(19) DANMARK

(10) **DK/EP 2946774 T3**

Patent- og Varemærkestyrelsen

(12) Oversættelse af europæisk patentskrift

(51) Int.Cl.: ***A 61 K 9/48 (2006.01)***

(45) Oversættelsen bekendtgjort den: **2020-05-25**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2020-04-22**

(86) Europæisk ansøgning nr.: **14168892.9**

(86) Europæisk indleveringsdag: **2014-05-19**

(87) Den europæiske ansøgnings publiceringsdag: **2015-11-25**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Tillotts Pharma AG, Baslerstrasse 15, 4310 Rheinfelden, Schweiz**

(72) Opfinder: **Bravo Gonzaléz, Roberto Carlos, Lindenstrasse 6, 4102 Binningen, Schweiz**
Oliveira Varum, Felipe José, Efringerstrasse 86, 4057 Basel, Schweiz
Buser, Thomas, Gempenstrasse 19, 4412 Nuglar, Schweiz

(74) Fuldmægtig i Danmark: **Zacco Denmark A/S, Arne Jacobsens Allé 15, 2300 København S, Danmark**

(54) Benævnelse: **Coatede kapsler med modificeret frigivelse**

(56) Fremdragne publikationer:

EP-A1- 0 580 861
WO-A1-03/013480
WO-A1-2013/054285
WO-A2-2004/030652
WO-A2-2012/058695

DESCRIPTION

[0001] The present invention relates to a modified release coated capsule and a process to obtain that capsule as defined by the claims.

[0002] When orally administered, pharmaceutical preparations are generally disintegrated in the stomach. However, when a certain release profile of the pharmaceutical or nutritional ingredient is desired, oral pharmaceutical preparations can be coated with a so-called functional or modified release coating to achieve delayed or controlled release of an active pharmaceutical ingredient (API). Those coatings intended to protect the drug from the acidic environment of the gastric medium, to prevent the drug release in the stomach, or to provide release of an active ingredient to certain and specific section of the gastrointestinal tract (GIT) as e.g. the jejunum, duodenum, ileum, the colon and the rectum are commonly called delayed release coating formulations using enteric polymers.

[0003] In contrast to delayed drug release coatings, controlled release coatings are requested to control the release of the drug over a prolonged period of time. Depending on the drug release mechanism, controlled release approaches are also known in the pharmaceutical area as sustained, extended and prolonged release, respectively. Combinations of these coatings are possible as well.

[0004] Attempts have been made to provide drug-filled hard capsules with a modified release coating. During this development precoatings were found to be necessary because of imperfect adhesion of modified release coatings on hard gelatin capsules (K. S. Murthy et al., Pharm. Tech. 10, 36 (1986)). However, a precoating has the disadvantage of requiring more preparation steps resulting in more preparation time and material to be used, higher energy consumption and higher costs.

[0005] To overcome the disadvantages associated with a precoating, US 4,670,287 discloses a method of film coating hard capsules under a vacuum. However, because of high technical efforts this technique has its limitations in industrial applicability.

[0006] In an alternative approach to overcome the disadvantages of precoatings enteric coated HPMC (hydroxypropyl methylcellulose) capsules were suggested to achieve intestinal targeting (E. T. Cole et al., Int. J. Pharm. 231 (2002) 83-95). Prior to the coating, the capsules were sealed with the LEMs (liquid encapsulation by microspray) process. Enteric coatings with an amount of enteric polymer of at least 6 mg/cm^2 showed no pores or cracks. However, E. T. Cole et al reported that due to the good compatibility between HPMC and the enteric films, variation in coating levels showed little influence on the dissolution profiles.

[0007] Furthermore, liquid filled capsules are frequently sealed either by using a band or using the LEMs technology to avoid leakage during further manufacturing steps, such as coating steps, packaging and so on. For powder or granules filled capsules, normally a band or other seal is not considered, even if a coating process is involved, as there is less risk of capsule opening. To avoid the additional sealing step, US 2011/0033530 suggests coating each capsule half before closing the capsule. It is said that as a result of coating the capsule halves prior to closing the capsule, in the closed state, the enteric coating of the lower part is partially overlapped by the upper part. The overlapped part of the coating is assumed having a sealing function which prevents the penetration of fluid through a possible gap between the lower part and the upper part. However, coating the two halves of a capsule shell prior to closing the capsule is a cumbersome process. Furthermore, there remains the risk that the coating may be damaged during capsule closure. WO 03/013480 discloses Fluoxetin tablets in hard gelatin capsules sealed with a gelatin band to provide a uniform surface and in order to avoid possible ingress of solvent during enteric coating.

[0008] Thus, there is still a need for modified release coated capsules not encountering the above problems. In particular, it would be desirable to provide modified release coated capsules which can be easily prepared at reduced costs using usual manufacturing processes. Furthermore, it would be desirable to provide a modified release coated capsule which can be prepared by the same method and with the same coating materials independent of the capsule shell material. Additionally, it would be desirable to provide a modified release coated capsule with a drug release profile which can be easily tailored according to the requirements.

[0009] It has now surprisingly been found that the above and other problems can be solved by applying a relatively thin modified release coating onto the capsule shell of a capsule comprising a band seal as defined by the claims.

[0010] The present invention therefore relates to a capsule comprising a band seal and a modified release coating, characterized in that the modified release coating comprises a film forming agent in an amount 4 to 7mg/cm^2 of the modified release coating and wherein the band seal is a gelatin band sealing between body and cap of the capsule.

[0011] While applicants do not wish to be bound to any theory it is believed that the imperfect adhesion of enteric coatings on capsule shells might at least partly be associated to the gap between the body and the cap of the capsule. At this gap, mechanical stress might occur leading to possible cracks in the coating and reduced adhesion of the coating. However, it turned out that neither the prior art recommended sub-coating nor sealing the gap by LEMs technology, nor the combination of both techniques, provided a satisfactory solution to the above problems. On the other hand, sealing the gap with a band surprisingly allowed to directly apply the enteric coating onto the capsule shell without any precoat between the capsule shell and the enteric coating. Furthermore, it was found that sealing the gap by a band allows the reduction of the amount of enteric polymer required for obtaining the same or even improved level of enteric coating compared to prior art coatings. This has the advantage that manufacturing costs are not only reduced by omitting the precoat, but can additionally be reduced by reducing the amount of enteric polymer. This reduction has the further advantage that the thickness of the enteric coating can be reduced thereby reducing the overall size and weight of the final capsule. Additionally, based on this invention resistance to release under simulated stomach conditions can be achieved already with very thin enteric coating films. In this context, the invention is of further advantage for tailoring drug release profile by adjusting the coating thickness according to the desired area of release within the gastrointestinal tract.

[0012] The capsule of the present invention in particular is for oral administration, such as for oral administration of a pharmaceutical or nutritional ingredient.

[0013] The size of the capsule is not particularly limited and can be any usual size, such as 000, 00, 0, 1, 2, 3, 4 or 5.

[0014] The capsule shell can be of any suitable material, such as gelatin, HPMC, pullulan or polyvinyl alcohol (PVA). Hard gelatin capsules are preferred.

[0015] Capsules and in particular hard capsules are usually prepared by closing a capsule body with a cap. According to the invention, the gap between the body and the cap of the capsule is sealed with gelatin band.

[0016] The modified release coating of the capsule according to the invention may be a delayed release coating, such as an enteric coating, or a controlled release coating. Combinations of these coatings are also possible.

[0017] The function of the coating is usually attained by a film forming agent, in particular a film forming polymer. Any usual film forming agent known to the person skilled in the art for forming the desired coating may be used.

