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Pulsatile drug release control using hydrogels

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Abstract

Current research in the field of drug delivery devices, by which pulsed and/or pulsatile release is achieved, has been intensified. In this article several types of drug delivery systems using hydrogels are discussed that showed pulsed and/or pulsatile drug delivery characteristics. As is frequently found in the living body, many vital functions are regulated by pulsed or transient release of bioactive substances at a specific site and time. Thus it is important to develop new drug delivery devices to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of the living systems, while minimizing undesired side effects. Special attention has been given to the thermally responsive poly(N-isopropylacrylamide) and its derivative hydrogels. Thermal stimuli-regulated pulsed drug release is established through the design of drug delivery devices, hydrogels, and micelles. Development of modified alginate gel beads with pulsed drug delivery characteristic is also described in this article. ' 2002 Elsevier Science BY. All rights reserved.

Keywords: Intelligent materials; Stimuli-responsive; Hydrogel; Regulated drug release; Time-programmed drug release; Release onset time; Lag time control; Pulsed drug release

Contents

1. Introduction.. 54
2. Time-controlled pulsatile release systems..55
3. Stimuli-induced pulsatile release..60 3.1. Temperature-induced pulsatile release...60 3.1.1. Thermoresponsive hydrogel systems..60
3.1.2. Thermoresponsive polymeric micelle systems..62
3.2. Chemical stimuli-induced pulsatile release...65 3.2.1. Glucose-responsive insulin release devices...65
3.2.2. Inflammation-induced pulsatile release..67
3.2.3, Drug release from intelligent gels responding to antibody concentration...68
3.3. Electric stimuli-responsive pulsatile release..68 3.4. Other physical/ chemical stimuli for pulsatile release..69
4. Pulsed macromolecular drug release from Ca’ -alginate gel beads..70
5. Conclusion...74 References..74

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A. Kikuchi, T. Okano / Advanced Drug Delivery Reviews 54 (2002) 53-77

In this article, several approaches for the delivery of drugs in pulsatile manner, mainly using polymeric carriers, will be reviewed. Our recent research using Ca talginate gel beads for the temporal delivery of macromolecular drugs is also presented here.

2. Time-controlled pulsatile release systems

As is often seen in human beings, hormone release is regulated with a certain rhythm, depending on the hormone type, in the order of several hours-, days, or months. Similarly, the action of a certain drug should coincide with the proper site and time for optimal effect. Therefore, the development of a time-con-trolled release system is desired for the treatment of patients.
Niwa et al. [8] prepared a novel capsule made from ethyl cellulose for the time-controlled release of drugs in the colon. Initially, the ethyl cellulose capsule was prepared using a gelatin capsule as a parent mold and then by coating the gelatin capsule with ethyl cellulose, followed by the dissolution of the gelatin in water. The thickness of the ethyl cellulose capsule body was varied and the effect of wall thickness on the release of drugs in the capsules was investigated. Ethyl cellulose capsules contained a large number of mechanically made micropores (400 pm) at the bottom. Also located in the bottom of the capsule body was a swellable layer, consisting of low-substituted hydroxypropylcellulose. Above the swellable layer was the drug reservoir, which contained a mixture of the model drug, fluorescein, and a bulking agent, such as lactose or starch. The capsule was thus capped and sealed with a concen-trated ethyl cellulose solution. After administration of drug-containing capsule, water molecules pene-trated the capsule through the micropores in the bottom of capsule body. Hydration and swelling of the hydroxypropylcellulose induced an increase in the internal osmotic pressure, which resulted in the ’explosion’ of the capsule and a burst-like drug release was observed. By altering the capsule thick-ness, the lag time of the drug release could be controlled, ranging from 2 h for a 44.1 -pm thick capsule to 6 h for a 76.7-pm thick capsule. An in vivo examination was further carried out using beagle dogs, which received capsules of varying

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thickness via oral administration. The drug con-centration was monitored from blood samples taken from the jugular vein at scheduled time intervals. In vivo drug release revealed that the time-controlled release of drugs correlated with the capsule thick-ness. Although further research is required, e.g. the number of pores and/or the quantification of en-vironmental water content in the GI tract could be optimised, this method holds promise for pulsed colon-specific delivery of drugs.
A similar approach for the pulsatile release of drugs was reported, in which a hydrostatic pressure was generated inside the capsules. To control the lag times of this pulsed drug release system, Jimoh et al. [9] utilized hollow biodegradable capsules with a thinner membrane at one end. The poly(lactic acid) (PLA) capsule was the effervescent agents, citric acid/sodium bicarbonate were entrapped within. A schematic representation of the capsule formulation is shown in Fig. 1. As water penetrated into the capsule through the thin poly(lactide-co-glycolide) (PLGA) membrane side, it generated an effervescent reaction caused by the citric acid/sodium bicarbon-ate mixture. Generated carbon dioxide gas accumu-lated in the capsule and finally ruptured the thin membrane, which was not resistant to the increased internal pressure. The burst time, i.e. lag time of drug release, can be modulated by the dimensions of capsule formulation (thickness of the membrane, hollow size, and the amount of effervescent agents). The capsule body, made from PLA with a molecular weight of 50 000, was molded on a stainless die and plunger at 700 psi and room temperature. The capsule has one open end covered with a thin PLGA membrane of varying thickness. Core composition was found to be a key factor in regulating the lag time (burst-like release). By altering the sodium carbonatecitric acid to glucose ratio, the capsule burst time could be modulated from 2 h up to 168 h (7days) in vitro. There was a linear relationship between the amounts of glucose in the core agents and in vitro burst time. Thus, the lag (burst) time could be predicted from the glucose percentage in the core agents and the capsule diameter obtained in in vitro experiments. These capsules were then utilized for the controlled release of follicle stimulat-ing hormone (FSH) in female rabbits. Several types of capsule formulations were implanted subcuta-

56 A. Kikuchi, T. Okano I Advanced Drug Delivery Reviews 54 (2002) 53-77

PLGA thin membrane
penetration of water molecules

F1IMI IjJj__III

PLA capsule

Ingredients
drugs, NaHC0313ItrIc acid/glucose

accumulation of
ntemal pressure

eruption of CO2 gas and drug release

1t\broken

up PLGA membrane

Fig. I. Scheme of the pulsed release biodegradable capsules.

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neously in the back of the neck of each rabbit to prevent the animals from reaching the samples. Blood samples were taken from the ear veins or arteries and FSH in the blood was monitored using the serum. Even though the membrane thickness varied, a maximum of the serum FSH level was observed at the same time-point. This suggests that the burst time is unchanged regardless of membrane thicknesses. Thus, as long as the capsules are of the same size and contain the same core ingredient formulations, the burst time is expected to be the same. Furthermore, the capsule material is biodegra-dable and, therefore, there is no need for the retrieval of empty capsules after complete release of drugs. This type of capsule may be useful for the pulsatile release of hormones with multiple administration, immunization, and animal reproduction management. Control of dissolution rate of the coating is another approach to achieve pulsed drug delivery. Pozzi et al. [10] proposed the TIME CLOCKfi system for oral dosage, which should enable a fast and complete release of drugs after a predetermined

lag time. A tablet core was made containing the drug molecule (samarium oxide for scintigraphic evalua-tion and salbutamol sulfate for the phase I testing on healthy volunteers) and bulking agents (lactose, poly(vinylpyrrolidone), cornstarch, and magnesium stearate). This core was coated with a hydran1hohic 10 dispersion of carnau a wax, bees wax, ppk(oxy-ethy ene sorbitan monooleate. and rhvfr0xvr0&1
By iftring the coating
thickness, the lag time could be proportionally modulated. In vitro tests indicated that the drug core-

ie drug core is xormuiatea
shell dissolution (or dis-

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A. Kikuchi, T. Okano / Advanced Drug Delivery Reviews 54 (2002) 53-77

integration) becomes the key factor controlling lag time. Furthermore, drug release is independent of normal physiological conditions, such as pH, diges-tive state, and anatomical position at the time of release. This approach may be applicable, not only for oral administration, but also for implantable drug formulations as well.
Noda and co-workers [11-14] carried out a series of experiments designed to develop sigmoidal releas-ing systems for novel oral controlled release formu-lations. Thjystnni-ennsistc4wo ptsj drug core. which is dissolved or able to swell in an

to

werT’tidTfiöüTºf shell materials. The coat thick-affected the

outer shell strength and water penetration time. With increasing PEG content, the water penetration rate increased, while a dramatic reduction in shell strength was observed. Thus, the lag time could be controlled by the composition of the outer shell components and its thickness. The core components consisted of the drug molecules and the swellable substances, which caused the instantaneous rupture of the tablet, to achieve a pulsatile release of drugs. The authors used carboxymethyl cellulose as a disintegration agent. The lag time was controlled by the total amount of shell components, as well as the PEG content in the shell. With decreasing PEG content in the shell, the lag time could be extended. Fluid composition and pH did not affect to the lag time and an identical lag time, as well as instanta-neous drug release was observed within a short time period in all fluid tested [12]. Ishino et al. [13] further investigated the applicability of the proposed pulsatile release system in in vivo experiments using beagle dogs. In this case, poly(vinyl chloride) was added to the shell component mixture of hydro-genated caster oil and PEG. The tablet core con-tained a model drug and carboxymethyl cellulose as the swelling agent. The formulated tablets showed a pulsed release of drug after a certain lag time (7–1 h) in vitro. Tablets were administered orally to beagle dogs and the plasma drug levels were evalu-ated at scheduled times. The plasma drug level

increased after a certain lag time. A lag time can be seen between 4 and 8 h for in vivo tests. The results suggested that the desired pulsatile release could be achieved using the prepared tablets.
Gazzaniga et al. [15] described on oral colon-specific delivery system which showed programmed lag times. The rug core was coatedwith various amounts of

lulose (HPMC), which acted as a retarding agent. In vitro release tests were performed using the USP XXII paddle method. A burst release immediately after the immersion of drug core was observed and release was completed within 15 min. On the con-trary, a burst release after a certain lag time was achieved with HPMC-coated drugs. Leg-times-were..

from 45 to 160 min with a weight gain from 35 to 115% HPlvC,...jcsecti’eltively. The lag time was

HPMC. Thus, it could be concluded that the lag time was regulated only by the change in the amount of HPMC. However, higher amounts of HPMC coating resulted in a slower release after the lag time, which continued for more than 1 h. Although the desired release pattern after the lag phase is dependent upon the mechanism of drug action, it may also be necessary to modify the core formulation to show either a burst release within a short time period or sustained release.

