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(54) Title: PROCESS FOR ENCAPSULATION OF CAPLETS IN A CAPSULE AND SOLID DOSAGE FORMS OBTAINABLE BY SUCH PROCESS

(57) Abrégé/Abstract:
A process for encapsulation of caplets in a capsule and the solid dosage capsules obtained thereby. In particular, the manufacture of a tamper-proof capsule containing a pharmaceutically active composition. In a preferred embodiment, the caplet is greater in length than both halves of the capsule shell. In this embodiment, part of the caplet remains exposed after the capsule is manufactured.

## ABSTRACT

A process for encapsulation of caplets in a capsule and the solid dosage capsules obtained thereby. In particular, the manufacture of a tamper-proof capsule containing a pharmaceutically active composition. In a preferred embodiment, the caplet is greater in length than both halves of the capsule shell. In this embodiment, part of the caplet remains exposed after the capsule is manufactured.


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# PROCESS FOR ENCAPSULATION OF CAPLETS IN A CAPSULE AND SOLID DOSAGE FORMS OBTAINABLE BY SUCH PROCESS

## Field of the Invention

The present invention relates to a process for encapsulation of caplets in a capsule and to solid dosage forms obtainable by such a process, and more particularly, to the manufacture of a tamper-proof capsule containing a pharmaceutically active composition.

## Background of the Invention

Various oral medications have been manufactured in the form of so called caplets, which can be swallowed by patients during their regiment of taking medication. Caplets, however, are not as easily swallowed by patients as capsules having, for example, a gelatin coating. Additionally, capsule coatings are desirable over caplets since the coatings provide a neutral taste in contrast to caplets per se which sometimes contain pharmaceutical substances that taste, for example, bitter. Thus, patients, in particular children, refuse to swallow such caplets per se. Attempts have therefore been made to encapsulate caplets in a capsule by means of a gelatin cover.

U.S. Patent No. 4,867,983 to Berta describes a method for double dipping gelatin coated caplets. The method provides a procedure for coating solid cores, such as caplets, with a first gelatinous coating on one end, and then with a second gelatinous coating on the other end which is thicker than the first, to simulate the interlocking halves of a hollow capsule. The second, thicker gelatinous coating can be provided with a single

gelatin coating from a bath having a higher viscosity than the bath used to provide the first gelatinous coating. Alternatively, the second gelatinous coating can be provided by double dipping to provide layers of gelatinous material or gelatin. This known coating is disadvantageous in that the gelatinous coating and the color distribution is not uniformly distributed over the caplets by this process. Moreover, an overlapping of the different coatings results in color changes of the coatings. Additionally, the dip margins obtained by the known process tend not to be straight. Furthermore, the coatings according to the above patent chip off under stress if the coated caplets are stored under dry conditions and/or high temperature. Finally, the dip coating process of U.S. Patent No. 4,867,983 is time consuming and expensive.

From U.S. Patent No. 5,081,822 to Boyd et al, an automatic caplet filler is known for filling normal gelatin capsules with caplets. The capsules formed by this automatic caplet filler, however, are disadvantageous in that they can be easily manipulated. Sealing of the capsules has to be effected by means of an additional gelatin strip or by gluing of the caplets in the capsule with an adhesive, as e.g. described in U.S. Patent No. 4,928,840 or European Patent Application No. 0435726. This further treatment of the capsules may have the effect that substances other than the medication are encapsulated in the capsule. If on one hand a water-based adhesive is used for gluing the capsule halves together, the capsule as well as the caplet may be deformed. If on the other hand, an adhesive containing an organic solvent is used, a brittleness of the capsule will be the result. Finally, if the capsule halves are connected with each other by means of a heat shrinking

process, a visible gap will remain between the capsule halves.

It is therefore the object of the present invention to provide a method for encapsulating caplets in a capsule in a tamper-proof form. It is yet another object of the invention to provide a cost-effective process for easily manufacturing tamper-proof solid dosage forms. It is yet another object of the present invention to provide a solid dosage form comprising a caplet covered by a capsule. It is yet another object of the present invention to provide a pharmaceutical dosage form having a greater resistance to breaking than known products. A further object of the present invention is to provide a tamper-proof solid dosage form.