[0018] For an enteric coating the film forming agent usually comprises a compound which is insoluble in the gastrointestinal juice at a pH of below 5 and which is soluble in the intestinal juice at a pH at or above 5. Thus, this film forming agent dissolves in a pH dependent manner. The film forming agent has a pH threshold which is the pH below which it is insoluble and at or above which it is soluble. The pH of the surrounding medium triggers the dissolution of the film forming agent. Thus, none (or essentially none) of the film forming agent dissolves below the pH threshold. Once the pH of the surrounding medium reaches (or exceeds) the pH threshold, the film forming agent becomes soluble. By "insoluble" it is understood that 1 g of the film forming agent requires more than 10,000 ml of solvent (surrounding medium) to dissolve at a given pH. By "soluble", it is understood that 1 g of the film forming agent requires less than 10,000 ml, preferably less than 5,000 ml, more preferably less than 1,000 ml, even more preferably less than 100 ml or 10 ml of solvent to dissolve at a given pH. "Surrounding medium" means the medium in the gastrointestinal tract, such as the gastric juice or intestinal juice. Alternatively, the surrounding medium may be an in vitro equivalent of the medium in the gastrointestinal tract.

[0019] The normal pH of gastric juice is usually in the range of 1 to 3. The film forming agent for intestinal, such as colon targeting should thus be insoluble below pH 5 and should be soluble at or above pH 5. The film forming agent therefore is usually insoluble in gastric juice.

Such material may be referred to as an "enteric" material. The pH of intestinal juice gradually increases to about 7 to 8 along the small intestine. A film forming agent for intestinal targeting therefore becomes soluble in the terminal ileum/colon and allows release of e.g. the active agent from the capsule. The film forming agent preferably has a pH threshold of 6.5, more preferably of 7.

[0020] Examples of suitable film forming agents for intestinal targeting and in particular for the preparation of the coating surrounding the capsule are acrylate polymers, cellulose polymers and polyvinyl-based polymers, or other polymers. Examples of suitable cellulose polymers include cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate and carboxymethylethyl cellulose acetate butyrate. Examples of suitable polyvinyl-based polymers include polyvinyl acetate phthalate.

[0021] In a preferred embodiment the material for intestinal targeting is a co-polymer of a (meth)acrylic acid and a (meth)acrylic acid C_{1-4} alkyl ester, for instance, a co-polymer of methacrylic acid and methacrylic acid methyl ester. Suitable examples of such co-polymers are usually anionic. Furthermore, these co-polymers usually are not sustained release polymethacrylates. The ratio of carboxylic acid groups to methylester groups in these co-polymers determines the pH at which the copolymer is soluble. The acid:ester ratio may be from about 2:1 to about 1:3, e.g. about 1:1 or, about 1:2. The molecular weight of such anionic co-polymers is usually from about 120,000 to 150,000, preferably about 135,000.

[0022] Known anionic poly(methycrylic acid/methyl methacrylate) co-polymers include Eudragit® L (pH threshold about 6.0), Eudragit® S (pH threshold about 7) and Eudragit® FS (pH threshold about 7). Eudragit® L 100-55 which is a copolymer of methacrylic acid and ethylacetate and which has a pH threshold of about 5.5 is also suitable. The Eudragit® copolymers can be obtained from Evonik.

[0023] In addition or alternatively to the above described compounds having a pH threshold the film forming agent for intestinal, such as colon targeting may comprise a compound which is susceptible to attack by colonic bacteria, such as polysaccharides. Suitable polysaccharides are for example starch, amylose, amylopectine, chitosan, chondroitine sulfate, cyclodextrine, dextrane, pullulan, carrageenan, scleroglucan, chitin, curdulan and levan.

[0024] Alternatively or additionally, the modified release coating can be a controlled release coating. These coatings are able to provide release of the active substance after a predetermined time after administration or a controlled release over time.

[0025] Galenical principles used to achieve the different release forms typically reduce the dissolution of the active ingredient; establish diffusion barriers including osmotic systems and erosion systems. With regards to functional coatings the focus is on establishment of diffusion barriers. Diffusion barriers can be established by membranes controlling the diffusion being permeable or not; by using a controlling principle as pH or natural degradation during the GIT transit; by using a controlled release matrix releasing an active ingredient contained in the matrix controlled by diffusion; by using a membrane controlled osmotic effect, or by using a diffusion membrane eroding after degradation.

[0026] Suitable polymers for diffusion membranes that typically are gastric resistant are cellulose derivatives as cellulose acetate phthalate (CAP), Hydroxypropyl methylcellulose phthalate (HPMCP), polymethacrylates and polyvinylacetate phthalate.

[0027] Suitable polymers for a controlled release matrix coating are digestible, long chain (C8-C50 , especially C12-C40), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, polyalkylene glycols, hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials, and in general polymers that are insoluble over the entire pH-range, and combinations thereof.

[0028] Further suitable polymers are carboxy methylethylcellulose (CMEC) or ethylcellulose which provide a release by diffusion but are not entirely gastric resistant. Further examples include polymethacrylate sustained release polymers, such as Eudragit® RS, RL and NM.

[0029] Suitable polymers for an erosion system among others are cellulose ether derivatives and degradable natural polymers as polysaccharides.

[0030] With the materials mentioned above a person skilled in the art is able to tailor the composition of the coatings in a way that the release of the active ingredient starts, or takes place, specifically at the targeted site of the GIT. This can, among others, be achieved by the means of introducing pores to make the membrane permeable, or more permeable, by including pore formers and/or further excipients; by introducing further excipients for erosion as e.g. using degradable natural polymers as polysaccharides or synthetic polymers that dissolve at a certain pH.

[0031] Mixtures of two or more film forming agents may be used as appropriate.

[0032] Optionally, the modified release coating may additionally comprise conventional excipients, such as plasticizers for film formation (for example triethylcitrate), anti-tacking agents (such as glyceryl monostearate), colorants, pigments, solublilizers, dispersion agents and surfactants. For example such excipients may be included in amounts known to the skilled person of e.g. up to 30 % by weight of the total weight of the coating.

[0033] A particular advantage of the present invention is that the amount of film forming agent can be lower than usual. In fact, it was found that a modified release coating comprising a low amount of film forming agent being applied onto the capsule shell (with a band seal) with or without any precoat shows improved adhesion and can even impart improved dissolution properties to the capsule compared to a modified release coating comprising a higher amount of film forming agent. It was surprisingly found that this beneficial effect does not occur if the capsule is sealed using an alternative method, namely the LEMs technology. As demonstrated by the present comparative examples either sealing the capsules by LEMs technology alone or in combination with a precoat does not provide satisfactory acid resistance to the capsules even if a high amount of enteric coating is applied.

[0034] Consequently, the present invention does not only save material and, thus, costs, but constitutes a surprising beneficial technical effect over prior art coated capsules. Thus, the film forming agent according to the invention is present in an amount of 4 to 7 mg each amount per cm^2 of the modified release coating.

[0035] The capsule according to the invention may comprise one or more additional coatings, preferably above the modified release coating. In this context, "above" means that the additional coating may be coated on the modified release coating. The additional coating may also be between the capsule shell and the coating, although it is preferred that there is no coating and in particular no precoat between the capsule shell and the modified release coating. The additional coating may for example be present for increasing the stability of the capsule against humidity or for increasing the visual appearance of the capsule.

[0036] Any of the above coatings including the modified release coating may comprise one or more pharmaceutically active ingredients.

[0037] The capsule according to the invention may be filled with a liquid, semi-solid and/or solid material, such as a solution, dispersion, paste, gel, wax, powder or granules. The material may comprise a nutritional ingredient and/or an active pharmaceutical ingredient either alone or in combination with usual excipients. Capsules filled with liquid or semi-solid material are particularly preferred. Most preferred are capsules filled with liquid material. The present invention further relates to a process to obtain the above described capsule comprising the steps of optionally filling the capsule body with a liquid, semi-solid and/or solid material, closing the capsule with a cap, sealing the gap between body and cap with a gelatin band and applying a modified release coating onto the capsule shell such that the modified release coating comprises a film forming agent in an amount of 4 to 7 mg/cm^2 of the modified release coating.