Liposomes have been used as drug delivery car-riers because of their structural similarity to cell membranes. However, uptake by the reticuloen-dothelial system or a destabilization due to the adsorption of plasma proteins on the lipid bilayer have been major drawbacks and have thus limited the application of these formulations. To overcome the drawbacks of liposomes as a drug carrier system, Langer and co-workers [16,17] incorporated drug-loaded liposomes into microcapsules of alginate hydrogels. The hydrogel matrix was designed to protect the liposomes from degradation and/or dis-persion in vivo, as well as possibly regulate the release rate of the incorporated drug molecules. To achieve a pulsatile release of drug molecules the liposomes inside the microcapsules were coated with phospholipase A2 (Fig. 2a). Phospholipase A2 was shown to gather at the water/liposome interfaces and remove an acyl group from the phospholipid in the

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A. Kikuchi, T. Qkano / Advanced Drug Delivery Reviews 54 (2002) 53-77

complex

drug loaded liposome coated
with phosphollpasoA2

0 20 40 60 80
TIME (days)

Fig. 2. (a) Schematic representation of liposome-loaded alginate poly(L-lysine) microcapsules. (b) In vitro release profiles ofFITC BSA from microcapsules with different phospholipase A2 con-centrations (0)10 Units, () I Unit, (0) no enzyme coating. Reproduced from Ref. [16] by permission of the Federation of American Societies for Experimental Biology.

liposome, resulting in the destabilization of the liposome. Destabilized liposomes release their drug molecules from the interior, thus allowing drug release to be regulated by the rate determining microcapsule membrane. Langer and co-workers [16,17] first incorporated FITC-labeled bovine serum albumin (FITCBSA) as a model drug into hydro-genated lecithin or phosphatidylcholine/cholesterol based multi-lamellar liposomes with an entrapment efficiency of 20-50%. The liposome size (diameter) was 2.8–2 pm. Liposomes were then incubated with phospholipase A2 for 15 min at 20°C to allow for adsorption onto the liposome surfaces. The liposome pellets were re-suspended in a sodium alginate solution and the suspension was sprayed into a calcium chloride solution to form gel beads. The calcium alginate gel beads containing drug-incorpo-rated liposomes were then stabilized by complex formation with poly(lysine). Fig. 2b shows the release profile of FITCBSA from microcapsules. In

the case of soy lecithin, BSA release from mi-crocapsules was dependent upon the phospholipase A2 concentration which coated the liposome surface. Without phospholipase A2 there is only a 10% release of BSA for up to 63 days of observation. By increasing the amount of phospholipase A2 from 1 to 10 Units, it could be observed that the release process began earlier, on day 20 instead of 30 and was complete after 10-15 days. Phospholipase C and D cleave on either side of the phosphodiester link-age. When either enzyme was used instead of phospholipase A2, a different release profile could be observed. A zero-order release was obtained for liposome coated with phospholipase C, while only 10% release within 50 days was observed for phospholipase D [17]. Thus, release can be modu-lated with the type of enzymes used to destabilize liposomes in the microcapsules. In vivo studies were performed, in which horseradish peroxidase (HRP) release was measured by injecting the microcapsules subcutaneously in male mice. Within 15 days, ap-proximately 30% of the HRP was released by diffusion, followed by pulsed release of remaining HRP within 5 days. Thereafter, HRP lost its en-zymatic activity at 37°C within a few days, while microencapsulated HRP retained 40% of its bio-logical activity even after 30 days of incubation at 37’C. Thus, the microencapsulation of enzymes into liposomes inside the alginate microcapsules should be effective not only for maintaining biological activity but also for achieving pulsed release profiles. The molecular weight of the poly(lysine) coating on the calcium alginate gels also affected the release behavior of drug molecules. When lower molecular weight poly(lysine) was used the onset time of the drug release was retarded. This is probably due to the easier penetration of poly(lysine) molecules with a lower molecular weight inside the calcium alginate gel beads, which stabilized polyion complex-formed capsule layers. Histological studies of the implanted sites indicated that there is little inflammation after the injection of drug-incorporated microcapsules for up to 54 days following the injection. The authors concluded that this is indicative of microcapsules’ biocompatibility. Although the release profile seemed to be pulsed, drug release extended for several days after the lag time. Even though the lag time can be controlled by the rate of liposome

A. Kikuchi, T. Okano I Advanced Drug Delivery Reviews 54 (2002) 53-77

destabilization using phospholipase A2 and the stability of microcapsule membranes by poly(lysine) complex formation, release after the lag time should be more rapid (in the order of several hours or even minutes) to achieve an actual pulsatile release profile. Thus, this system may need some modification. It may be a promising approach for the delivery of drugs for immunization purposes using a cocktail of several types of microcapsules with different con-tents, as well as preparation methods.
Heller’s group [18,19] systematically investigated enzyme protective coatings for the use in triggered drug delivery. The basic method of formulation is as follows: Drug molecules are incorporated within the biodegradable matrix. The matrix is coated with enzymatically degradable materials. The modified matrix is then placed within a microporous mem-brane capsule with the antibody-protected enzymes. When the concentration of target molecule is in-creased, activation of the enzyme could occur. The activated enzyme would then degrade the coating layers of the biodegradable matrix, followed by drug release during matrix degradation. To realize this mechanism, cellulose acetate phthalate was used as a degradable matrix and naltrexone as the drug mole-cule. Drug-incorporated matrix microspheres were then coated with trilaurin, which is digested by the enzyme, lipase.
Drug-containing microspheres of 250-500 pm in diameter were prepared by emulsification [19]. Drug release from the microspheres into 0.01 M phos-phate-buffered saline (pH7.4) was very fast and complete within 1 h. By coating the microspheres with trilaurin using a spray-coating method, drug release was completely suppressed and less than 10% of incorporated drug was released after 28 days of
examination.

They then investigated enzyme-induced drug re-lease. The microspheres were placed in a dialysis membrane tube and suspended in the release medium at a temperature of 37°C. At time zero, varying concentrations of morphine-conjugated lipase were added to suspension in the dialysis membrane tube. When control microspheres were suspended in the release medium without lipase, drug release was suppressed up to 10% during the 24-h release period. In contrast, drug release from microspheres in the presence of lipase was significant. An immediate

effect was apparent after enzyme addition and ap-proximately 30% ofthe naltrexone was released with the first 30 min. Drug release was completed almost within 24 h. As the authors described in this report, the strategy of this device design is not limited to the treatment of narcotic addiction, but could be extend-ed to other therapies, as well.
Yui et al. [20] recently reported the development of a new drug delivery device, which exhibited a pulsatile peptide release. The drug formulation con-sisted of a poly(ethylene glycol) (PEG)-grafted dextran gel combined with an ungrafted dextran gel in a multi-layer structure located within an imperme-able silicone tube (3 mm I.D.) exhibiting an open end at both sides. Glycidyl methacrylate was intro-duced to the dextran hydroxyls and, thus, dextran was cross-linked by UV light irradiation. The peptide drug, insulin, was thought to accumulate within the PEG graft domains via two-phase partitioning be-tween the two aqueous dextran and PEG systems. In fact, when insulin was introduced to the PEG-grafted dextran, only 10% of the insulin was released during a 72-h incubation time, while a significant release was apparent for insulin in a dextran solution alone. Thus, insulin in the PEG-grafted dextran was not released spontaneously by simple immersion of the gels in the release medium.
Insulin release was also examined in the presence of dextranase, an enzyme that specifically digests dextran. Since the multi-layered gel formulations were located within the silicone tubing, the degra-dation fronts were limited to both ends of the tube and a surface erosion type of degradation could be observed. Insulin release from the multi-layered gels was examined in the presence of 0.1 U/ml dex-tranase in releasing medium. Dextran degradation was proportional to time regardless of the PEG chains and a pulsed-type insulin release was ob-served. When dextran gels without PEG chains were degraded enzymatically, no insulin was released. This result strongly suggests that the insulin mole-cules accumulated within the PEG-grafted dextran gel layers. Insulin release was thus characterised by a degradation-controlled mechanism. Conformational analysis of insulin using circular dichroism indicated that the insulin in PEG-grafted dextran showed an almost identical conformation, even after 60 h of incubation. In comparison, insulin in PEG-free dex-

60 A. Kikuchi, T. Okano / Advanced Drug Delivery Reviews 54 (2002) 53-77

tran showed significant conformational changes.
Thus, the released insulin should have a higher
bioactivity. Although this type of formulation could
guarantee the pulsatile release of peptide drugs,
dextranase does not exist in the human body. There-
fore, it would be necessary to use another matrix material which can be degraded in the human body before this system could be used for the treatment of patients.
Yui et al. [21] further developed an aqueous, two-phase partitioning system using hyaluronic acid (HA) and PEG graft chains. Similar to the PEG-grafted dextran, insulin molecules preferentially ac-cumulated within the PEG domains of the gel, rather than HA domains. Minimum leakage of insulin was observed from a PEG-grafted HA solution prepared with 7 wt% PEG grafts, while almost an 80% leakage of insulin was observed using a HA solution and PEG-grafted HA with more than 22 wt% PEG graft chains after a 60-h incubation time. Negligible conformational changes in the insulin structure were detected by circular dichroism. Since HA can be degraded enzymatically in the human body, this formulation should be able to release insulin through the matrix under in vivo conditions. Thus, the PEG-grafted HA system may be a feasible matrix for injectable, degradation controlled drug release.

