**Title:** DIRECT COMPRESSION TABLET EXCIPIENT

**Abstract**

An excipient for use in the manufacture of directly compressed tablets is formed by mixing an aqueous solution of a water-soluble or water-dispersible film-forming binder with a molten C₁₀₋₁₅ fatty acid or ester thereof to form a colloidal solution and drying the colloidal solution or a mixture thereof with one or more additional excipient components. Preferably the film-forming binder is polyvinylpyrrolidone and the fatty acid or ester thereof is stearic acid. It is also preferred that a particulate hydrophobic tablet excipient, especially a hydrogenated vegetable oil, is present as an additional excipient component. Sticking and tablet weakness problems encountered when using hydrogenated vegetable oil as an excipient in direct tablet compression are overcome by using the hydrogenated vegetable oil in the form of an excipient in accordance with the present invention.
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DIRECT COMPRESSION TABLET EXCIPIENT

The present invention relates to excipients for use in tablet manufacture, especially, but not necessarily, by direct compression. In particular, the invention provides a novel excipient, a method of preparing the novel excipient, a method of forming tablets by directly compressing a particulate mixture comprising a preferred embodiment of the novel excipient, and the directly compressed tablets obtained thereby.

It has been proposed to use hydrogenated vegetable oils ("HVO") and similar hydrophobic substances as sustained release excipients in the manufacture of tablets by direct compression. These substances, which are usually present in an amount of 30% to 60% by weight of the directly compressible tablet mixture, melt or soften and subsequently resolidify during the direct compression procedure to provide a sustained release matrix. However, although reasonably successful in small scale trials, problems have been encountered when attempting to scale up to production volumes. In particular, the presence of HVO concentrations required in order to provide sustained drug release causes the tablet mixture to stick to the punch face and, to a lesser extent, to the die producing rough and uneven tablets. Further, the mixture was found to have poor compressibility. Attempts to overcome these problems by the conventional practice of use of an external lubricant or binder polymer have not been successful.

The most commonly used external tablet lubricant is magnesium stearate. At conventional concentrations (0.5 to 1% by weight), it has little or no effect upon the sticking problem caused by the presence of HVO. If the magnesium stearate concentration is increased to a level (about 5%) which will prevent sticking, the tablets are weakened and
suffer from capping (i.e. laminar disruption of the tablet as a result of bond weakening believed to be due inter alia to elastic recovery.

Polyvinylpyrrolidone (PVP) is frequently used as a binder polymer in directly compressible tabletable compositions. Although incorporation of about 3% PVP improved the low compressibility problem when using HVO, it did not, even in the presence of magnesium stearate, prevent sticking.

It is known to use C_{10} - C_{26} fatty acids, usually in amounts of 1 to 2% by weight, as tablet excipients. The procedure involves dissolving the fatty acid in alcohol and then granulating the solution with the active ingredient(s) and any other excipients. However, this procedure is not compatible with modern tableting techniques, especially direct compression. Furthermore the use of alcohol is undesirable for both environmental and health & safety reasons.

The Inventor has surprisingly found that the sticking and poor compressibility problems encountered when directly compressing a tabletable mixture containing HVO can be avoided, or at least significantly reduced, by pre-treating the HVO with a colloidal suspension of stearic acid in aqueous PVP and drying the resultant mixture. The colloidal suspension is formed by mixing an aqueous solution of PVP with molten stearic acid. The technique is applicable to hydrophobic tablet excipients other than HVO and to other C_{10} - C_{26} fatty acids or esters thereof and water-soluble or water-dispersible film-forming binders than stearic acid and PVP respectively.

According to a first aspect of the present invention, there is provided an excipient formed by mixing an aqueous
solution of a water-soluble or water-dispersible film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution and drying said solution or a mixture thereof with one or more additional excipient components. In a preferred embodiment of this aspect, the invention provides an excipient formed by mixing an aqueous solution of a water-soluble or water-dispersible film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution; mixing said colloidal solution with a particulate hydrophobic tablet excipient; and drying the resultant mixture.