[0038] Coating can be carried out by any usual method known to the person skilled in the art. For example, a film comprising the film forming agent and optional excipients can be applied as an organic solution, as an aqueous-organic coating emulsion, as an aqueous-organic coating solution, as an aqueous dispersion or as a neutralized aqueous solution. As organic liquids, alcohols and in particular ethanol may be used.

[0039] For example, the solution, emulsion or dispersion of the film forming agent and optionally excipients may be sprayed onto the capsule in an amount required for providing the desired amount of dry film forming agent per cm^2 of the final modified release coating.

Figure 1 shows capsules according to example 1 and according to comparative example 1A after immersion into acid solution.

Figure 2 shows capsules according to comparative example 1B after immersion into acid solution.

Figure 3 shows the release profiles of the capsules according to example 1 and according to comparative example 1A.

Figure 4 shows the release profiles of the capsules according to example 1 and according to comparative example 1A (with a higher amount of coating).

Figure 5 shows capsules according to example 2 and capsules according to comparative example 2A after immersion into acid solution.

Figure 6 shows capsules according to comparative example 2B after immersion into acid solution.

Figure 7 shows capsules according to example 3 and capsules according to comparative example 3 after immersion into acid solution.

Figure 8 shows capsules according to example 3 and capsules according to comparative example 3 after immersion into acid solution.

Figure 9 shows capsules according to comparative example 3 after immersion into acid solution.

Figure 10 shows capsules according to example 4 and capsules according comparative example 4 after immersion into acid solution.

Figure 11 shows dissolution profiles of capsules according to example 3 and of capsules according to comparative example 3.

[0040] The invention will now be further illustrated by the following examples which are not intended to be construed as being limiting.

Example 1

[0041] Size 1 hard gelatin capsules were filled with a model powder formulation containing methylene blue as marker. The capsules were closed and sealed with a gelatin band. Without any precoat, the capsules were then coated with aqueous Eudragit L30D-55 in amounts of 4 mg/cm^2 and 6 mg/cm^2, respectively, each relating to the dry amount of film forming agent per cm^2 of the final coating.

Comparative example 1A

[0042] Capsules were manufactured in the same manner as in example 1 but without sealing the capsules with the gelatin band prior to the enteric coating.

Comparative example 1B

[0043] Capsules were manufactured in the same manner as in comparative example 1A but with 3 mg/cm^2 HPMC precoat between the gelatin capsule shell and the Eudragit L30D-55 enteric coating.

Evaluation of capsules according to example 1 and comparative examples 1A and 1B

[0044] The acid resistance of the capsules obtained in example 1 and comparative examples 1A and 1B was tested by immersing the capsules for 120 minutes in 0.1 N HCl solution. After the capsules were recovered from the solution, they were visually controlled. Due to the use of methylene blue as marker in the model powder formulation filled into the capsules even small leakages could be easily observed.

[0045] The results of this test are shown in figures 1 and 2. Figure 1 shows the capsules of example 1 being coated with 4 mg/cm^2 of the film forming agent after recovering from the acid solution. No deterioration of the capsules or leakage was observed.

[0046] In contrast thereto, the capsules of comparative example 1A showed strong deterioration and leakage (capsules turned blue) after immersion in the acid solution although they were coated with three-times the amount of enteric coating compared to example 1, namely 12 mg/cm^2 of film forming agent. This comparative example demonstrates that sealing the capsules with a band allows the use of much lower amounts of enteric coating material for obtaining capsules having even improved properties.

[0047] The capsules of comparative example 1B after immersion into the acid solution are shown in figure 2. These capsules were prepared according to usual prior art methods using a HPMC precoat and being enterically coated with 6 mg/cm^2 of the film forming agent. Despite the precoat the capsules showed strong deterioration. Furthermore, the capsules turned blue indicating that the marker substance leaked out of the capsules. Again, the banded capsules without any precoat according to the invention (example 1) exhibit an improved acid resistance although they are coated with a lower amount of enteric coating.

[0048] Furthermore, the release profiles of the capsules were measured using pH 6.8 Hanks buffer. *In vitro* dissolution studies were performed on a USP type II apparatus using a paddle speed of 50 rpm and a media temperature of 37 ± 0.5 °C. Capsules were first tested in 900 ml 0.1 N HCl for 2 hours followed by 8 or 10 hours in Hanks buffer (pH 6.8). The pH of the buffer was stabilized at 6.8 ± 0.05 by continuously sparging with 5% CO_2 / 95% O_2. Methylene blue absorbance measurements were taken at 5 minute intervals, with an absorbance wavelength of 663 nm. The composition per litre of Hanks buffer was 0.06 g of KH_2PO_4, 0.06 g $Na_2HPO_4.2H_2O$, 8.0 g NaCl, 0.4 g KCl, 0.2 g $MgSO_4.7H_2O$, 0.139 g $CaCl_2.2H_2O$ and 0.350 g $NaHCO_3$.

[0049] The release profiles of the capsules according to example 1 (banded capsules) and of the capsules of comparative example 1A (non-banded capsules) are shown in figure 3. Both capsules were coated with 4 mg/cm^2 of the film forming agent. As expected from the above acid resistance test, release of the model active pharmaceutical ingredient (API) from the non-banded capsules according to comparative example 1A started already under the simulated stomach conditions in the 0.1 N HCl solution. Furthermore, the non-banded capsules did not release all of the API even after prolonged time in Hanks buffer. In contrast thereto, the capsules according to the invention (banded; example 1) did not release any of the API under the simulated stomach conditions but released their complete API content after a lag time of about 20 minutes in the bicarbonate buffer.

[0050] Figure 4 shows a comparison of the release profiles of banded capsules according to example 1 coated with 4 mg/cm^2 of the film forming agent and non-banded capsules according to example 1A being coated with as much as 16 mg/cm^2 of the film forming agent. While the significant increase in the amount of enteric coating suppressed the premature release of the API under simulated stomach conditions, the API was released at a later lag time, which could results in a too late release in vivo leading to lower oral bioavailability of drugs preferably absorbed in the proximal small intestine. Only up to about 60 % of API was released even after prolonged time in the bicarbonate buffer solution.

Example 2

[0051] Capsules were prepared in the same manner as in example 1 but using organic Eudragit L100-55 for preparing the enteric coating.

Comparative example 2A

[0052] Capsules were prepared in the same manner as in example 2 but without sealing the capsules with the gelatin band prior to the enteric coating.

Comparative example 2B

[0053] Capsules were prepared in the same manner as in comparative example 2A but using a precoat of 3 mg/cm^2 of HPMC prior to the enteric coating.

Evaluation of capsules according to example 2 and comparative examples 2A and 2B

[0054] The acid resistance of the capsules obtained in example 2 and comparative examples 2A and 2B were tested as described above with respect to the capsules of example 1 and comparative examples 1A and 1B. The results are shown in figures 5 and 6 for the capsules obtained in example 2 being coated with 4 mg/cm^2 of the film forming agent (figure 5), the capsules obtained in comparative example 2A being coated with 16 mg/cm^2 of the film forming agent (figure 5) and the capsules obtained in comparative example 2B being coated with a precoat and with 4 mg/cm^2 of the film forming agent (figure 6).

[0055] As can be seen, the capsules according to the invention (example 2) exhibited no deterioration or leakage while the capsules being coated with even four times the amount of enteric coating obtained in comparative example 2A and the capsules being coated with the same amount of enteric coating as the capsules of example 2 but additionally comprising a precoat obtained in comparative example 2B exhibited strong deterioration and leakage.