## Summary of the Invention

According to a first aspect, the present invention provides a process for encapsulation of a caplet in a capsule by cold shrinking together capsule parts, which are filled with a caplet. According to another aspect, the present invention provides a solid dosage form obtainable by such a process. The solid dosage form according to the present invention is tamper-proof in that the caplet contained in the capsule cannot be removed from the capsule without destroying same.

The process according to the present invention furthermore provides a capsule product comprising several parts, which are combined with each other in a way that no visible slits between the capsule parts are present after the cold shrink procedure. The solid dosage forms of the present invention have a completely smooth surface, so that same can be swallowed easily by patients.

More specifically, a process for encapsulating caplets in a capsule is provided, which comprises the following steps:

a. providing empty capsule parts,

b. filling at least one of said capsule parts with one or more caplets,

c. putting said capsule parts together, and

d. treating the combined capsule parts by cold shrinking.

Moreover, a solid dosage form comprising a caplet and a capsule coating obtainable by such process is described.

Description of Preferred Embodiments of the Invention

The capsule shell in which the caplet is to be enclosed preferably comprises two shell halves, a body portion and a cap portion. Other capsules comprising more than two parts are also possible. The capsule is typically a hollow shell of generally cylindrical shape having a diameter and length sufficient so that the caplet fits appropriately in the empty capsule. The clearance of the capsule shell and the caplet is preferably about + 0.5 mm. According to a specifically preferred embodiment of the present invention, the clearance of the capsule shell and the caplet is in the range of from about 0 to about - 0.5 mm, which means that the caplet is compressed in the capsule.

I.) Moisture content of the capsule shells:

A specifically preferred process of the present invention is carried out as follows. Empty capsule parts are either kept after production at humid conditions of 40 to 90 %, particularly 60 to 80 %, relative humidity to retain a moisture content of 14 to 19 %, preferred 15 to 18 % and more preferred 16 to 18 % by weight of the

capsule shell or are re-humidified to said moisture content before feeding into a capsule filling machine.

The first capsule shell part is then kept under humid conditions within the filling machine at said moisture content during rectifying and assembling with a caplet having a moisture content in the range of from about 0 to about 12 % by weight.

A second or further capsule shell part is processed in the same manner as the first one. Finally, the encapsulated dosage form is dried at a relative humidity in the range of from about 20 to about 40 % and a temperature in the range of from about 15 to about 60°C, preferably from about 15 to about 40°C, more preferably from about 18 to about 25°C.

Caplets having a low moisture content of in the range of from about 0 to about 6 % by weight, or more preferably of from about 0 to about 3 % by weight, are especially suitable to be used in the process of the present invention. Conical ends of the caplet make the insertion of the caplet into one half of the capsule easier. After drying and shrinking the capsule parts together, the capsule can be further film coated, which coating may be enteric.

The capsule shell material can be a hydrophilic polymer, gelatin being the preferred choice. Other suitable capsule shell materials include starch, casein, chitosan, soya bean protein, safflower protein, alginates, gellan gum, carrageenan, xanthan gum, phtalated gelatin, succinated gelatin, cellulosephtalate-acetate, polyvinylacetate, hydroxypropyl methylcellulose, polyvinylacetate-phtalate, polymerisates of acrylic or methacrylic esters or

mixtures thereof. The capsule shell material may furthermore contain from about 0 to about 40 % pharmaceutically acceptable plasticizers based upon the weight of the hydrophilic polymer. The plasticizer which may be employed can be selected from polyethylene glycol, glycerol, sorbitol, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propyleneglycol, mono-, di, or tri-acetates of glycerol or mixtures thereof.