In a second aspect, the invention provides a method of preparing an excipient which comprises mixing an aqueous solution of a water-soluble or water-dispersible film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution and drying the solution or a mixture thereof with one or more additional excipient components. In a preferred embodiment of this aspect, the method comprises mixing an aqueous solution of a film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution; mixing said colloidal solution with a particulate hydrophobic tablet excipient; and drying the resultant mixture.

In a third aspect, the present invention provides a directly compressed tablet comprising a tablet excipient formed by mixing a water-soluble or water-dispersible film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution; mixing said colloidal solution with a particulate hydrophobic tablet excipient; and drying the resultant mixture.

In a fourth aspect, the present invention provides a method of forming a tablet which comprises directly
compressing a particulate mixture comprising a tablet
excipient formed by mixing a water-soluble or water-
dispersible film-forming binder with a molten C_{10} - C_{26}
fatty acid or ester thereof to form a colloidal solution;
mixing said colloidal solution with particulate hydrophobic
tablet excipient; and drying the resultant mixture.

The film-forming binder used in the present
invention can be any pharmaceutically acceptable water-
soluble or water-dispersible film-forming binder which is
compatible with the fatty acid or ester thereof and any
other excipient component(s). Examples of suitable binders
are polysaccharides, for example gum acacia, agar, agarose,
cellulose ethers and esters, starches and gum tragacanth;
proteins, for example gelatin and zein; and synthetic
polymers, for example methacrylic acid/methacrylic acid
methyl ester copolymers available under the Trade Mark
EUDRAGIT, polyvinylalcohol, polyvinylacetatephthalate, and
polyvinylpyrrolidone (PVP). Examples of suitable cellulose
ethers and esters include hydroxypropylcellulose,
hydroxypropyl-methylcellulose, methylcellulose,
ethylcellulose, cellulose acetate and cellulose acetate
phthalate. It is presently preferred that the binder is
water-soluble. The presently most preferred binder is PVP.

In the preferred embodiments where a hydrophobic
tablet excipient is present, the film-forming binder
usually will be present in an amount of 25% or less,
preferably 10% or less, especially 0.25 to 5%, by weight on
a dry weight basis.

The fatty acid or ester thereof used in the present
invention has 10 to 26, preferably 14 to 20, carbon atoms
in the acid moiety. Usually, the acid or ester thereof
will be saturated but unsaturated fatty acids and esters
can be used. Suitable acids include lauric, linoleic,
oleic, palmitic, and stearic acids. Suitable esters include glycercyl behenate, sodium stearoyl lactylates, sodium stearyl fumarate, and stearyl monoglyceridyl citrate. Preferably, the fatty acid or ester is stearic acid.

In the preferred embodiments using a hydrophobic tablet excipient, the amount of fatty acid or ester thereof usually will be 10% or less, preferably 0.25 to 5%, on a dry weight basis.

Usually the ratio by weight of film-forming binder to fatty acid or ester thereof will be in the range 2:1 to 1:2 with a ratio of about 1:1 being preferred.

Although the presence of a hydrophobic tablet excipient is a preferred feature of the present invention, it is not an essential feature. In particular, the invention includes, in its broadest aspect, the fatty acid or ester/binder product obtained on drying a colloidal solution containing only the fatty acid or ester and binder. Such a product can be reconstituted into a colloidal solution for mixing with a particulate hydrophobic tablet excipient and/or other tablet excipients and the resultant mixture dried. Alternatively, the product can be used as such as an excipient in direct compression or other tableting procedures.

When, in accordance with the preferred embodiments of the present invention, a hydrophobic tablet excipient is present, it will be a solid oil derivative, a fat or a fat derivative having a liquid/solid phase transition temperature of 40°C to 120°C, preferably 60 to 80. Below 40°C, particles of the substances are likely to agglomerate and hence be insufficiently particulate to prepare a satisfactory excipient. Above 120°C, the substances are
unlikely to soften or melt sufficiently to form the required matrix during direct tablet compression.