Example 3

[0056] Capsules were manufactured in the same manner as in example 1 but being filled with a model liquid formulation containing methylene blue as marker.

Comparative example 3

[0057] Capsules were prepared in the same manner as in example 3 but being sealed with the LEMs technology instead of the sealing band.

Example 4

[0058] Capsules were prepared in the same manner as in example 3 but being precoated with 3 mg/cm^2 of HPMC prior to the coating with the enteric coating.

Comparative example 4

[0059] Capsules were prepared in the same manner as in comparative example 3 but being precoated with 3 mg/cm^2 of HPMC prior to the coating with the enteric coating.

Evaluation of capsules according to examples 3 and 4 and comparative examples 3 and 4

[0060] The acid resistance of the capsules obtained in example 3 and 4 and comparative examples 3 and 4 was tested as described above for the capsules of example 1 and comparative examples 1A and 1B. The results are shown in figures 7 to 10. While the capsules according to the invention (example 3) being coated with 4 mg/cm^2 (figure 7) and 6 mg/cm^2 (figure 8) of the film forming agent exhibited no deterioration or leakage (the red color of the capsules remained unchanged), the capsules of comparative example 3 being sealed with the LEMs technology instead of the sealing band and being coated with the same amount (4 mg/cm^2) (figure 7), 6 mg/cm^2 (figure 8), 10 mg/cm^2 (figure 9) and even 16 mg/cm^2 (figure 9) of the film forming agent showed strong leakage of the blue marker agent (as observed by the blue color of the capsules after immersion).

[0061] Furthermore, the capsules according to the invention (example 4) being coated with 3 mg/cm^2 HPMC precoat and 4 mg/cm^2 enteric coating exhibited no deterioration or leakage (figure 10; capsules remained red). However, the capsules of comparative example 4 being sealed with the LEMs technology instead of the sealing band and being coated with as much as 10 mg/cm^2 of the enteric film forming agent and additionally comprising the precoat also showed leakage of the marker agent (as observed by the blue color of the capsules after immersion).

[0062] Additionally, the release profiles of the capsules being coated with 4 mg/cm^2 of the film forming agent obtained in example 3 and comparative example 3 were measured. The results are shown in figure 11. While the capsules according to the invention show no significant release during immersion in 0.1 N HCl for 120 minutes and complete release after a lag time of about 37 minutes in Hanks buffer, the capsules of comparative example 3 being sealed with the LEMs technology instead of the sealing band showed significant release already during immersion in 0.1 N HCl.

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- US4670287A [0005]
- US20110033530A [0007]
- WO03013480A [0007]

Non-patent literature cited in the description

- **K. S. MURTHY et al.**Pharm. Tech., 1986, vol. 10, 36- [0004]
- **E. T. COLE et al.**Int. J. Pharm., 2002, vol. 231, 83-95 [0006]

P a t e n t k r a v

1. Kapsel omfattende en båndtætning og en coating med modificeret frigivelse, **kendetegnet ved at** coatingen med modificeret frigivelse omfatter et filmdannende middel i en mængde på 4 mg/cm^2 til 7 mg/cm^2 af coatingen med modificeret frigivelse, og hvor båndtætningen er en gelatinebåndtætning mellem kapslens krop og hætte.

2. Kapsel ifølge krav 1, hvor kapselskallen er en gelatineskal, hydroxypropylmethylcelluloseskal, en pullulanskal eller en PVA-baseret skal.

3. Kapsel ifølge et hvilket som helst af de foregående krav, hvor coatingen med modificeret frigivelse er en coating med forsinket frigivelse og/eller en coating med kontrolleret frigivelse.

4. Kapsel ifølge krav 3, hvor coatingen med modificeret frigivelse er en enterisk coating, og det filmdannende middel er udvalgt fra gruppen bestående af acrylatpolymerer, cellulosepolymerer, polyvinyl-baserede polymerer og blandinger deraf.

5. Kapsel ifølge krav 4, hvor det filmdannende middel er udvalgt fra gruppen bestående af co-polymerer af (meth)acrylsyre og en (meth)acrylsyre-C_{1-4}-alkylester, celluloseacetatphthalat, celluloseacetattrimellitat, celluloseacetatsuccinat, hydroxypropylmethylcellulosephthalat, hydroxypropylmethylcelluloseacetatsuccinat, carboxymethylethylcelluloseacetatbutyrat, polyvinylacetatphthalat og blandinger deraf.

6. Kapsel ifølge et hvilket som helst af de foregående krav, hvor coatingen med modificeret frigivelse omfatter mindst en excipiens udvalgt fra gruppen bestående af blødgørere, antiklæbemidler, farvestoffer, pigmenter, solubiliseringsmidler, dispergeringsmidler og overfladeaktive stoffer.

7. Kapsel ifølge et hvilket som helst af de foregående krav, yderligere omfattende en eller flere yderligere coatings.

8. kapsel ifølge et hvilket som helst af de foregående krav, hvor kapslen ikke omfatter et mellemlag mellem kapselskallen og coatingen med modificeret frigivelse.

9. Kapsel ifølge et hvilket som helst af de foregående krav, hvor kapslen er fyldt med et flydende, halvflydende og/eller fast materiale.

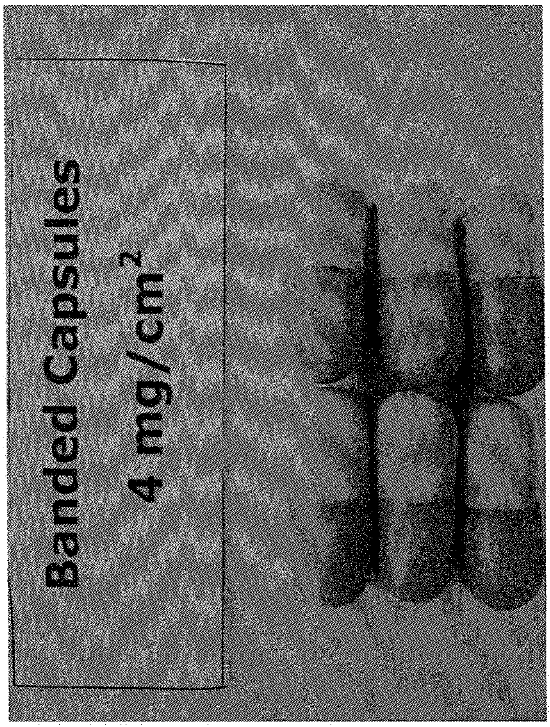
10. Kapsel ifølge krav 9, hvor kapslen er fyldt med et flydende materiale, og det flydende materiale omfatter en næringsbestanddel og/eller en aktiv farmaceutisk bestanddel.

11. Fremgangsmåde til opnåelse af en kapsel ifølge et hvilket som helst af de foregående krav, omfattende trinnene eventuelt at fylde kapselkroppen med et flydende og/eller fast materiale, at lukke kapslen med en hætte, at tætne mellemrummet mellem krop og hætte med et gelatinebånd og at påføre en coating med modificeret frigivelse på kapselskallen, således at coatingen med modificeret frigivelse omfatter et filmdannende middel i en mængde på 4 til 7 mg/cm^2 af coatingen med modificeret frigivelse.