Additionally, the capsule shell material may contain pharmaceutically acceptable lubricants in the range of from about 0 to about 10 % based upon the weight of the hydrophilic polymer. The lubricant may be selected from aluminiumstearate, calciumstearate, magnesiumstearate, tinstearate, talc, sodium lauryl sulfate, lecithins, mineral oils, stearic acid or silicones or mixtures thereof.

Moreover, the capsule shell material may contain pharmaceutically acceptable coloring agents in the range of from about 0 to about 10 % based upon the weight of the hydrophilic polymer. The coloring agent may be selected from azo-quinophthalone-, triphenylmethane-, xanthene-dyes, iron oxides or hydroxides, titanium dioxide or natural dyes or mixtures thereof. Further suitable coloring agents are sunset yellow, allura red, amaranth, cochineal red, azogeranine, tartrazine, brilliant black, canthaxanthin, patent blue, fast green, brilliant blue, acid green, erythrosine, quinoline yellow, indigotine, curcumin or carbon black.

Furthermore, the capsule shell material may contain pharmaceutically acceptable extenders in the range of from about 0 to about 95 % based upon the weight of the

hydrophilic polymer. The extender may be selected from sunflower proteins, soybean proteins, cotton seed proteins, peanut proteins, rape seed proteins, lactose, gum arabic, acrylates or methacrylates, cellulose acetyl phthalates, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulosephthalate, hydroxymethylcellulose, polyvinylpyrrolidone, shellac, bentonite, polyvinyl-acetatephtalate, phthalated gelatin, succinated gelatin, agar agar, hydroxyalkylstarches or mixtures thereof.

The solid pharmaceutical dosage form according to the present invention also may comprise a coating selected from cellacephate, polyvinyl acetate phthalate, methacrylic acid polymers, hypromellose phthalate, hydroxyalkyl methyl cellulose phthalates or mixtures thereof.

The capsule parts of the solid dosage form of the present invention may have the same or different lengths and/or the same or different color. In the contact area of the capsule parts, the solid dosage form may be banded or easily dividable. The caplet being contained in the capsule can have a preformed step or groove in the dividing position of the capsule. To furthermore improve the caplet which is contained in the capsule, the caplet can be coated with an acceptable coating for tablet processing. In some cases, uncoated caplets are, however, preferred. A better contact between the inner shells of the capsule parts and the caplets can be obtained by treating the inner shells and/or the surface of the caplet with an adhesive. A suitable technique to apply the adhesive is spraying same on the shells and caplets immediately before assembling same. Suitable adhesives are e.g. tackidex or an aqueous gelatin solution.

II. Capsule shell halves cover not completely the caplet:

A further aspect of the invention is to provide encapsulated dosage forms in which the capsule shell halves do not completely cover the whole caplet, which means the caplet is longer than the two combined shell halves. This will provide capsules with additional advantageous features. If each of the capsule halves have a different color and the caplet has a third color, a three-colored capsule will be obtained, or, if the shell halves have the same color and the caplet has a different color, a color banded capsule will be obtained. A second optional feature may be obtained by use of enteric coated capsule shell halves. In such a case a capsule with delayed release will be obtaind, releasing the medicament in the stomach first from the small release band between the shell halves and later on from the capsule openings.

III. Global concept of moisture control:

A further aspect of the invention is use of the described moisture control and rehumidification on common encapsulation machines with all kinds of common hard gelatin capsule types. The inventive process gives much better filling results especially with filling machines in hot and dry areas for the encapsulation of all kinds of fillings like powders, pellets, liquids, microcapsules, tablets etc. The preferred process in this case is carried out as follows. Empty capsule bodies and caps preferred assembled in a pre-lock state are either kept after production at humid conditions of 40 to 90 %, particularly 60 to 80 %, relative humidity to retain a moisture content of 14 to 19 %, preferred 15 to 18 % and more preferred 16 to 18 % by weight of the capsule shell or are re-humidified to said moisture before opening and sorting in the capsule filling machine. Capsule bodies are then kept under humid

conditions within the filling machine at said moisture content during rectifying and filling with the desired product. In the same way the capsule caps are kept at moisture content during rectifying and finally assembling with the filled capsule bodies. Finally, the capsule is dried at 20 to 40 % relative humidity and 15 to 60°C, preferably 15 to 40°C, more preferably 18 to 25°C.