It is preferred that the hydrophobic tablet excipient is a hydrogenated vegetable oil ("HVO"). HVOs includes hydrogenated natural oils and waxes such as canola oil, castor oil, coconut oil, cottonseed oil, illipe oil, palm oil, palm kernel oil, safflower oil, and sunflower oil. Presently, hydrogenated cottonseed oil and, especially, hydrogenated castor oil are preferred. Further, the HVO can be replaced completely or in part by one or more other particulate hydrophobic tablet excipients, for example acetylated monoglycerides; beeswax; carnauba wax; non-hydrogenated vegetable oils or waxes, lactylated fatty acid esters of glycerol and propylene glycol; lactylated mono- and di-glycerides; stearyl monoglyceridyl citrate; succinylated monoglycerides; and triacetin.

The excipient of the invention may include one or more components conventionally used in tabletable formulations. For example, it can include one or more of an ionic surfactant, for example sodium lauryl sulphate; a non-ionic surfactant, for example a poloxamer; or other surface active materials such as polyethylene glycols, sucrose esters and distilled monoglycerides.

The excipient of the invention is formed by drying a colloidal suspension formed by mixing an aqueous solution of the film-forming binder with the fatty acid or ester thereof in its molten state. Usually, the fatty acid or ester is melted prior to addition to the aqueous binder but the colloidal solution can be formed by heating an agitated suspension of the fatty acid or ester thereof in the aqueous binder.

If other components are to be present in the
excipient, they can be present in the aqueous solution or added to the colloidal solution before drying. If any additional water-soluble or water-dispersible component is to be incorporated in the excipient, it will usually be present in the aqueous solution unless its presence interferes with formation of the colloidal solution. In this connection, it will be appreciated that the components of the excipient will be selected to be compatible both in terms of preparation of the excipient and the tableting performance thereof. It is well within the ability of those of average skill in the art to determine by simple experimentation whether or not a particular combination of components is compatible and, if necessary, to modify that combination to avoid any incompatibility between the components thereof. Any water-insoluble additional component, especially the preferred hydrophobic tablet excipient, usually will be added to the colloidal solution because its presence in the aqueous solution would interfere with formation of the colloidal solution. Typically, the colloidal solution will be cooled before addition of water-insoluble components.

It is preferred that mixing of water-insoluble components, especially the preferred hydrophobic tablet excipient, with the colloidal suspension is conducted by granulation, especially in a high speed mixer granulator.

At least some of the excipients in accordance with the preferred (i.e. hydrophobic tablet excipient - containing) embodiments of the present invention have unexpected properties. In particular, excipients obtained using PVP as the binder, stearic acid or ester thereof as the fatty acid and HVO as the hydrophobic tablet excipient appear to have a sustained drug release profile which is more or less independent of excipient particle size, compaction force and the presence of surfactant in the excipient. It was
expected that the rate of drug release would be increased by increasing particle size, decreasing compaction strength and adding surfactant.

5 In use, the excipient of the invention can be mixed with one or more additional conventional excipients if required.

The invention is illustrated by the following non-limiting examples:-

EXAMPLE 1

HVO (Sterotex K*) 4000g
15 Stearic acid BP 160g
PVP K90* 200g
Water 700g

* Sterotex K is hydrogenated castor oil and PVP K90 has a molecular weight of about 360,000.

The stearic acid was melted and added to a solution of the PVP in water which had been heated to 70°C whilst agitating the solution using a Silverson homogeniser for about 5 minutes. The resultant colloidal solution was cooled and then granulated with the Sterotex in a Lődige high speed mixer granulator for successive periods of 2 minutes, 1 minute and 1 minute using a main impeller setting of 20 and a chopper speed setting I (equivalent to about 1,000 rev min⁻¹) The granulate was then dried for 12 hours at 30°C and dry screened through a 1.25mm diameter screen using Frewitt.

The screened excipient was dry mixed with propranolol hydrochloride to provide a directly compressible tablet formulation comprising 70% excipient and 30% drug.
milligram tablets were successfully directly compressed over compaction forces ranging between 6 and 18kN. The tablets were smooth and even and of good strength.