3. Stimuli-induced pulsatile release

3.1. Temperature-induced pulsatile release

3.1.1. Thermoresponsive hydrogel systems Thermoresponsive hydrogels have been investi-gated as possible drug delivery carriers for stimuli-responsive drug delivery systems [22-25]. PIPAAm cross-linked gels have shown thermoresponsive, discontinuous swelling/ deswelling phases: swelling, for example, at temperatures below 32°C, while shrinking above this temperature. A sudden tempera-ture increase above the transition temperature of these gels resulted in the formation of a dense, shrunken layer on the gel surface (’skin layer’), which hindered water permeation from inside the gel into the environment. Drug release from the PIPAAm hydrogels at temperatures below 32°C was governed by diffusion, while above this temperature drug

release was stopped completely, due to the ’skin layer’ formation on the gel surface (onoff drug release regulation) [23,24,26].
Swellingdeswelling kinetics of conventional cross-linked hydrogels are normally reciprocal of the square of gel dimension [27]. The mobility of the cross-linked chains in the gel is affected by the surrounding chains and the swelling/deswelling phases of the gel are governed by the collective diffusion of the network chains. Thus, to accelerate structural changes of the gel in response to external stimuli, several approaches have been developed which form porous structure within the gel and decrease gel size [28-32].
We have recently reported a new method to accelerate gel swelling/deswelling kinetics based on the molecular design of the gel structure. Free mobile linear PIPAAm chains were grafted within the cross-linked PIPAAm hydrogels [33-35] as shown in Fig. 3. These novel graft-type PIPAAm gels had the same transition temperature as the conventional cross-linked PIPAAm gels and existed in the swollen state below the transition temperature, while above this temperature they shrank. The molecular weight of the graft chains had a significant effect on the gel deswelling kinetics and also on the drug release profiles, especially for large molecular weight drugs. A dense skin layer was formed on the conventional PIPAAm gels upon temperature change above the transition temperature, which limited the complete shrinkage of the gel. In contrast, the PIPAAm-grafted gels showed rapid deswelling kinet-ics without the formation of a skin layer on the gel surface. This is probably due to the rapid dehydra-tion of the graft chains formed by hydrophobic aggregation on the three-dimensional cross-linked gel chains. The hydrophobic cores might accelerate the entire dehydration and shrinking processes of the gel. Cylinder-shaped gels showed fast and large changes in length when subjected to repetitive temperature cycles between 20 and 40°C [35]. Thus results indicated the feasibility of our concept that the introduction of freely mobile, linear PIPAAm chains into PIPAAm cross-linked gels is effective for fast gel deswelling kinetics.
The drug release profiles from the graft-type PIPAAm gels were monitored after the immersion of drug-containing gels in a suitable release medium

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Organic solvent-free polymeric microspheres prepared
from aqueous colloidal polymer dispersions by a w/o-emulsion technique

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Received 20 June 1995; accepted 16 August 1995

Abstract

Polymeric microspheres were prepared from water-insoluble polymers by a novel technique without the use of organic solvents. Aqueous colloidal polymer dispersions (latexes or pseudolatexes) were emulsified into a heated external oil phase to form a w/o emulsion. The

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t ea-dditiOnó gsur ptastitizers. as icizers a o a e to colloidal dispersions with high minimum film formation temperatures. The resulting microspheres were spherical with a smooth surface and non-agglomerated. The_prticle size could be varied between 5 a Water-soluble compounds such as propranolol HC1 could be apped thdg l6adings thin the microspheres by dissolving the drug in the aqueous polymer dispersion prior to the emulsification step. T g ___ease was sustained over a 6-h period with mic! es tred with the acrylic lolatex, Eudragit RS3tJD.

mum Keywords: Aqueous colloidal polymer dispersion; Latex; Microencapsulation; Microsphere: Polymer: Sustained
release

1. Introduction

Microparticles can be formed by a variety of
microencapsulation techniques (Kondo, 1979;
Deasy, 1984). The choice of one particular

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method is determined to a large extent by the solubility characteristics of the active compound and the carrier material. Although various carrier materials (e.g., water-soluble and -insoluble-mers or waxes)are available, water-insoluble poi such as ethyl cellulose, cellulose acetate butyrate, poly(lactides), and various acrylic and vinyl polymers have bejrimarilv used forthe

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188 C. Chang, A. Bodmeier I International Journal of Pharmaceutics 130 (1996) 187-194

preparatio of sustained release micro articles.
Microencaps ation me o ese p0 y-
mers include organic phase separation (Kondo,
1979; Deasy, 1984), aqueous and non-aqueous
solvent evaporation (Huang and Ghebre-Sell-
assie, 1989; Bodmeier et al., 1991), and spray-drying techniques (Bodmeier and Chen, 1988). Water-soluble drugs can be encapsulated by organic phase separation or non-aqueous sol-vent evaporation techniques; the drugs are insol-uble in the organic solvents or oils used as external phases in these methods. In the non-aqueous solvent evaporation method, the drug is dissolved in an organic polymer solution fol-lowed by emulsification of this phase into an external oil phase and solvent evaporation to form the microspheres (Beyger and Nairn, 1986; Kawata et al., 1986; Huang and Ghebre-Sell-assie, 1989; Bodmeier et at., 1994). The major disadvantage of these microencapsulation meth-ods is the use of organic solvents, which are required to dissolve the water-insoluble poly-mers. Safety and toxicit concerns make the de-velopmeEtol velopmento so - ncau1aion
methods desirable.

dolatexes) have found widespread applications in the painting and coating industry where they have replaced coating with organic solvents (Lehmann, 1986; Steuernagel, 1989). Water-in-soluble films are formed through the coalescence of the colloidal polymer particles upon water evaporation in a completely aqueous environ-ment. The principle of coalescence of the col-loidal polymer particles (not into films but into spherical particles) was used in this study to form microspheres from an emulsion of the aqueous colloidal polymer dispersions in an ex-ternal oil phase.

2. Materials and methods

2.1. Materials

The following materials were used as received from commercial suppliers: propranolol HCI (Sigma Chemical Co., St. Louis, MO), dibutyl sebacate (Eastman Kodak Co., Rochester, NY), triacetin, tributyl citrate, triethyl citrate (Morfiex, Inc., Greensboro, NC), Aquacoat (ethyl cellulose dispersion, FMC Corporation, Newark, DE), Surelease (ethyl cellulose dispersion. Colorcon Inc., West Point, PA), Eudragit NE 30D (polyethylacrylate, methylmethacrylate disper-sion), Eudragit RS 30D and RL 30D (poly-ethylacrylatemethyl methacrylatetrimethylam-monioethyl methacrylate chloride dispersions) (Röhm Pharma, Darmstadt, Germany), cotton-seed oil (Sigma Chemical Co., St. Louis, MO), corn oil, sesame oil, soybean oil (Fisher Scientific, Fair Lawn, NJ), mineral oil (Sigma Chemical Co., St. Louis, MO), methanol (Baxter Healthcare Co., McGaw Park, IL), n-hexane (J.T. Baker Inc., Phillipsburg, NJ).

2.2. Methods

2.2.1. Preparation of microspheres
A schematic diagram of the preparation method is shown in Fig. 1. The colloidal polymer dispersions (2 g, 30% w/v solids content) were

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Olocllm_’?’e
drug + latex oil \

microsphere W/O-emulslon
Fig. I. Schematic diagram of the preparation of the micro-spheres by a w/o-emulsion technique using aqueous colloidal polymer dispersions (latexes).