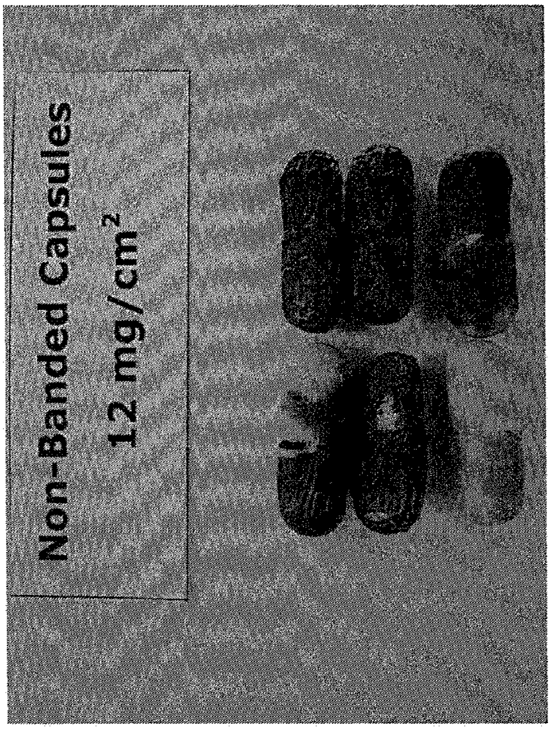
12. Fremgangsmåde ifølge krav 11, hvor coatingen med modificeret frigivelse påføres på kapselskallen i form af en vandig eller ikke-vandig flydende sammensætning omfattende det filmdannende middel.

DRAWINGS

Figure 1

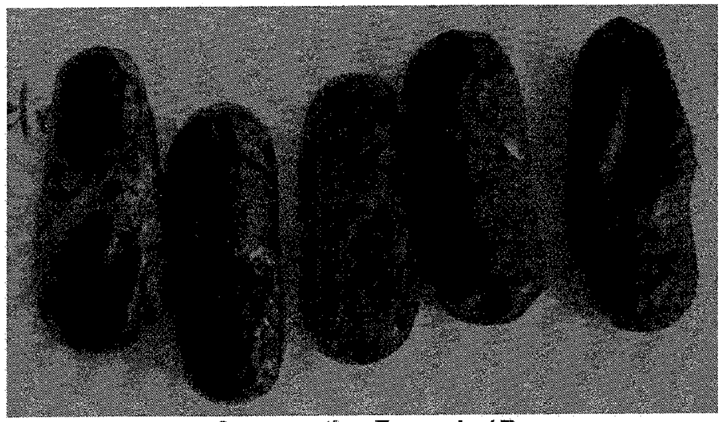


Example 1



Comparative Example 1A

Figure 2



Comparative Example 1B

Figure 3

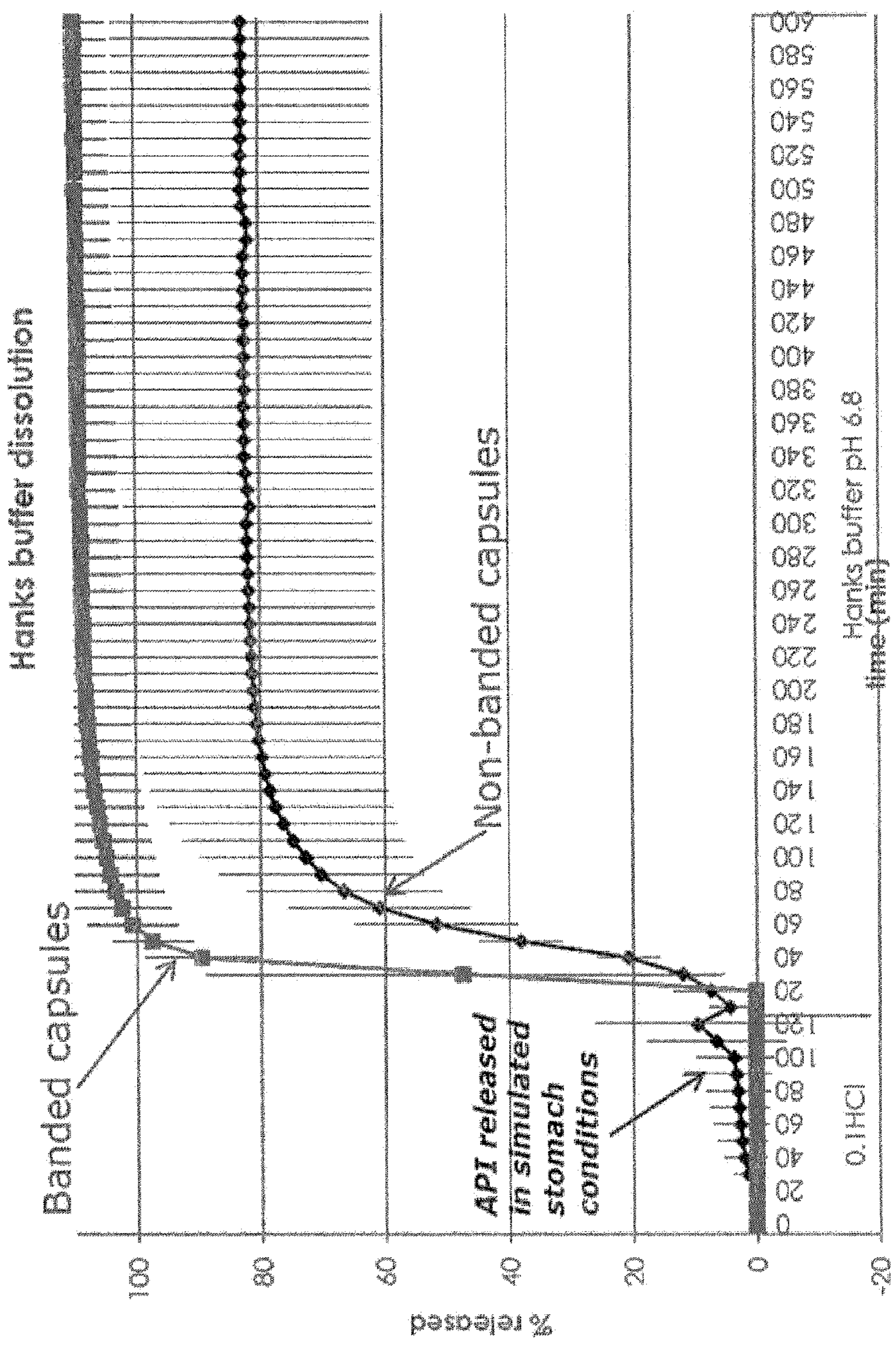

Hanks buffer dissolution
Banded capsules
Non-banded capsules
API released in simulated stomach conditions
% released
0. 1HCl
Hanks buffer pH 6.8
time (min)