EXAMPLE 2

HVO (Sterotex K*) 4000g
Stearic acid BP 220g
PVP K30* 220g
Water 700g

* Sterotex K is hydrogenated castor oil and PVP K30 has a molecular weight of about 30,000.

The procedure of Example 1 was repeated using the above components but adding the colloidal suspension to the Sterotex K powder in a food processor and blending for about 3 minutes. The blended mixture was passed through a 710 - 1000μm screen and dried over night at 40°C. The dried product was then dry screened through a 500μm sieve.

The excipient was mixed with the following additional ingredients to form a directly compressible tablet formulation:-

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<th>INGREDIENT</th>
<th>WEIGHT %</th>
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<tr>
<td>Morphine Sulphate</td>
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<tr>
<td>Excipient</td>
<td>45</td>
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<tr>
<td>Fast Flo</td>
<td>33</td>
</tr>
<tr>
<td>Sodium Stearyl Fumarate</td>
<td>0.7</td>
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<tr>
<td>Aerosil 200</td>
<td>0.7</td>
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</table>

Fast Flo is spray dried lactose present as a bulking agent, compression aid and release modifier; sodium stearyl
fumarate is a lubricant; and Aerosil 200 is colloidal silicon dioxide and is a flow aid.

The formulation was directly compressed to form tablets containing 100mg morphine sulphate. These tablets were smooth and even and of good strength. Figure 1 shows the release profile of the tablets under standard conditions (plotted as △).

**EXAMPLE 3**

<table>
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<th>Ingredient</th>
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<tr>
<td>HVO (Sterotex K*)</td>
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<tr>
<td>Stearic acid BP</td>
<td>220g</td>
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<tr>
<td>PVP K90*</td>
<td>220g</td>
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<tr>
<td>Sodium lauryl sulphate</td>
<td>90g</td>
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<tr>
<td>Water</td>
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* Sterotex K is hydrogenated castor oil and PVP K90 has a molecular weight of about 30,000.

The procedure of Example 2 was repeated to provide 100mg tablets by direct compression of the formulation of Example 2 but using the excipient of the present Example. The tablets were smooth and even and of good strength. Figure 1 shows the release profile of the tablets under standard conditions (plotted as □).

**EXAMPLE 4**

The excipient of Example 2 was mixed with the following additional ingredients to form directly compressible tablet formulations:
(A)

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<td>Morphine Sulphate</td>
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<td>Excipient</td>
<td>60</td>
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<td>Emcompress</td>
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<td>Magnesium Stearate</td>
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<tr>
<td>Aerosil 200</td>
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10 Emcompress is dicalcium phosphate dihydrate and Aerosil 200 is colloidal silicon dioxide.

(B)

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<th>INGREDIENT</th>
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<tr>
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<td>Magnesium Stearate</td>
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<tr>
<td>Aerosil 200</td>
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Emcocel is microcrystalline cellulose.

(C)

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<tr>
<td>Magnesium Stearate</td>
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<td>Aerosil 200</td>
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35 Fast Flo is spray dried lactose
Each of Formulations A, B and C were directly compressed to form tablets containing 30mg morphine sulphate. These tablets were smooth and even and of good strength. Figure 2 shows the release profile of the tablets under standard conditions (A plotted as ◊; B plotted as △; and C plotted as ○).

EXAMPLE 5

The excipient of Example 2 was mixed with the following additional ingredients to form a directly compressible tablet formulation:

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<td>Fast Flo</td>
<td>40</td>
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<tr>
<td>Aerosil 200</td>
<td>1.3</td>
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Fast Flo is spray dried lactose and Aerosil 200 is colloidal silicon dioxide.

The formulation was directly compressed to form tablets containing 100mg morphine sulphate. These tablets were smooth and even and of good strength. Figure 3 shows the release profile of the tablets under standard conditions (plotted as △).

