The solid dosage form of claim 32, further comprising at least a partial coating of a support platform.
77. A solid dosage form of a compressed mixture of from about 1% to about 99% of an excipient comprising a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% by weight silicon dioxide, the microcrystalline cellulose and silicon dioxide being in intimate association with each other, said silicon dioxide portion of said agglomerate being derived from a silicon dioxide having an average primary particle size from about 1 nm to about 100 μ m, and from about 99% to about 1% of a locally active therapeutic agent.
78. The solid dosage form of claim 77, wherein the locally active therapeutic agent is selected from a group consisting of antifungal agents, antibiotic agents, antiviral agents, breath fresheners, antitussive agents, anti-cariogenic compounds, analgesic agents, local anesthetics, oral antiseptics, anti-inflammatory agents, hormonal agents, anti-plaque agents, acidity reducing agents, and tooth desensitizers.
79. The solid dosage form of claim 77, wherein the solid dosage form provides a sustained-release of the locally active therapeutic agent.
80. The solid dosage form of claims 69, wherein the solid dosage form includes a sufficient amount of the coating to provide a sustained release of the active agent over a predetermined period.
81. The solid dosage form of claim 70, wherein the predetermined period is 12 hours.
82. The solid dosage form of claim 70, wherein the predetermined period is 24 hours.
83. The solid dosage form of claim 66, wherein the coating further includes an additional amount of the active agent.

* * * * *

dón, la lactosa o el fosfato dicálcico. Este tipo de sustancias están adquiriendo cada vez más importancia en la formulación de comprimidos, y la continua investigación sobre el tema ha incrementado el número de excipientes de compresión directa disponibles y la cantidad de fármaco que pueden incorporar.

2.2.6. *Comprimidos obtenidos por compresión directa*

La importancia del proceso tecnológico en la elaboración de comprimidos, hace que éstos puedan clasificarse según el método de obtención en comprimidos obtenidos por compresión directa del fármaco o de una mezcla del fármaco con excipientes y comprimidos obtenidos por compresión de un granulado.

Por compresión directa se entiende la compresión de fármacos pulveriformes o de mezclas de éstos con coadyuvantes, sin tratamiento previo. Sólo un pequeño número de sustancias pueden comprimirse directamente con buenos resultados (bromuro y cloruro sódicos, yoduro potásico, ácido bórico, ácido acetilsalicílico...). Las propiedades que hacen posible la compresión directa son poco conocidas; se sabe que ello depende, en parte, del sistema de cristalización que adopta la sustancia, lo que condiciona su capacidad de deformación plástica y engarzamiento de partículas. Así, las sustancias cristalizadas en un sistema isométrico pueden, en la mayoría de los casos, comprimir directamente. Por el contrario, la compresión directa es prácticamente imposible en las sustancias de naturaleza orgánica que cristalizan en el sistema monoclinico o triclinico, como es el caso de la mayoría de las sustancias farmacológicamente activas. Estas consideraciones deben ser interpretadas como una regla orientativa, ya que algunas sustancias que cristalizan en los sistemas monoclinico y triclinico comprimen de forma directa.

Otros parámetros indicativos de la compresibilidad de las sustancias son los puntos de fusión y ebullición, que dan una idea de la cohesión intermolecular, la simetría molecular y la presencia de agua de cristalización. De igual modo, el tamaño de los cristales también parece influir en la capacidad de compresión; así, por ejemplo, el permanganato potásico sólo puede comprimirse directamente, en estado cristalino, a un determinado tamaño de partícula.

A la compresión directa se oponen las escasas fuerzas de ligazón entre las partículas, lo que da lugar a comprimidos con poca consistencia, y la escasa o mala capacidad de fluencia del polvo del que se parte. En consecuencia, las estrategias enfocadas a favorecerla serían:

- Modificar, por vía física, la estructura y propiedades de las partículas del fármaco, fundamentalmente el tamaño, la forma, el contenido en humedad, el estado cristalino, confiriéndoles las características deseables comentadas anteriormente en los excipientes de compresión directa.
- Emplear dispositivos de alimentación forzada para mejorar el flujo de las mezclas de polvos. Los alimentadores de flujo forzado son dispositivos mecá-

nicos que facilitan la eliminación del aire del material liviano y voluminoso, manteniendo un flujo constante del polvo que pasa a las matrices. Ello se reduce al mínimo el atrapamiento de aire, evitando la formación de casquetes (*capping*) en el comprimido terminado. Además, al aumentar la densidad del polvo se obtiene una mayor uniformidad de peso.