Figure 4

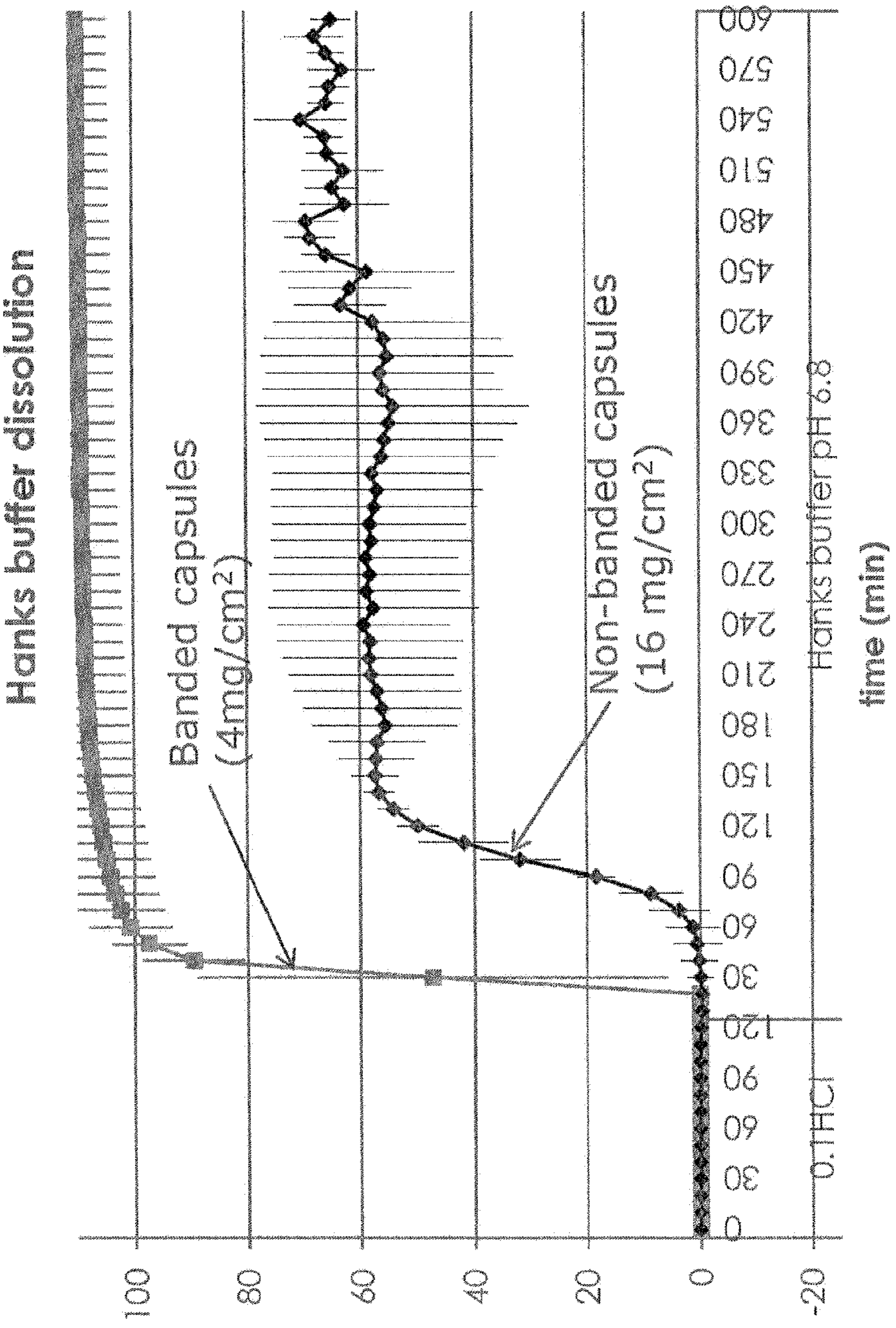
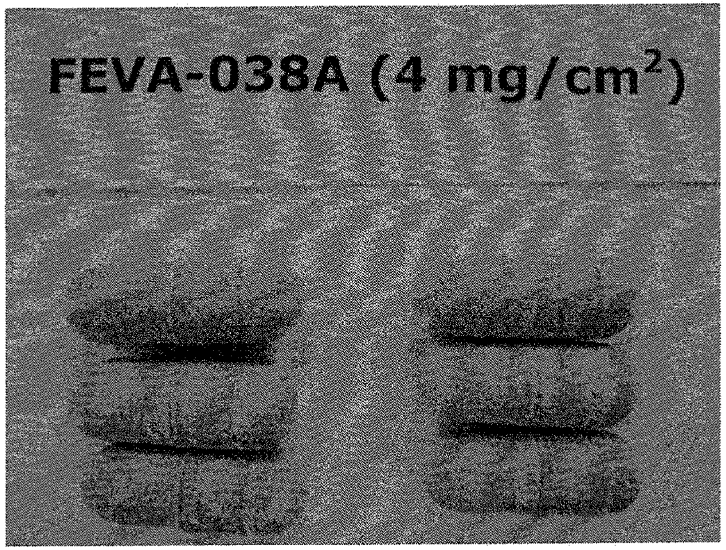
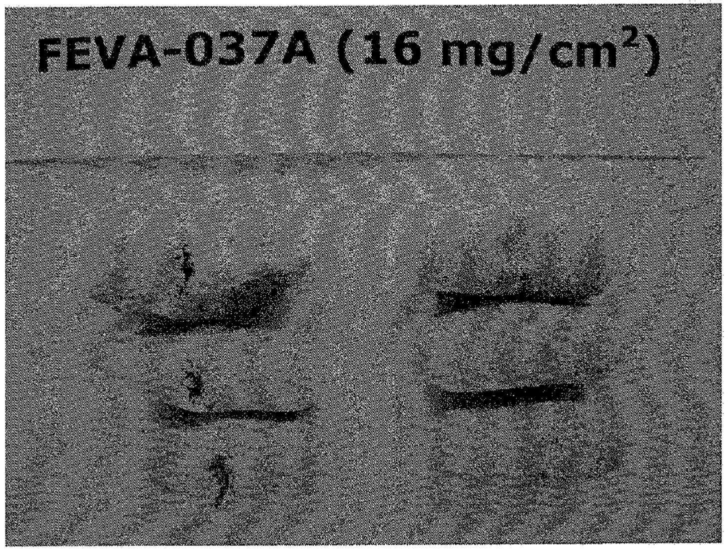

Hanks buffer dissolution
Banded capsules
(4mg/cm²)
Non-banded capsules
(16 mg/cm²)
% released
100
80
60
40
20
0
-20
0.1HCl
Hanks buffer pH 6.8
0
30
60
90
120
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
510
540
570
600
time (min)