The solid dosage form according to the present invention may, for example, comprise a pharmaceutically or agrochemically active composition. Furthermore comprised in the solid dosage form can, for example, be a foodstuff or a dyestuff composition. In case the solid dosage form of the present invention contains a pharmaceutical composition, the active substance of same can, for example, be selected from betamethason, thioctacid, sotalol, salbutamol, norfenefrin, silymarin, dihydergotamin, buflomedil, etofibrat, indometacin, oxazepam, acetyldigoxin, piroxicam, haloperidol, isosorbide mononitrate, amitriptylin, diclofenac, nifedipin, verapamil, pyritinol, nitrendipin, doxycyclin, bromhexin, methylprednisolon, clonidin, fenofibrat, allopurinol, pirenzepin, levothyroxin, tamoxifen, metildigoxin, o-(β-hydroxyethyl)-rutoside, propicillin, aciclovirmononitrat, paracetamol, naftidrofuryl, pentoxifyllin, propafenon, acebutolol, 1-thyroxin, tramadol, bromocriptin, loperamid, ketotifen, fenoterol, ca-dobelisat, propranolol, minocyclin, nicergolin, ambroxol, metoprolol, β-sitosterin, enalaprilhydrogenmaleate, bezafibrat, isosorbide dinitrate, gallopamil, xantinolnicotinat, digitoxin, flunitrazepam, bencyclan, dexapanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylpenicillin, furosemid, bromazepam, flunarizin, erythromycin, metoclopramid, acemetacin, ranitidin, biperiden, metamizol, doxepin, dipotassium-chlorazepat, tetrazepam,

estramustinphosphate, terbutalin, captopril, maprotilin, prazosin, atenolol, glibenclamid, cefaclor, etilefrin, cimetidin, theophyllin, hydromorphon, ibuprofen, primidon, clobazam, oxaceprol, medroxyprogesteron, flecainid, Mg-pyridoxal-5-phosphateglutaminate, hymechromon, etofyllinclofibrat, vincamin, cinnarizin, diazepam, ketoprofen, flupentixol, molsidomin, glibornurid, dimetinden, melperon, soquinolol, dihydrocodein, clomethiazol, clemastin, glisoxepid, kallidinogenase, oxyfedrin, baclofen, carboxymethylcystsin, thioridacin, betahistin, 1-tryptophan, myrtol, bromelaine, prenylamin, salazosulfapyridin, astemizol, sulpirid, benzerazid, dibenzepin, acetylsalicylic acid, miconazol, nystatin, ketoconazol, sodium picosulfate, colestyramin, gemfibrocil, rifampicin, fluorcortolon, mexiletin, amoxicillin, terfenadrin, mucopolysaccharidpolysulfuric acid, triazolam, mianserin, tiaprofensaure, amenziniummetilsulfate, mefloquin, probucol, quinidine, carbamazepin, Mg-1-aspartate, penbutolol, piretanid, amitriptylin, caproteron, sodium valproinate, mebeverin, bisacodyl, 5-amino-salicyclic acid, dihydralazin, magaldrat, phenprocoumon, amantadin, naproxen, carteolol, famotidin, methyldopa, auranofin, estriol, nadolol, levomepromazin, doxorubicin, medofenoxat, azathioprin, flutamid, norfloxacin, fendilin, prajmaliumbitartrate, aescin, acromycin, anipamil, benzocain, $\beta$-carotin, cloramphenicol, chlorodiazepoxid, chlormadinonacetat, clorothiazid, cinnarizin, clonazepam, codein, dexamethason, dicumarol, digoxin, drotaverin, gramicidin, griseofulvin, hexobarbital hydrochlorothiazide, hydrocortison, hydroflumethiazid, ketoproten, lonetil, medazepam, mefrusid, methandrostenolon, sulfaperin, nalidixic acid, nitrazepam, nitrofurantoin, estradiol, papaverin, phenacetin, phenobarbital, phenylbutazon, phenytoin, prednison, reserpin, spironolacton,

streptomycin, sulfamethazin, sulfamethizol, sulfamethoxazol, sulfamethoxydiazin, sulfathiazol, sulfisoxazol, testosteron, tolazamid, tolbutamid, trimethoprim, tyrothricin or mixtures thereof.