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C. Cluing, R. Rodmeler / International Journal of Pharmaceutics 130 (1996) 187-194

emulsified into an external cottonseed oil phase (30 ml) with a magnetic or propeller stirrer. The resulting w/o emulsion was heated and agitated in a water bath at 60°C for 30 min to evaporate water and to induce fusion of the colloidal poly-mer particles into larger microspheres. After cool- - ing the microparticle/oil suspension to room temperature, the microspheres were collected by filtration, washed with n -hexane to remove excess oil from the microsphere surface, and dried under vacuum in a desiccator overnight.
The following formulation and process vari-ables were investigated: theoretical propranolol HCI loading (10-400/o), type of oil (cottonseed, corn, mineral, sesame and soybean oil), volume of EudragitRS3OD (2-20 ml, into 60 ml cottonseed oil), type of colloidal polymer dispersion (Aqua-coat, Surelease, Eudragit NE 30D, RS 30D, RL 3013), solids content of Eudragit RS30D (10-30%, 5% interval), temperature of cottonseed oil (26-70°C).

2.2.2. Determination of drug loading
The propranolol HCl content of the micro-spheres (10 mg, 150-250 sum) was determined by UV-spectrophotometry after extraction in methanol (20 ml). Encapsulation efficiency is the ratio of the actual drug content to the theoretical drug content, expressed in %.

2.2.3. Drug release study
The dissolution profiles were obtained by a horizontal shaker-water bath method. The micro-spheres (150-250 um) were placed into dialysis bags (molecular weight cut-off 6000-8000; Spec-trum Medical Industries, Inc., Los Angeles, CA), then placed into glass vials containing 20 ml of 0.1 M phosphate buffer, pH 7.4, and shaken in a horizontal shaker-water bath (70 strokes/mm, 37°C, n = 3). The vials were removed from the water bath at predetermined time intervals and the amount of drug released was determined by circulating the dissolution medium through a UV sipper cell.

2.2.4. Scanning electron microscopy
Scanning electron microscopy (SEM) was used to characterize the surface and cross-section of the

microparticles. The samples were coated for 70 s under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater) and examined with a scanning electron microscope (Jeol JSM 35C). Cross-sections were obtained by dispersing and drying the microparticles in a glue (Testor Corporation, Rockford, IL), followed by cutting the dried matrix with a razor blade.

3. Results and discussion

Microspheres of water-soluble carriers such as albumin have been prepared by emulsifying aqueous drug-carrier solutions into an external oil phase to form a w/o emulsion; the microparticles were formed after water removal (Tomlinson et al., 1984). With water-insoluble polymers, drug-containing microparticles have been prepared by emulsifying solutions of the drug and polymer in an organic solvent into an external oil phase, followed by solvent evaporation (Huang and Ghebre-Sellassie, 1989).
In this study, instead of emulsifying aqueous or organic polymer solutions, aqueous colloidal polymer dispersions were emulsified into an exter-nal oil phase to form a w/o emulsion. The emul-sion was heated to evaporate the water and to form the microspheres through coalescence of the colloidal polymer particles within the individual emulsion droplets.
Various colloidal polymer dispersions used in the coating of pharmaceutical dosage forms were evaluated using this microencapsulation method. The polymer dispersions were based on either cellulosic (ethyl cellulose, Aquacoat and Sure-lease) or acrylic (poly (ethylacrylate, methyl-methacrylate), Eudragit NE 3013; poly (ethylacrylatemethyl methacrylatetrimethylam-monioethyl methacrylate chloride, Eudragit RS 30D and RL 3013; poly (methacrylic acid, ethy-lacrylate), Eudragit L 3013) polymers. The coales-cence or fusion of the colloidal polymer particles into a homogeneous polymer film or matrix de-pends on the glass transition temperature of the polymer and the minimum film formation temper-ature of the colloidal polymer dispersion. The minimum film formation temperature is the tern-

190 C. Chang, R. Bodmeler / International Journal of Pharmaceutics 130 (1996) 187-194

perature at which coalescence of the polymer
particles occurs. A fine polymer powder or only
partially coalesced particles were obtained if dry-
ing occurred at temperatures below this tempera-
ture. With polymers having high glass transition
temperatures, plasticizers had to be added to the polymer dispersions to reduce the film formation temperature below the drying temperature. Aquacoat and Eudragit RS or RL 30D re-quired the addition of plasticizers to induce/en-hance the coalescence of the colloidal polymer particles. Both water-insoluble (dibutyl sebacate and tributylcitrate) and -soluble (tnethyl citrate and triacetin) plasticizers gave free-flowing, indi-vidual microparticles. Although the water-insolu-ble plasticizers were miscible with the external oil phase, the resulting microparticles were nonag-glomerated at the plasticizer levels (20-301/o w/w based on the polymer) investigated. Microspheres could also be formed with Surelease which is an ethylcellulose pseudolatex already plasticized with dibutyl sebacate. Eudragit NE 30D could be emulsified into the oil phase to form a w/o-emul-sion, however, the particles agglomerated upon evaporation of water. This could be explained with the low glass transition temperature of the polymer, the polymer being in the rubbery state during microparticle preparation and cooling. Another important consideration is the interac-tion between the oil phase and the polymer. Sticking could result from partial swelling of the polymer by the external oil phase. The polymer therefore should be insoluble and should not swell in the oil used.
One advantage of colloidal polymer disper-sions is their low viscosity at a high polymer solids content when compared with organic poly-mer solutions. The latexes or pseudolatexes typi-cally have a solids content of 30% or more while organic polymer solutions used in the microen-capsulation of drugs generally have a polymer content of less than 10%. More concentrated polymer systems can therefore be processed with colloidal polymer dispersions.
Various drugs were evaluated with this mi-croencapsulation method. As with most microen-capsulation techniques, partitioning between two immiscible phases needs to be minimized in order

to maximize the drug loading of the micro-spheres. This w/o-microencapsulation technique is most suitable for water-soluble drugs being soluble in the internal aqueous and insoluble in the external oil phase. A solvent- and oil-free method for the encapsulation of lipophilic drugs based on aqueous colloidal polymer dispersions has been recently developed (Bodxneier and Wang, 1993).
A prerequisite for the successful preparation of the microparticles was the compatibility between the colloidal polymer dispersion and the drug. Colloidal polymer dispersions are stabilized against premature flocculation and coalescence or settling during storage by either anionic or nonionic surfactants or by charged groups present in polymer sidechains. The ethyl cellulose dispersions, Aquacoat and Surelease, are stabi-lized with the anionic surfactants, sodium lauryl sulfate and ammonium oleate, respectively. The addition of cationic drugs such as chlorpheni-ramine maleate, pseudoephedrine HCl, or pro-pranolol HCl to these pseudolatexes resulted in immediate flocculation or precipitation and no particle formation after injection of this disper-sion into the oil. Eudragit RS and RL 30D pseu-dolatexes are stabilized by quaternary ammonium groups present on the polymer sidechain; the cationic drugs can be dissolved in these dispersions without causing flocculation. Various formulation and process variables were investigated in order to understand and characterize the formation of the microparticles. The encapsulation efficiencies with Eudragit RS 30D were close to 100% for theoretical propra-nolol HCl loadings up to 40%. Propranolol HCl was insoluble in the oil and therefore did not partition into the external oil phase. The encap-sulation was not affected by the solids content of the polymer dispersion (10 vs. 30% w/w). Scan-ning electron micrographs of the surface and a cross-section of the microparticles are shown in Fig. 2. The microparticles were spherical and non-agglomerated, the cross-section revealed a homogeneous, dense matrix structure without visible drug crystals at a drug content of 30%.

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C. Chang, R. Bodmeler / International Journal of Pharmaceutics 130 (1996) 187-194

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Fig. 2. Scanning electron micrographs of propranolol HCl (30% w/w)-Eudragit RS microspheres. (A) surface, (B) cross-section.

192 C. Chang, R. Bodmeler / International Journal of Pharmaceutics 130 (1996) 187-194 L)r\
Table I

Effect of type of oil on the propanolol hydrochloride loading of Eudragit RS 30D microspheres

Oil Theoretical drug loading (%) Actual drug loading (1o) Encapsulation efficiency (%)

Corn oil 25.53 25.33 99.21
Cottonseed oil 25.53 23.88 93.53
Sesame oil 25.53 25.21 98.74
Soybean oil 25.53 23.39 91.61

Table 2

Effect of the temperature of the cottonseed oil phase on the propanolol hydrochloride loading of Eudragit RS 30D microspheres

Temperature (°C) Theoretical drug loading (%) Actual drug loading (%) Encapsulation efficiency

26 16.67 16.53 99.16
40 16.67 16.74 100.42
50 16.67 16.36 98.14
60 16.67 16.84 101.02
70 16.67 16.34 98.02

Table 3

Effect of the volume of the internal phase on the propranolol hydrochloride loading of Eudragit ES 30D microspheres

Internal phase Theoretical drug Loading (%) Actual drug loading (%) Encapsulation efficiency (%)

2 22.65 21.55 95.15
5 22.65 22.01 97.18
10 22.65 23.80 105.08
15 22.65 22.82 100.75
20 22.65 22.04 97.31

9n 60 ml of cottonseed oil.

The propranolol HC1 content of the microparti-
des was not affected by type of oil used, the
temperature of the external phase and volume of
internal phase in the ranges investigated as shown
in Tables 1-3. The solubility of the drug in the external phase was minimal at all temperatures and therefore was not a significant factor. The encapsulation efficiencies were close to 1001/6 in most cases. Higher temperatures are preferred because of shorter stirring times and faster co-alescence of the colloidal polymer particles. From a scale-up point of view, a higher internal to external phase ratio will result in higher product yields.