Figure 5

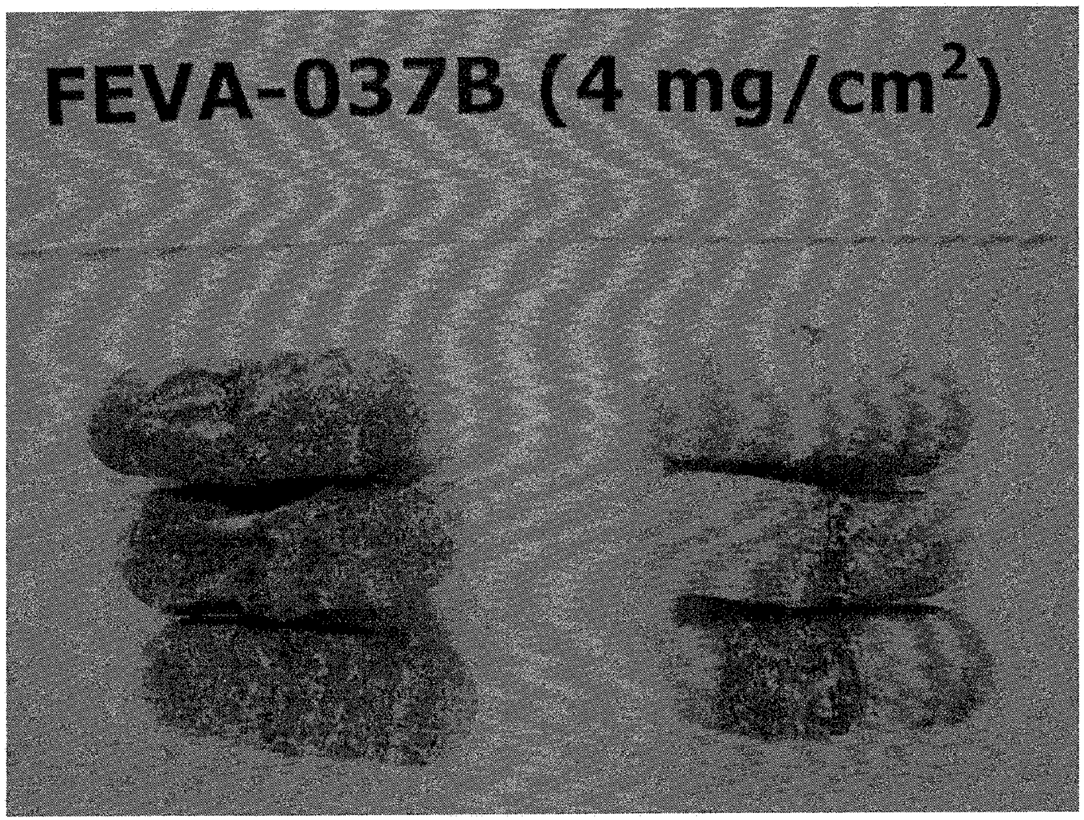


Example 2



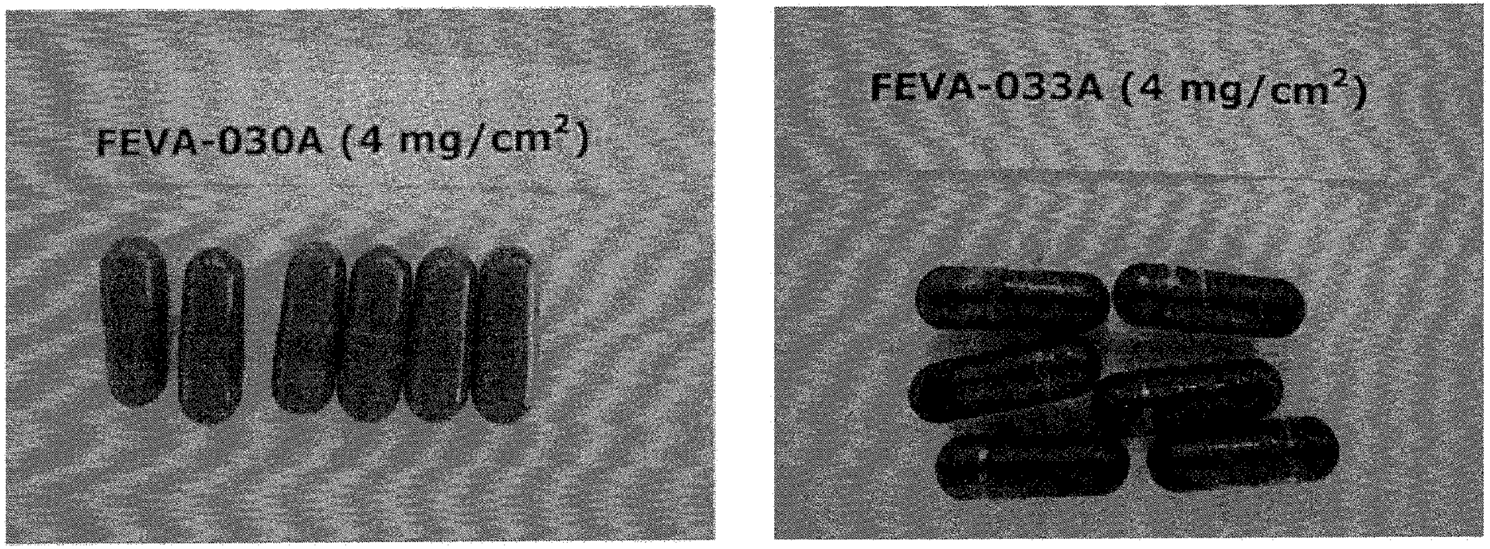
Comparative Example 2A

Figure 6



Comparative Example 2B

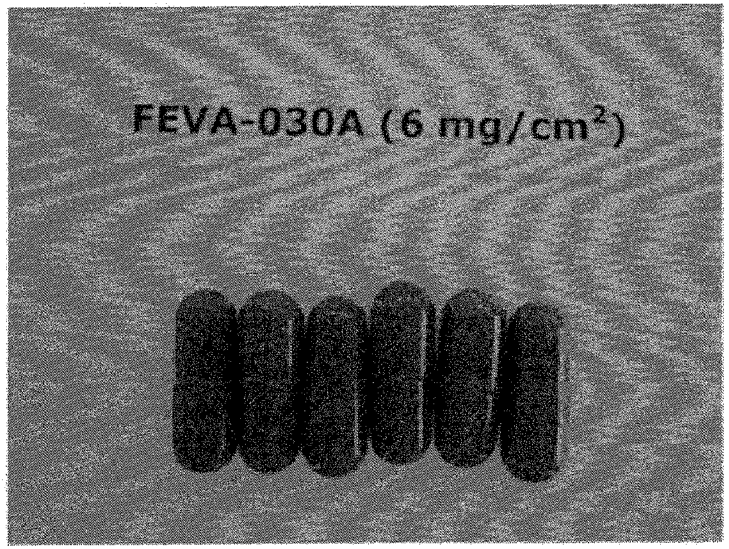
Figure 7



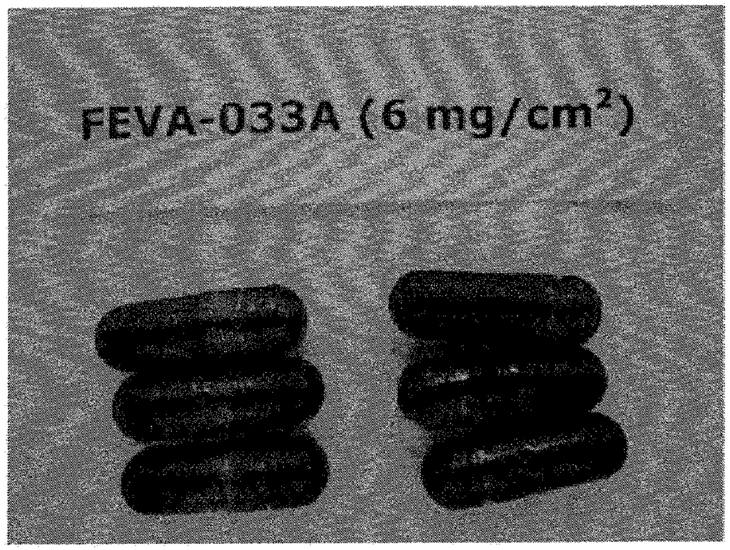
Example 3

Comparative Example 3

Figure 8

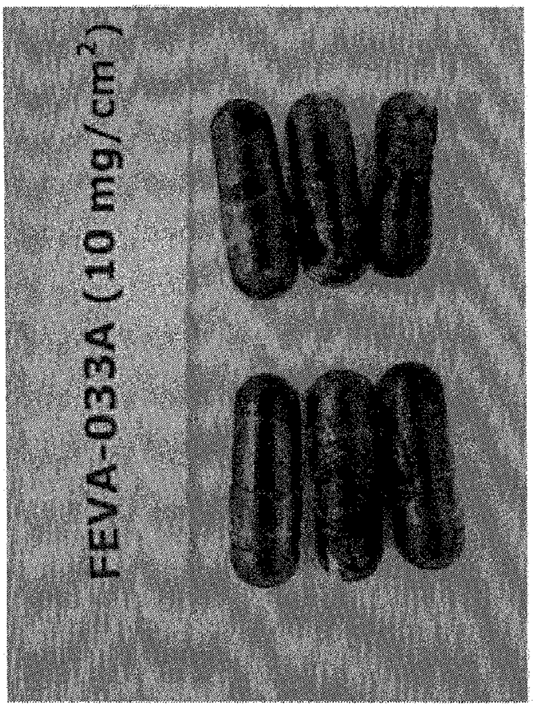


Example 3

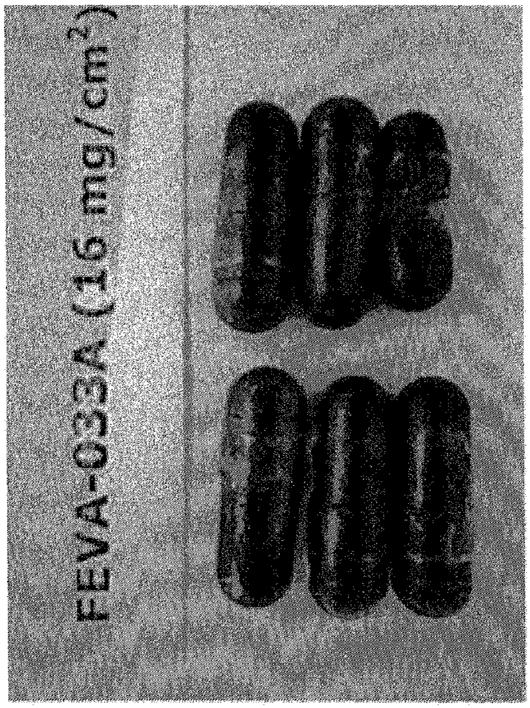


Comparative Example 3

Figure 9

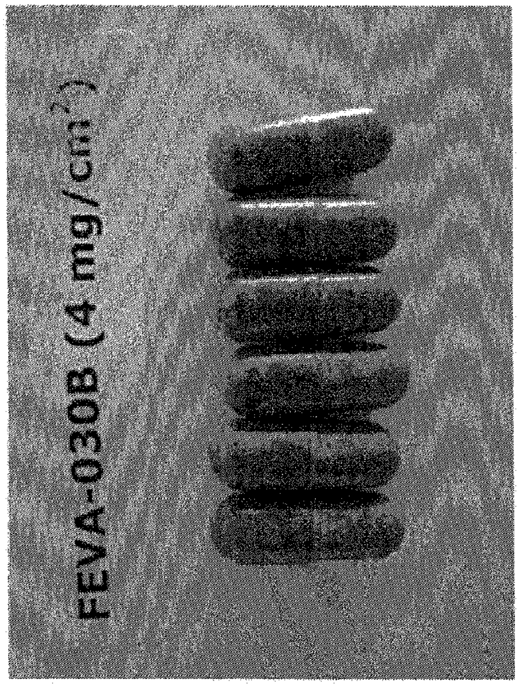