EXAMPLE 6

The procedure of Example 2 was repeated except that the amount of HVO (Sterotex X) was decreased to 3750g and the amount of Stearic acid was increased to 450g to provide more efficient anti-adherent protection.
EXAMPLE 7

HVO (Sterotex K*) 3710g
Stearic acid BP 204g
PVP K30 200g
Water 900g

* Sterotex K is hydrogenated castor oil and PVP K30 has a molecular weight of about 30,000.

The PVP was dissolved in the water at 70°C, the stearic acid added in the molten state and the mixture homogenized in a Silverson homogenizer for 2 minutes. The HVO was then added in a mixer/granulator and blended at high speed for 4 minutes. The resultant mixture was dried and screened through a 710μm to provide an excipient, which was mixed with propranolol in the weight ratio 70:30 (excipient: active) to form a directly compressible tablet formulation. This formulation was directly compressed into 150mg tablets.

Figure 4 shows the release profile of the tablets under standard conditions.

Figure 5 shows the effect on the release profile of particle size of the excipient component of the tabletable formulation. Particle size less than 90 μm is plotted as ○; particle size 90 to 250 μm is plotted as x; particle size 250 to 500μm is plotted as ◆; and particle size 500 to 710 μm is plotted as △.

Figure 6 shows the effect of tablet compaction force on the release profile of the tablets. Compaction at 15000N is plotted as ○ and compaction at 18000N is plotted as x.
Figure 7 shows the effect on $T_{50}$ (ie time required to release 50% of the propranolol content) of tablet compaction force.

Figure 8 shows the effect on tablet lubricity of particle size of the excipient component of the tablettable formulation. The value "LP/UP" is the ratio of lower punch force to upper punch force. High values (close to unity) indicate good transmission of forces and hence good lubricity. A represents a particle size of 500 to 710 $\mu$m (mean upper punch force 17592.9N); B represents a particle size 250 to 500$\mu$m (mean upper punch force 18224.3N); C represents a particle size 90 to 250 $\mu$m (mean upper punch force 18016.7N) and D represents a particle size below 90$\mu$m (mean upper punch force 18020.0N).

Figure 9 shows the effect on tablet lubricity of changes in tablet compaction force when the excipient particles are unfractionated (ie passes the 710$\mu$m sieve).
CLAIMS

1. An excipient formed by mixing an aqueous solution of a water-soluble or water-dispersible film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution and drying said solution or a mixture thereof with one or more additional excipient components.

2. An excipient as claimed in Claim 1, wherein the film-forming binder is selected from polysaccharides; proteins; methacrylic acid/methacrylic acid methyl ester copolymers; polyvinylalcohol; polyvinylacetatephthalate; and polyvinylpyrrolidone (PVP).

3. An excipient as claimed in Claim 1, wherein the film-forming binder is water-soluble.

4. An excipient as claimed in Claim 3, wherein the film-forming binder is polyvinylpyrrolidone.

5. An excipient as claimed in Claim 1, wherein the fatty acid or ester thereof is a C_{14} to C_{20} fatty acid or ester thereof.

6. An excipient as claimed in Claim 5, wherein the fatty acid or ester thereof is stearic acid.

7. An excipient as claimed in Claim 1, wherein the film-forming binder and fatty acid or ester thereof are present in the weight ratio of 2:1 to 1:2.

8. An excipient as claimed in Claim 7, wherein said ratio is about 1:1.
9. An excipient as claimed in Claim 1 formed by mixing an aqueous solution of a water-soluble or water-dispersible film-forming binder with a molten $\text{C}_{10} - \text{C}_{26}$ fatty acid or ester thereof to form a colloidal solution, mixing said colloidal solution with a particulate hydrophobic tablet excipient; and drying the resultant mixture.

10. An excipient as claimed in Claim 9, wherein said hydrophobic excipient comprises a solid oil derivative, a fat or a fat derivative having a liquid/solid phase transition temperature of 40°C to 120°C.

11. An excipient as claimed in Claim 10, wherein said hydrophobic excipient has a liquid/solid phase transition temperature of 60°C to 80°C.