The coalescence and hence solidification and formation of the microparlicles was primarily affected by the solids content of the polymer dispersion, the amount of internal phase emulsified, and the temperature of the external oil phase. The solidification time (the time necessary to obtain individual, non-agglomerated micro-spheres after filtration) decreased with increasing solids content because less water had to be evapo-rated (Fig. 3). Increasing the amount of polymer dispersion emulsified increased the time necessary prior to separation of the microspheres (Fig. 4). The stirring time also decreased with increasing temperature of the oil phase because of a more

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C. Chang, R. Bod,neier / International Journal of Pharmaceutics 130 (1996) 187-194

0 5 10 15 20 25 30

solids content of Eudragit RS, %

Fig. 3. Effect of the Eudragit RS30D solids content on the solidification time.

rapid evaporation of water (Fig. 5).
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Initial aqueous phase, ml

Fig. 4. Effect of the amount of the internal aqueous phase (Eudragit RS30D) on the solidification time.

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D I I I I I I I
35 40 45 50 55 80 85 70 75

temperature, °C

Fig. 5. Effect of the temperature of the cottonseed oil phase on
the solidification time.

The propranolol HCI release from microspheres prepared from Eudragit RS 30D could be sus-tained over a 6-h period as shown in Fig. 6. Eudragit RS contains quaternary ammonium groups which are responsible for the hydration of and drug release from the microparticles. A fur-ther retardation of the drug release could possibly be achieved with more hydrophobic polymers. In conclusion, microspheres in the pm size range were prepared from water-insoluble poly-mers by a novel technique without solubilization of the polymer in organic solvents. The micro-spheres were formed by a ulsioc

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0 2 4 6 8 10 H
time, hours

Fig. 6. Drug release from propranolol HCI-Eudragit RS30D microspheres with drug loadings 01 If and 247n.

194 C. Chang, R. &eier / International Journal of Pharmaceutics 130 (1996) 187-194 I3.
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microencapsulation of pharmaceuticals with cellulose ac-
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

2020

Bogota, D.C., 22/01/2010

Abogado
Emilio Ferrero
(Apoderado)

ASUNTO RadicaciOn 053952
TrÆmite 002
Evento 001
ActuaciOn 430
Oficio
Folios 011

Patente de lnvención Patente de Modelo de Utilidad

Via Nacional

Via PCT (fase nacional) Cap. I Cap. II FRI Como resultado del examen de fondo, realizado con fundamento en el artIculo 45 de la Decision 486 de Ia ComisiOn de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. DescripciOn:

1.2. Reivindicaciones:

1.3. DatosPCT:

1.4. Prioridad:

Folios: 47 a 69

Folios: 70 a 72

Folios: 126 y 127 Memorial de 07/11/2008

Solicitud Internacional:
CapItulo II
Fecha Sol. Internacional:
PublicaciOn. Internacional:
Fecha Pub. Internacional:
Fecha Inicio Fase Nacional:
Fecha Sol. Nacional:

FR 02/07778 de 24/06/2002

PCT/FR03/001 931

24/06/2003
W004/000286
31/12/2003
24/01/2005
19/01/2005

1.5. Respuesta del solicitante: Folios: 116 a 128 Memorial de 07/11/2008

2. Objeto de la invención

Titulo de la so!icitud

Microcªpsulas para Iiberaciôn retardada y controlada de perindopril

1k;

Reivindicaciones

Reivindicaciones I a 6: Se reivindican microcÆpsulas"reserva" para la liberaciôn retardada y controlada de perindopril o de sus sales farmacØuticamente aceptables destinadas a la administraciOn oral, caracterizadas en que las microcÆpsulas estÆn:

Constituidas por microparticulas de perindopril o de una de sus sales farmacØuticamente aceptables recubiertas cada una por al menos una peilcula de revestimiento, siendo constituida esta pelicula de revestimiento
por una material compuesto el cual incluye:
Al menos un polimero hidrôfilo A portador de agrupaciones ionizadas con pH neutro, el cual se selecciona entre derivados de
celulosa, copolImeros de Æcido metacrilico y de ester de Æcido
metacrilico, los copolimeros de Æcido metacrilico y de ester de
Æcido acrIlico,copolimero de Æcidometacrilico y de metacrilato de
metilo o el copolimero de Æcidometacrilico y de acrilato de etilo.
o Al menos un compuesto hidrOfobo B que representa una fracciOn
, mÆsica (% peso con respecto a la masa total de las microparticulas) inferior o igual a 40. El compuesto hidrófobo se
elige entre ceras vegetales, aceites vegetales hidrogenados,
trigliceridos hidrogenados y sus mezclas
Tienen un diÆmetroinferior a 1200 micrones

La pelIcula de revestimiento estÆconstituida por una mezcla de polimero hidrôfilo
A y por el compuesto hidrófobo B en proporción 0,2 y 4.

Reivindicaciôn 7: Se reivindican microcÆpsulassegün las clÆusulasprecedentes caracterizadas en que:

A un pH 1,4 obtener un perfil de disolución incluye una fase de latencia con una duraciôn superior o igual a media hora, preferiblemente comprendida entre 1 y 8 horas y mÆspreferible entre I y 5 horas.
Una fase de liberaciôn del perindopril en cualquier momento durante la fase de latencia despuØs del paso de pH 1,4 a pH 6,8.

Reivindicaciones 8y 9: Se reivindican microcÆpsulassegün las reivindicaciones precedentes que se caracterizan porque el Perindopril se encuentra bajo la forma de sal de tert-butilamina, o bajo la forma de sal de arginina.

Reivindicación 10: Se reivindican microcÆpsulas caracterizadas porque el perindopril o una de sus sales se deposita sobre un nücleo neutro de diÆmetro comprendido entre 50 y 600 micrones.

Reivindicación 11: Se reivindican microcÆpsulas caracterizadas porque el nücleo neutro hidrôfilo es de sucrosa, dextrosa, lactosa o celulosa.

Reivindicaciones 12 y 13: Se reivindica una composiciôn que se caracteriza porque comprende microcÆpsulas como las definidas en las reivindicaciones precedentes y que se presenta bajo la forma de comprimidos, polvos o cÆpsulas.

Sustento Descriptivo

La presente invenciôn se relaciona con cÆpsulas que permiten la liberaciOn retardada y controlada de perindopril o de una de sus sales farmacØuticamente

aceptables para la cual las fases de liberaciOn retardada y controlada se manen de manera segura gracias a un mecanismo doble: liberación tiempo dependiente iniciada despuØs de cierto tiempo de permanencia en el estomago y liberación pH dependiente iniciada mediante un cambio de pH en el momento dela entrada de las particulas en el intestino delgado. Las microparticulas de la presente invenciôn son microparticulas con una granulometrIa comprendida entre 100 y 1200 micrones que contienen perindopril e individualmente recubiertas por la menos una peilcula de revestimiento que permite la liberación retardada y controlada de perindopril.

Los comprimidos de perindopril convencionales permiten una cobertura tensional sobre el conjunto del nictØmero pero no permiten preservarse totalmente contra la subida de tensiOn observada en la madrugada en pacientes que sufren de hipertensión. Un estudio clinico en los pacientes con hipertensiOn demostrO que con el comprimido convencional las concentraciones plasmÆticasen principio activo logradas entre las 4 y las 8 de la maæanason insuficientes para hacer desaparecer la abrupta elevaciOn de la tensiOn.

Con el fin de solucionar este problema se desarrolla una nueva forma de administraciOn que garantiza la liberación y absorción del principio activo en el momento deseado y que permite controlar eficazmente la tensiOn arterial durante todo el dia y especialmente en la maæana.

Una vez cataloada la invenciOn Østa se clasificô en la secciOn: A 61 K 31/40 II

314 II A 61 P /12 de la Clasificación Internacional de Patentes.

3. De la solicitud de Patente

3.1. Reivindicaciones (artIculo 30 D. 486)

De conformidad con el contenido y alcance de la materia reivindicada en la clÆusula 7 esta Dependencia se permite reiterar lo siguiente:

El contenido de la clÆusula 7 hacereferenda al resultado que se pretende alcanzar con el diseæo de unafOrmula de liberación controlada y retardada,
cual es la liberaciOn del agente activo en dos fases claramente diferenciadas
por efecto del tiempo y del pH. Y tal como se encuentra caracterizada la formula en dicha clÆusula no solo se incorporan los atributos esenciales inherentes al sistema de entrega farmacØutico reivindicado como es el caso de sus componentes y proporciones, sino todas las soluciones y alternativas presentes 0 futuras que puedan conlievar al mismo resultado, es decir, a obtener un perfil de disoluciOn que incluya una fase de latencia con una duraciOn superior o igual a media hora, preferiblemente comprendida entre I
y 8 horas y en particular entre I y 5 horas y ademÆsobtener un fase de IiberaciOn del perindopril en cualquier momento durante la fase de latencia despuØs del paso de pH 1,4 a pH 6,8.

Por las razones seæaladas es preciso requerir al solicitante en los tØrminos del presente examen tØcnico para que elimine el contenido de la clâusula en comento ya que desdibuja el alcance real de la invenciOn y en estricto sentido no constituye un elemento caracteristico de la formulaciOn sino una propiedad o efecto tØcnico derivado de la composiciOn cuali-cuantitativa.