- Adicionar excipientes capaces de conferir a la formulación las características requeridas para la compresión (excipientes de compresión directa). Ésta constituye la forma más fácil y habitual de conferir a un principio activo la capacidad de comprimir directamente; sin embargo, el elevado costo de estos excipientes puede llegar a constituir un inconveniente frente a métodos convencionales.

La compresión directa presenta un creciente interés debido a que simplifica significativamente el proceso de elaboración del comprimido, reduciendo de forma importante los costos, aunque presenta algunas limitaciones, entre las que destacan las siguientes:

- Diferencias en la densidad y el tamaño de partícula del fármaco y el excipiente pueden dar lugar a una estratificación del granulado, lo que se traduce en problemas en la uniformidad de contenido del fármaco, en especial en los principios activos que se utilizan a bajas dosis. Por ello, se aconseja que todos los componentes de la formulación tengan un tamaño y una densidad similares.
- Fármacos que se dosifican en cantidades grandes, si no comprimen algo por sí mismos, pueden plantear problemas en la compresión directa. Considerando que la proporción de fármaco en el comprimido suele ser del orden del 25%, se requeriría una cantidad tan grande de excipiente que daría lugar a un comprimido caro y difícil de deglutir.

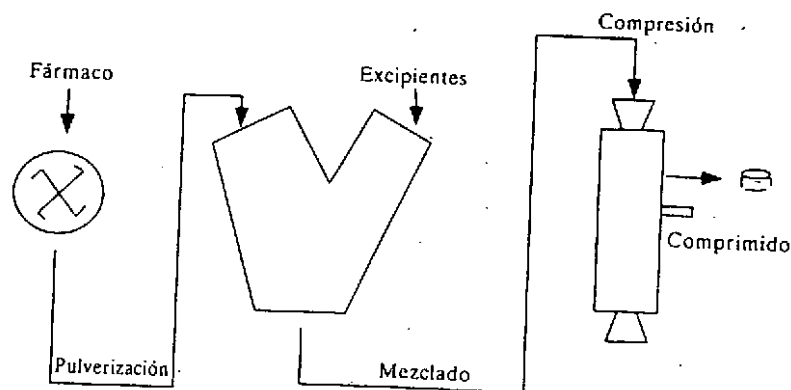


FIGURA 2.23. Etapas del proceso de compresión directa.

- Debido a que el proceso se realiza en seco, se produce gran cantidad de polvo y se generan cargas electrostáticas en los componentes durante las operaciones de pulverización y mezclado, las cuales pueden originar una distribución no uniforme del principio activo en el comprimido final.

Las etapas previas, utilizadas básicamente en la compresión directa, incluyen únicamente las operaciones de pulverización y mezclado. Un esquema de este método de preparación de comprimidos se recoge en la figura 2.23.

2.2.7. Comprimidos obtenidos por compresión de un granulado

La granulación tiene como objetivo la transformación de partículas de polvo cristalizado o amorfo en agregados sólidos más o menos resistentes y porosos denominados granulados. Las partículas se unen mediante enlaces interatómicos e intermoleculares de diferente naturaleza: fuerzas de Van der Waals, enlaces por puentes de hidrógeno, puentes sólidos de sustancias cristalinas, etc. El granulado constituye un estado intermedio, no sólo en la fabricación de comprimidos sino también de otras formas farmacéuticas como cápsulas rígidas, sellos y sobres, aunque puede utilizarse como tal.

Las principales razones por las que se recurre a la granulación son:

- Prevenir la segregación de los componentes en el mezclado de polvos, debidas a diferencias en el tamaño y densidad de las partículas de los componentes. Un granulado ideal (figura 2.24) contendrá todos los componentes de la mezcla en cada gránulo, evitando de esta forma la segregación de componentes.
- Mejorar las propiedades de flujo de la mezcla. Los gránulos obtenidos a partir de un sistema cohesivo son más grandes, esféricos e isodiamétricos que los componentes iniciales, mejorándose así la capacidad de flujo. Además, estas propiedades reducen las fuerzas de fricción y son menores los efectos de carga eléctrica.
- Aumentar las características de compresión de la mezcla. Ello se consigue por la homogénea distribución del aglutinante como película adhesiva en la superficie de las partículas dentro del granulado.
- Favorecer la expulsión del aire interpuesto. El aire se expulsa más fácilmente al comprimir un sólido constituido por gránulos que por un polvo fino.
- Reducir significativamente la cantidad de polvo generado en el proceso de fabricación. La liberación al medio de polvo que contenga un fármaco de gran actividad puede tener graves consecuencias sobre el personal que lo maneja.
- Reducir la higroscopicidad de la mezcla. Los componentes que son ligeramente higroscópicos en forma de polvo pueden adherirse y formar una pas-