12. An excipient as claimed in Claim 10, wherein said hydrophobic excipient comprises a hydrogenated vegetable oil.

13. An excipient as claimed in Claim 12, wherein said hydrogenated vegetable oil is a hydrogenated castor or cottonseed oil.

14. An excipient as claimed in Claim 10, wherein said hydrophobic excipient comprises an acetylated monoglyceride; beeswax; carnauba wax; non-hydrogenated vegetable oils or waxes; a lactylated fatty acid esters of glycerol and propylene glycol; a lactylated mono- and di-glyceride; stearyl monoglyceridyl citrate; a succinylated monoglyceride; or triacetin.

15. An excipient as claimed in Claim 9, wherein the film-forming binder is present in an amount of 25% or less by weight (dry weight basis).
16. An excipient as claimed Claim 15, wherein the film-forming binder is present in an amount of 10% or less by weight (dry weight basis).

17. An excipient as claimed in Claim 16, wherein said amount of film-forming binder is 0.25 to 5% by weight (dry weight basis).

18. An excipient as claimed in Claim 9, wherein the fatty acid or ester thereof is present in an amount of 10% or less by weight (dry weight basis).

19. An excipient as claimed in Claim 18, wherein said amount of fatty acid or ester thereof is 0.25 to 5% by weight (dry weight basis).

20. A method of preparing an excipient which comprises mixing an aqueous solution of a water-soluble or water-dispersible film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution and drying the solution or a mixture thereof with one or more additional excipient components.

21. A method as claimed in Claim 20 which comprises mixing an aqueous solution of a film-forming binder with a molten C_{10} - C_{26} fatty acid or ester thereof to form a colloidal solution; mixing said colloidal solution with a particulate hydrophobic tablet excipient; and drying the resultant mixture.

22. A method as claimed in Claim 20, wherein the colloidal solution is cooled and one or more additional excipient components mixed with the cooled solution prior to drying.
23. A method as claimed in Claim 21, wherein one or more water-insoluble additional excipient components are granulated with the cooled colloidal solution.

24. A directly compressed tablet comprising a tablet excipient formed by mixing a water-soluble or water-dispersible film-forming binder with a molten C₁₀ - C₂₆ fatty acid or ester thereof to form a colloidal solution; mixing said colloidal solution with a particulate hydrophobic tablet excipient; and drying the resultant mixture.

25. A method of forming a tablet which comprises directly compressing a particulate mixture comprising a tablet excipient formed by mixing a water-soluble or water-dispersible film-forming binder with a molten C₁₀ - C₂₆ fatty acid or ester thereof to form a colloidal solution; mixing said colloidal solution with particulate hydrophobic tablet excipient; and drying the resultant mixture.
FIG. 1.

FIG. 2.

PERCENT RELEASED

TIME (HRS)

PERCENT RELEASED

TIME (HRS)

SUBSTITUTE SHEET
FIG. 3.

FIG. 4.

PERCENT RELEASED

TIME (HRS)

0 2 4 6 8 10 12

0 20 40 60 80 100

SUBSTITUTE SHEET
FIG. 7.

FIG. 8.
FIG. 9.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

Int. C15 A61K9/20, A61K47/10, 47/26

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. C15 A61K9/20, A61K47/06-47/26, 47/36-47/40

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>JP, A, 61-205208 (Yamanouchi Pharmaceutical Co., Ltd.), September 11, 1986 (11. 09. 86), (Family: none)</td>
<td>1-6</td>
</tr>
<tr>
<td>A</td>
<td>JP, A, 53-44618 (Takeda Chemical Industries, Ltd.), April 21, 1978 (21. 04. 78), (Family: none)</td>
<td>1-6</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document but published on or after the international filing date
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  "L" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
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  "&" document member of the same patent family

Date of the actual completion of the international search
May 20, 1993 (20. 05. 93)

Date of mailing of the international search report
June 8, 1993 (08. 06. 93)

Name and mailing address of the ISA/
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Form PCT/ISA/210 (second sheet) (July 1992)