4. Determinación del Estado de la TØcnica

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Considerando que la fecha de presentaciôn de Pa primera solicitud de patente dØ la cual se reivindica prioridad es: 24/06/2002, se procediO a efectuar la büsqueda de documentos relacionados en el estado de la tØcnica con fecha de publicación anterior a Østa.

No Documento TItulo Fecha de

Publicación

"Controlled-release pharmaceutical
Dl US6267990 preparation comprising an ACE inhibitor as 31/07/2001
active ingredient"
"Oral pharmaceutical preparation
D2 US6306435 embedded in an oily matrix and methods 23/10/2001
of making the same"

"Pulsatil drug release control using January D3 ArtIculo I hydrogels" 2002
"Organic solvent-free polymeric

D4 Aculo 2 microspheres prepared from aqueous 1996 colloidal polymer dispersions by a w/o-
emulsion technique" I

Anterioridades Dl y D2 en los folios 94 a 106, antenoridades D3 y D4 en los folios 129 a 143

S. AnÆlisis depatentabilidad (artIculo 14 D. 486)

5.1 Nivel lnventivo (artIculo18 D. 486)

El nivel inventivo del objeto reclamado se evaluó por comparación entre las caracterIsticas esenciales de los microencapsulados definidas en el pliego reivindicatorio y los elementos esenciales de las composiciones reveladas por el arte
previo en los documentos Dl y D2.

Sereivindican:

S MicrocÆpsulas"reserva" para la liberación retardada y controlada de perindopril o

de sus sales farmacØuticamente aceptables destinadas a la administración oral,
caracterizadas en que las microcÆpsulasestÆn:

Constituidas por microparticulas de perindopril o de una de sus sales
farmacØuticamente aceptables recubiertas cada una por al menos una
pelicula de revestimiento, siendo constituida esta pelicula de revestimiento
por una material compuesto el cual incluye:
o Al menos un polImero hidrôfilo A portador de agrupaciones ionizadas con pH neutro, el cual se selecciona entre derivados de celulosa, copolimeros de Æcido metacrilico y de ester de Æcido metacrilico, los copolimeros de Æcido metacrilico y de ester de
â cido acrilico, copolImero de Æcidometacrilico y de metacrilato de metilo o el copolImero de Æcidometacrilico y de acrilato de etilo.
o Al menos un compuesto hidrôfobo B que representa una fracciôn mÆsica (% peso con respecto a la masa total de las microparticulas) inferior o igual a 40. El compuesto hidrôfobo se elige entre ceras vegetales, aceites vegetales hidrogenados, triglicØridos hidrogenados y sus mezclas
Tienen un diÆmetroinferior a 1200 micrones

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La pelicula de revestimiento esta constituida por una mezcla de polimero hidrofilo A y por el compuesto hidrôfobo B en proporciOn 0,2 y 4.

El estado del arte previo a la invención presenta los siguientes documentos:

Anterioridad Dl:

La publicación Dl revela microgrÆnulosque contienen:

Una sustancia activa inhibidora de la enzima convertidora de angiotensina tal
es el caso de Perindopril.

Los microgranulados presentan una especie de recubrimiento que los hace
resistentes al medio gastrico compuesto principalmente de polImeros de Æcido
metacrHico de metil-metacrilato.

Anterioridad 132:

’ La publicaciOn D2 revela matrices oleosas encapsuladas de Iiberación controlada en pH neutro. La matriz contiene un principio activo embebido en su nücleo que se
encuentra encapsulado y protegido mediante un recubrimiento entØrico para que su
absorciôn se produzca en la zona intestinal.

Los compuestos que se incorporan en estos nücleos presentan caracterIsticas de
Æcido obase libre y se acompanan de aceites y grasas como triglicØridos, aceites
vegetales, aceites minerales o aceites animales, ceras y Ilpidos. En particular se prefieren los aceites vegetales hidrogenados y entre otros el aceite de ricino, aceite de canela, aceite de coco, aceite de maiz, aceite de eucalipto, aceite de oliva, aceite de palma, aceite de cacahuete, aceite de sØsamo. Dentro de las ceras se prefieren la parafina, la cera carnauba, la cera candelilla, entre otras y dentro de los lipidos se seleccionan los fosfolipidos y glicolipidos.

La cubierta entØrica de la formula se prefiere de copolImeros de Æcidometacrilico y de metil-metacrilato. Y la preparaciOn farmacØutica comprende otros excipientes seleccionados entre lactosa, sucrosa, manitol, sorbitol, almidOn, amilopectina,

Is celulosa, celulosa microcristalina, talco, gelatina y polivinilalcohol.

Anterioridad 133:

La publicaciOn D3 revela los tôpicos en ciencias farmacØuticas para la fabricación de sistemas de liberaciOn pulsÆtil apartir de hidrogeles. La publicaciOn menciona por ejemplo que para la obtenciOn de microparticulas de liberaciOn controlada, tipo tiempo dependiente se utilizan excipientes como etil-celulosa para preparar las cÆpsulas de gelatina,debido a que esta sustancia permite dejar Iibres unos poros de un tamaæoaproximado de 40jm. TambiØn indica que el cuerpo de la cÆpsula se fabrica con HPMC porque la hidrataciOn e hinchamiento de la celulosa induce el incremento de la presiôn osmOtica lo que resulta en la explosion de la cÆpsula.

Y dentro de las aplicaciones de este sistema se encuentra el disenado y desarrollado por Pozzi et al denominado sistema de IiberaciOn a tiempo (TIME CLOCKS system for oral dosage) que permite efectuar una primera IiberaciOn acelerada y una IiberaciOn completa en un intervalo predeterminado. El nücleo contenla salbutamol y como agentes excipientes inclulan PVP, lactosa, almidOn de maIz y estearato de magnesio. Los nicIeos presentan un recubrimiento fabricado a partir de una dispersiOn hidrofObica de una cera carnauba, cera de abejas, polioxietilensorbitÆn monooleato e hidroxipropilmetilcelulosa. El test in vivo de IiberaciOn permitiO

ILl

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demostrar que la desintegracion fue modulada por la peilcula de recubrimientt1(

Anterioridad D4:

La publIcaciôn D4 presenta una metodologla para Ia fabricación de microesferas recubiertas con poilmeros, para tal efecto recurre a la utilización de polimeros hidrosolubles y polimeros insolubles o ceras. Los polimeros solubles disponibles para tal efecto son etil-celulosa, acetato butirato de celulosa y varios polimeros de Æcidoacrilico ya que permiten micropartIculas de Iiberación sostenida.

Los fÆrmacos hidrosolubles puedenser encapsulados por separaciôn de la fase orgÆnica o evaporación de los solventes no acuosos, dado que los fÆrmacos
utilizados son insolubles en solventes organicos o en los aceites usados.

Para ello se puede utilizar el mØtodo de emulsificaciOn agua en aceite mediante la
formaciôn de dispersiones acuosas de polimeros coloidales o como alternativa la emulsificaciôn de las soluciones del polimero orgÆnico enuna fase oleosa.

Los materiales utilizados para obtener las micropartIculas son dispersiones de

etilcetulosa, dispersiones de polietilacrilato y metilmetacrilato, dispersiones de qk polietilacrilato-metil metacrilato, cloruro de trimetilamonioetil metacrilato, aceite de

semilla de algodOn, aceite de sØsamo, aceite de semilla de soya, aceite mineral.

Para la fabricaciôn de las microesferas se prepararon las dispersiones coloidales del
polimero y se emulsificó la fase externa con aceite de semilla de algodon. Luego se
calentO y agitô la mezcla en baæo de agua hasta una temperatura de 600 por
30minutos para lograr evaporar el agua e inducir la fusion de las particulas coloidales
del polimero a lo largo de la superficie de las microesferas. Luego se enfria la
suspensiOn de las micropartIculas en aceite a temperatura ambiente y las
microesferas se recolectan por filtraciOn.

Tabla 1. ComparaciOn tØcnica

Materia Reivindicada Dl D2 D3 D4
MicrocÆpsulas reserve para Composiciones Composiciôn Sistemas de liberaciôn Microesferas de
Iiberación controlada farmacØuticas farmacØutica para pulsÆtil (TIMECLOCK) de IiberaciOn extendida
retardada de perindopril para administraciôn oral de salbutamol que usan
Wainistraciôn oral liberaciôn pH dependiente hidrogeles que se
cterizadas porque: que consiste en: presentan en forma de
tableta, caracterizadas
porgue comprenden:
Microparticulas de perindopril Pellets que contienen un Matrices oleaginosas de N(icleos de lactose, PVP, Microparticulas de
recubiertas con una pelicula de principio activo inhibidor omeprazol hechas de almidón de maiz propanolol HCl
revestimiento constituida por: de la enzima convertidora aceite mineral, aceite estearato de magnesio recubiertas con:
de angiotensina como vegetal hidrogenado, recubierto con:
Perindopnl al menos un parafina, escualeno,
excipiente e incluye un vaselina o lanolina, que
recubrimiento constituido presentan Un
por: recubrimiento pH
dependiente de:
a) Un polimero hidrôfilo Polimero de Æcido a) Un pollmero elegido Dispersiones de HPMC Polietilacrilato
portador de agrupaciones metacrllico, metil entre acetato ftalato de metilmetacrilato o
ionizadas con pH neutro metacrilato, HPMC, entre celulosa, copoilmero de Polietilacrilato-
otros. metacrilato Æcido metilmetacrilato-
metacrilico tnmetilamonioetil
metacrilato

b) Un compuesto hidrôfobo B V de sustancias Aceite de semillas de
con fracciôn mÆsica inferior o hidrófobas como: Cera algodôn o
igual a 40 carnauba, cera de abejas Aceite de sØsamo o
monooleato de sorbitÆn. Aceite de soya o
Aceite mineral o

DiÆmetro inferior a1200pm 150 -250pm

AnÆlisis deDiferencias tØcnicas:

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Al realizar la valoración de la altura inventiva de la materia reclamada se tuvieroi(en cuenta las diferencias con respecto al arte mÆs cercanoa la invención y que se encuentra reportado en las publicaciones Dl y D2.