Comparative Example 3

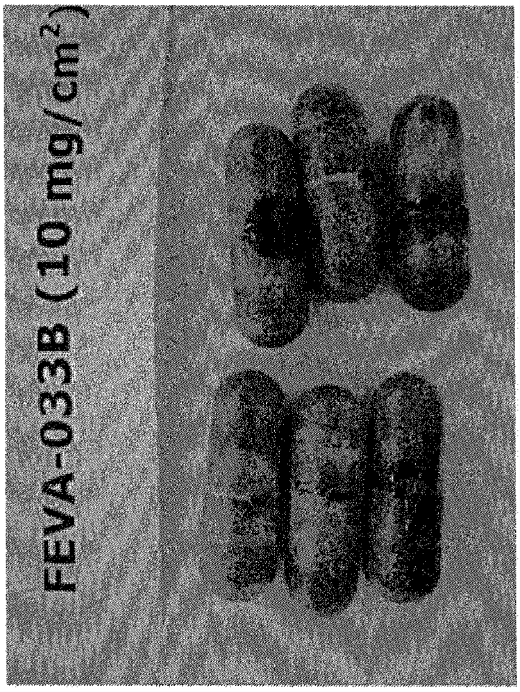


Comparative Example 3

Figure 10

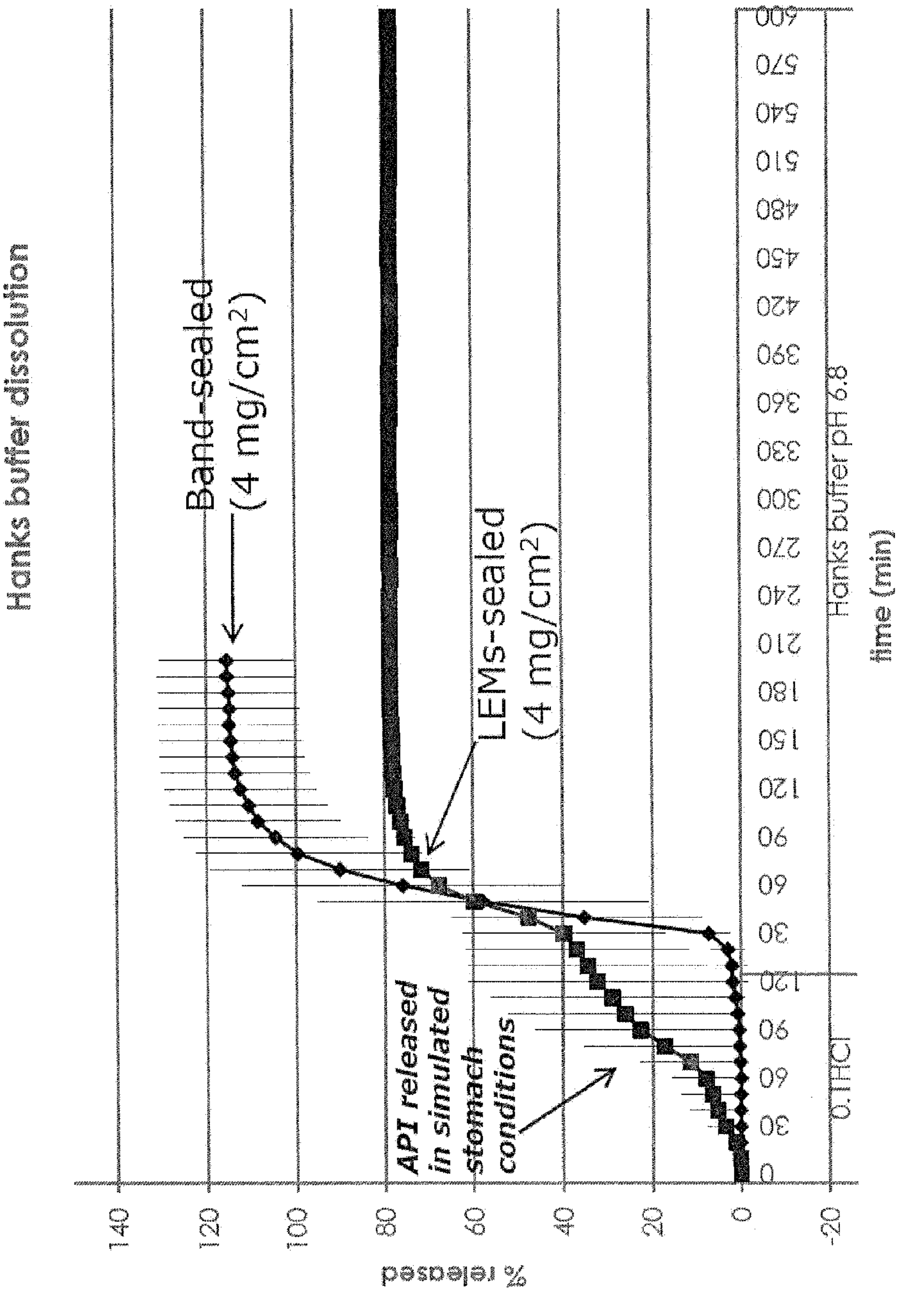


Example 4



Comparative Example 4

Figure 11


Hanks buffer dissolution
Band-sealed
(4 mg/cm2)
LEMs-sealed
(4 mg/cm2)
API released
in simulated
stomach
conditions
% released
140
120
100
80
60
40
20
0
-20
0
30
60
90
120
30
60
90
120
150
180
210
240
270
300
330
360
390
420
450
480
510
540
570
600
0.1HCl
Hanks buffer pH 6.8
time (min)