The purpose of the above description is to illustrate some configurations and uses of the present invention, without implying any limitation. It will be apparent to those skilled in the art that various modifications and variations may be made in the process and product of the invention without departing from the spirit or scope of the invention.

**What is claimed is**

1. A process for encapsulation of one or more caplets in a capsule comprising the following steps:

a) providing empty first and second capsule shell parts wherein said first and second shell parts are coated with an enteric coating,

b) filling at least one of said capsule parts with the one or more caplets,

c) putting said capsule parts together, and

d) treating the combined capsule parts by cold shrinking,

wherein the one or more caplets have a length greater than the first and second capsule shell parts combined; and wherein the first and second capsule shell parts do not completely cover the one or more caplets.

2. The process of claim 1 wherein each of the first and second capsule shell parts have different colors.

3. The process of claim 1 wherein the first and second capsule shell parts have the same color and the one or more caplets have a different color.

4. A process for the encapsulation of caplets in a capsule to prepare a solid dosage form, comprising the following steps:

a. providing empty first and second capsule shell parts,

b. filling at least one of said capsule parts with one or more caplets,

c. putting said capsule parts together to prepare an encapsulated dosage form, and

d. treating the combined capsule parts by cold

shrinking,

wherein the first and second capsule shell parts do not completely cover the one or more caplets;

wherein the first and second capsule shell parts are either kept after production at humid conditions in the range of from about 40 to 90% relative humidity to retain a moisture content in the range of from about 16 to 18% by weight of the capsule or are re-humidified to said moisture content before feeding into a capsule filling machine and wherein the first capsule shell part is kept under humid conditions within the filling machine at said moisture content during rectifying and assembling with a caplet having a moisture content in the range of from about 0 to about 12 % by weight, the second capsule shell part is processed in the same manner, and the encapsulated dosage form is dried at a relative humidity in the range of from about 20 to about 40% and a temperature in the range of from about 15 to about 60°C and wherein after drying and shrinking of the capsule parts the encapsulated dosage form is film-coated to provide the solid dosage form.

5. The process according to claim 4 wherein the caplets comprise a compressed material.

6. A process according to claim 4, wherein an adhesive is sprayed:

a) onto the surface of the caplet,

b) onto the inner surface of the first and second capsule shell parts, or

c) onto both the surface of the caplet and the inner surface of the first and second capsule shell parts, immediately before assembling.

7. A process according to claim 6, wherein the adhesive is tackidex or an aqueous gelatin solution.

8. The process according to claim 4, wherein the encapsulated dosage form is dried at a temperature in the range of from about 18 to about 25°C.

9. The process according to claim 4, wherein the first and second capsule shell parts are maintained at a relative humidity in the range of from about 60 to about 80% during the steps of feeding into a capsule filling machine, rectifying and assembling.

10. A solid dosage form prepared according to the process of claim 9, wherein the caplet contained in the capsule is uncoated or coated with an acceptable coating for tablet processing.

11. The process according to claim 4, wherein the moisture content of the caplet is in the range of from about 0 to about 6% by weight.

12. The process according to claim 4, wherein the moisture content of the caplet is in the range of from about 0 to about 3% by weight.

13. The process according to claim 4, wherein the caplet has conical ends.

14. A solid dosage form prepared according to the process of claim 1 or 4.

15. Process according to claim 4, wherein the coating is enteric.

16. A solid dosage form according to claim 14 comprising a pharmaceutically active composition.

17. A solid dosage form according to claim 14, comprising an agrochemically active composition.

18. A solid dosage form prepared according to the process of claim 9, wherein the capsule part material comprises a hydrophilic polymer.