Respecto de la publicaciôn Dl esta Dependencia encuentra que la materia revelada por el documento corresponde a microgranulados de perindopril con recubrimiento hidrofilico de tipo copolimero de Æcidometacrilico. Y entre su contenido y la materia reivindicada existen dos diferencias tØcnicas a saber: la primera relacionada con la utilización exciusiva de un agente de relleno convencional como lactosa 0 celulosa, el cual, si bien forma parte de las caracteristicas de las formulaciones reivindicadas, en ellas no se encuentra combinado con un aceite vegetal y como parte esencial del recubrimiento sino como agente de relleno de los nücleos y la segunda, la falta de informaciôn respecto del tamano de los pellets de perindopril desarrollados por los investigadores Fischer y colaboradores.

Se debe destacar que si bien en dicha formulación se encuentran tres clases de pellets, para efectos de Ia presente comparaciôn se tiene en cuenta solo la , composición cuali-cuantitativa de los nUcleos con recubrimiento.

La publicaciOn D2, por su parte, revela sistemas de formulaciôn farmacØutica de tipo microgranulado que contienen un nücleo de carÆcter oleoso (hidrOfobo) y una cubierta entØrica de un copollmero de Æcido metacrIlico para la formulaciOn de principios activos que son!Æbiles porque contienen dentro de su estructura estructuras de tipo bencimidazol o grupos ester, lactona, amida, lactama, oxima, imida, entre otros. En los ejemplos mÆs representativos de la publicación se encuentran referencias sobre la formulación de Omeprazol en aceite mineral y con recubrimiento entØrico de acetato ftalato de celulosa. Sin embargo, el documento erifatiza en el hecho de la versatilidad del sistema reivindicado y la posibilidad de formular toda clase de activos que puedan considerarse Miles por efecto de condiciones Æcido-base.

As!, de acuerdo con la descripción de la formula revelada por D2 las diferencias estriban en que alIt no se revelan pellets de perindopril recubiertos con polimeros hidrofilicos e hidrofóbicos, sino matrices oleaginosas de omeprazol recubiertas con polimeros hidrofilicos de metacrilato de liberaciôn pH dependiente.

Con respecto a D3 la diferencia estriba en que alIt no se revelan composiciones microparticuladas de perindopril sino tabletas que presentan como agente activo salbutamol, aün cuando si presentan recubrimiento compuesto por dispersiones de HPMC y ceras, es decir, de un polimero hidrofilico y una sustancia hidrofôbica.

Con respecto a D4 la diferencia estriba en que las microesferas de Iiberación extendida alit reveladas contienen el principio activo salbutamol, sin embargo, su fabricaciOn consiste en obtener un recubrimiento de un pollmero hidrofilico y una sustancia oleosa tipo cera.

Del problema tØcnico objetivo y del efecto inesperado:

De acuerdo con la memoria descriptiva de la solicitud existla la necesidad de disenar una forma de administraciOn que permitiera retardar o garantizar con certeza la Iiberaciôn del principio activo mediante un doble mecanismo: tiempo dependiente y pH dependiente para un principio activo antihipertensor de tipo inhibidor de la enzima de conversiOn de la angiotensina, para ello se combinan efectivamente polimeros hidrOfilos e hidrOfobos en la pellcula de recubrimiento, con el fin de conseguir un

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periodo de latencia de aproximadamente 3 horas en el que se libera en menor porcentaje el activo par causa de un valor de pH entre I y2 y cuando se alcanza un pH de 6,8 se consigue la liberación completa y prolongada del activo par un espacio de 5 horas (ver ejemplos de formulaciones y figuras I a 5 folios 66 a 69 y73 a 75).

Al respecto es preciso senalar que de acuerdo con las caracteristicas tØcnicas de la invenciôn y del principio activo formulado: perindopril, es posible afirmar que la liberación tiempo dependiente y pH dependiente constituye una propiedad derivada de las caracteristicas esenciales de la composicion y esta situaciOn se evidencia claramente con las enseæanzasdel documento D4 en el que se menciona que la solubilidad del principio activo y la cubierta es un tôpico a tener en cuenta cuando se pretende diseæary desarrollar un sistema que contenga una cubierta de polImeros hidrosotubles y poilmeros insolubles o ceras.

En el caso de D4 se plantea que a partir de esta clase de recubrimiento es posible
obtener una liberación sostenida del principio activo par mÆs de 6horas, tat y coma
to evidencia la figura 6 para las microesferas recubiertas con polietilacrilato-metilmetacrilato y cloruro de trimetilamonioetil metacrilato y aceite de semillas de

italgodón. Y al analizar este resultado con el obtenido por la formulaciôn 5 en la figura 5 de la memoria descriptiva se hace evidente que el sistema de Iiberaciôn revelado
en D4 constituye una evidencia clara sobre la posibilidad de mantener una Iiberación
de tan solo el 40% del principio activo durante las ties primeras horas y tan solo del
90% de la formula hasta la hora 6, situación que permite concluir que la cubierta de
poilmero hidrófilo tipo metacrilato en asociaciOn con una sustancia oleosa garantiza
una Iiberación pulsÆtil del agente activo, es decir, una liberaciOn inicial que se retarda en el tiempo y que luego se completa de manera controlada por efecto de la permanencia en el media.

Y si bien es cierta este documento (D4) presenta un sistema para la liberaciOn de salbutamol, al combinar sus enseæanzascon las del documento Dl en el que se presenta un sistema para la Iiberaciôn de perindopril microparticulado, es posible derivar las caracterIsticas tØcnicas de la materia reivindicada.

Ahora bien, el documento D3 seæala que el uso de hidrogeles permite diseæar sistemas de liberaciOn pulsÆtil, esto es, tiempo dependientes que garantizan la entrega del fÆrmaco par periodosprolongados. Y aün cuando el documento presenta un sistema tipo tableta con recubrimiento, alli se trazan las estrategias farmacotØcnicas bâsicas para conseguir una desintegraciOn modulada por efecto de la camposiciOn de la peilcula de recubrimiento, par Ia que al combinar sus enseæanzas conlas del documento Dl en el que se revelan microparticulados de perindopril es posible concluir razonablemente que una persona versada en ciencias farmacØuticas se encontraba en capacidad de Ilegar a una soluciOn coma la que aporta el solicitante, con el fin de canseguir un sistema de IiberaciOn que combine la IiberaciOn retardada con la posibilidad de permanecer par periodos prolongados en el tracto gastrointestinal debido a la composiciOn de la pelicula de recubrimiento.

Par otra parte, las enseæanzas de lapublicaciOn D2 indican claramente que debido a la combinaciôn de las caracteristicas de lipofihicidad de los nücleos en asociación con las caracteristicas de la pehIcula de recubrimiento es que se consiguen sistemas de IiberaciOn pH dependientes, por Jo que una persona conocedora de la matena habria reconocido coma obvio que si se busca un sistema dual: pH dependiente y con capacidad para pemianecer par periodos prolongados en el tracto gastrointestinal to que debe lograr es combinar efectivamente la capacidad hidrOfila de los polimeros como el Æcidometacruhico y la lipofilicidad que presentan las ceras y los aceites de semilla de algadan, tal y coma Ia senala claramente el documento D4, par Ia que las

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caracteristicas de la cubierta no evidencian un salto cualitativo en la regla tØcnia y por el contrarlo, constituyen enseæanzasderivadas del estado del arte que revelan los documentos D2 y D4. Lo anterior, debido a que el documento D2 enseæa claramente sobre la posibilidad de formular molØculas lÆbilesen nücleos de Indole hidrofóbica y con cubierta de tipo polimØrica.

En consecuencia, esta Superintendencia considera que la materia reivindicada carece de altura inventiva y por lo tanto incumple las disposiciones normativas seæaladaspor el artIculo 18 del ordenamiento juridico andino.

6. Conclusion:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados as!:

No Documento N° Reivindicaciones

Afectadas Requisito que Afecta
DI US6267990 I a 13 Nivel Inventivo
D2 US6306435 I a 13 Nivel Inventivo
D31 ArtIculo I I a 13 Nivel Inventivo
D4 I ArtIculo2 1a13 Nivel Inventivo

7. Respuesta a los argumentos del solicitante:

Mediante memorial de fecha 07/11/2008 el seæorsolicitante argumenta lo siguiente:

ael rasgo caracterIstico de las microcÆpsulas deacuerdo con la presente invenciOn reside en Ia composiciOn de Ia pelicula de recubrimiento y no an el uso de una dosis inicialyde dos pellets
que contienen diferentes proporciones tal como indica Dl. Ninguna enseæanzapresente en Dl llevarla al tOcnico versado an la materia a simplificarla composiciOn farmacØutica partiendo de
los tres tipos de microparticulas a un solo tipo de microparticulas sin perder, de manera inesperada, las propiedades originales que consisten en Ia!iberaciOn retardada y controlada de ingrediente activo.