19. A solid dosage form prepared according to the process of claim 9, wherein the capsule part material is selected from the group consisting of gelatin, starch, casein, chitosan, soya bean protein, safflower protein, alginates, gellan gum, carrageenan, xanthan gum, phtalated gelatin, succinated gelatin, cellulosephtalate-acetate, polyvinylacetate, hydroxypropyl methylcellulose, polyvinylacetate-phtalate, polymerisates of acrylic or methacrylic esters and mixtures thereof.

20. A solid dosage form according to claim 18, wherein the capsule part material contains pharmaceutically acceptable plasticizers in the range of from about 0 to about 40% based upon the weight of the hydrophilic polymer.

21. A solid dosage form according to claim 20, wherein the plasticizer is selected from the group consisting of polyethylene glycol, glycerol, sorbitol, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate,

1,2-propyleneglycol, mono-, di- or tri-acetates of glycerol and mixtures thereof.

22. A solid dosage form according to claim 18, wherein the capsule part material contains pharmaceutically acceptable lubricants in the range of from about 0 to about 10% based upon the weight of the hydrophilic polymer.

23. A solid dosage form according to claim 22, wherein the lubricant is selected from the group consisting of aluminiumstearate, calciumstearate, magnesiumstearate, tinstearate, talc, sodium lauryl sulfate, lecithins, mineral oils, stearic acid or silicones and mixtures thereof.

24. A solid dosage form according to claim 18, wherein the capsule part material contains pharmaceutically acceptable coloring agents in the range of from about 0 to about 10% based upon the weight of the hydrophilic polymer.

25. A solid dosage form according to claim 24, wherein the coloring agent is selected from the group consisting of azo-, quinophthalone-, triphenylmethane-, xanthene-dyes, iron oxides or hydroxides, titanium dioxide or natural dyes and mixtures thereof.

26. A solid dosage form according to claim 24, wherein the coloring agent is selected from sunset yellow, allura red, amaranth, cochineal red, azogeranine, tartrazine, brilliant black, canthaxanthin, patent blue, fast green, brilliant blue, acid green, erythrosine, quinoline yellow, indigotine, curcumin or carbon black.

27. A solid dosage form according to claim 18, wherein the capsule part material contains pharmaceutically acceptable extenders in the range of from about 0 to about 95% based upon the weight of the hydrophilic polymer.

28. A solid dosage form prepared according to the process of claim 4, wherein the capsule part material contains an extender.

29. A solid dosage form according to claim 28, wherein the extender is selected from the group consisting of sunflower proteins, soybean proteins, cotton seed proteins, peanut proteins, rape seed proteins, lactose, gum arabic, acrylates or methacrylates, cellulose acetyl phthalates, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulosephthalate, hydroxymethylcellulose, polyvinyl pyrrolidone, shellac, bentonite, polyvinyl-acetatephtalate, phthalated gelatin, succinated gelatin, agar agar, hydroxyalkylstarches and mixtures thereof.

30. A solid dosage form according to claim 14 comprising a foodstuff composition.

31. A solid pharmaceutical dosage form prepared according to the process of claim 15.

32. A solid dosage form prepared according to the process of claim 4, comprising a coating selected from the group consisting of cellacephate, polyvinyl acetate phthalate, methacrylic acid polymers, hypromellose phthalate, hydroxyalkyl methyl cellulose phthalates and mixtures thereof.

33. A solid dosage form prepared according to the process of claim 9, wherein the first and second capsule parts have the same or different lengths.

34. A solid dosage form prepared according to the process of claim 4, wherein the first and second capsule parts have the same or different colors.

35. A solid dosage form prepared according to the process of claim 5, wherein the caplet contained in the capsule has a preformed step or groove so that the solid dosage form may be dividing into separate portions.

36. A solid dosage form according to claim 14 comprising a dyestuff composition.