Adicional a esto, la invenciOn revelada en Dl se relaciona con Ia liberaciOn controlada de una preparaciOn farmacOutica, logrando Ia liberaciOn mejorada de un ingrediente activo en funciOn
del tiempo y deipH en los alrededores. Pore! contrario, la presente invenciOn se relaciona con microcÆpsulas parala liberaciOn retardada y controlada de perindopriL La presente invenciOn propone una forma mØdica que permite que el perindopril sea liberado con un perill de ilberaciOn retardada que posee un periodo!atente (I a 8 horas) seguida de una fase de
Iiberación"

Al respecto es preciso seæalar que estaSuperintendencia se encuentra de acuerdo con el seæor solicitante respecto de las caracteristicas de las formulaciones reveladas en Dl, en particular en lo que concierne al hecho de que las composiciones aIll divulgadas presentan tres tipos de microgrªnulos diferentes que permiten modificar la liberación del agente activo, evocando sistemas de Iiberación pulsÆtil asecuenciales, donde el principio activo se libera en varias fases.

Sin embargo, es importante senalar que de acuerdo con los ejemplos representativos de la invención la liberación del agente activo en un pH de 1,4 inicia despuØs de un tiempo de latencia y transcurridas 3 horas se alcanza una liberaciOn del 40% y con pH evolutivo pasando de 1,4 a 6,8, al transcurrir 3 horas se libera un 38% de la formula y Ilegando a las 4 horas se libera el 80% del activo segün la figura
4. En consecuencia, dicha fOrmula que logra retardar el comienzo de la liberaciOn y la prolonga por un periodo de 5 horas mÆsse asemeja a un sistema de Iiberaciôn pulsÆtil, enla que el principio activo se libera de forma secuencial, es decir, en un

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primer evento se realiza una liberación del 40% y al cabo de las 5 horas siguites se consigue la liberación del porcentaje restante del fÆrmaco. (

En consecuencia, si bien la composicion cuali-cuantitativa de los pellets revelados en DI difiere de la reivindicada, en dicho documento se hace referencia a la posibilidad de formular perindopril en forma de granulados con recubrimiento de polimeros de Æcidometacrilico, no en vano en los ejemplos de preparaciOn de dicho antecedente se menciona que la segunda y tercera clase de pellets presentan un recubrimiento con un copolimero aniónico a base de Æcidometacrilico y metilmetacnlato mÆsdibutil ftalato, es decir, ya se tenia conocimiento acerca de la viabilidad tØcnica de combinar perindopril en pellets y recubrirlo para lograr modificaciones en su IiberaciOn. Y si bien es cierto no contempla recubrimientos que incluyan sustancias hidrôfobas, tal y como claramente lo ha indicado el seæorsolicitante, si es posible afirmar que en el estado del arte se conoclan formulas de liberaciôn prolongada de perindopril de acuerdo con las enseæanzas de Dl.

Ahora bien, las curvas de Concentración plasmÆtica vstiempo presentadas por el seæorsolicitante mediante el memorial de respuesta (ver folios 121 y 122) permiten

evidenciar

claramente el tiempo de latencia al que ha hecho referencia el seæor solicitante en la memoria descriptiva de la solicitud y corroborar 10 resultados que se presentan mediante las figuras I a 5. No obstante, mediante el presente requerimiento tØcnico se traslada un documento nuevo en el que se menciona el comportamiento de las formulas de liberaciOn que recurren a la utilizaciOn de microesferas recubiertas con polimeros insolubles o ceras y polimeros hidrofIlicos, en dicho documento D4 queda evidenciado que el efecto inesperado al que hace referencia el seæor solicitanteconstituye informaciOn tØcnica comprendida en el estado del arte desde la dØcada de los 90’s, pero aplicada a otra clase de principios activos, como es el caso de propanolol clorhidrato, por lo que si bien es cierto se reconoce que dicha tecnologIa no habla sido aplicada al principio activo perindopril,
tambiØn es cierto que existlan formas de dosificaciôn en sistemas tipo microesferas
cuya composición de recubrimiento es el mismo que reivindica el seæorsolicitante,
pero aplicado a otro agente.

"el rasgo caracteristico de las microcÆpsulas deacuerdo con Ia presente invenciOn reside en Ia
composiciOn de la pelicula de recubrimiento y no en el uso do una matriz oloosa y un
. recubrimiento entØnco de acuerdo con el arte previo do D2. Adicionalmente, en D2 no existe ninguna enseæanza que loveal tØcnico versado en la materia a recubrirlas microparticulas y
no a cubrir las microcapsulas, sin perder de manera inesperada, las propiedades originales
que consisten en la liberaciOn retardada y controlada del ingrediente activo"

Al respecto es preciso seæalar que sibien en el documento D2 no se menciona la
manera de combinar los polimeros para obtener un recubrimiento que permita Ia
liberaciOn retardada y controlada del agente activo, en dicho documento se menciona que el uso de recubrimientos entØricos, fabricados a partir del mismo polimero hidrofilico que precisa el solicitante en la reivindicaciOn 2, esto es copolimeros de Æcidometacrilico y de un ester de Æcidometacrilico o de copolimeros de Æcidometacrilico y de un ester de Æcidoacrilico, permiten modificar la liberaciOn del agente activo y se pueden comportar como cubiertas entØricas de liberaciOn pH dependiente, es decir, permiten conocer el efecto tØcnico que se logra con su utilizaciOn. En consecuencia, la manera de lograr el mecanismo de liberación dual, esto es tiempo dependiente, iniciada despuØs de cierto tiempo de permanencia en el estomago y liberaciOn pH dependiente iniciada mediante un campo de pH en el momento de la entrada de las partIculas en el intestino delgado, encuentra en cierta medida antecedentes en el documento D2, en particular en lo que tiene que ver con la liberaciôn pH dependiente, situación que configura que para una persona versada

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en ciencias farmacØuticas existia la manera de lograr por lo menos uno de{os efectos buscado con la formulación reivindicada, gracias a las enseæanzas del estado del arte.

En cumplimiento del artIculo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dIas contados a partir de la fecha de notificaciOn de la presente comunicaciôn. En caso de no dar respuesta al presente requerimiento, 0 si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegara la patente.

Notifiquese el presente oficio conf rme a lo dispuesto en el numeral 5.2, literal e), del
capItulo quinto del tit la Circular Unica N° 10 de 2001.

ALIX CARMENJi. CESPEDES DE VERGEL
Directora de Kevas Creaciones (c)

IPEl anterior requerimiento fue notificado por fijaciOn en lista, de fecha

EXAMINADOR TECNICO CONCEPTO TECNICO No. 398 Cadigo No. 202044

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CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA4 No. 72-35
BOGOTA 8, COLOMBIA
Seæora Directora
DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio E. S. D.

Referenda
Asunto

Solicitante
Clase
Fecha de Solicitud

Expediente No. 05.003.952
Solicitud de Patente para
LIBERACION RETARDADA
PERINDOPRIL
LES LABORATOIRES SERVIER
A61 K 009/050
19 de enero de 2005

TelØfono: (57-1) 347 3611

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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No. 05-003952. -00008-000o

Fecha: 2010-04-30 16:42:17 Dep. 2020 DIR.NUEVASCR Trn. 11 PATENTEy Eve: 379 FASENACIONALII Act. 467 SOLICIPRORROGA Folios: 3

TrÆmite: 011
Evento : 379
Actuación: 467

MICROCAPSULAS PARA
Y CONTROLADA DE

1. Yo, LUZ CLEMENCIA DE PAEZ, identificada como aparece al pie de ml firma, actuando como apoderada en el asunto de la referenda, atentamente solicito a Usted se sirva concederme un plazo de treinta (30) dlas, para atØnder el oficio No. 1370 notificado por fijaciOn en

lista del 5 de febrero de 2010.

2. Presento junto con este memorial, el recibo expedido por el Fondo Especial de la Superintendencia de Industria y Comercio, en donde costa el pago hecho por valor de $83.000 en confomiidad con lo dispuesto en Ia resolución No. 69699 del 30 de diciembre de 2009.

Anexos:

Presento asi mismo sustituciOn del poder otorgado por el Doctor EMILIO FERRERO, a mi favor, y para lo cual solicito me sea reconocida personerla para proseguir con el trÆmite de
este asunto en favor de la sociedad solicitante.

SeæoraDirectora,

N. T. 15-JUNIO-2010

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No. M-201 0-1 70208\.ASG

i&
LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de UsaquØn
T.P.A. No. 23.555

NIT. 860.041.367-3

CAVELIER

AOGADOS
EDIFICIO SISKI
WEB SITE: www.cavelier.com CARRERA 4 No. 72 -35
E-MAIL: cavelier@cavelier.com BOGOTA 8, COLOMBIA

Seæores
SUPERINTN1DNCIA DE INDUSTRIA Y CORCIO
E. S. D.

Poderdante : LES LABORATOIRS SERVIER

Poder conferido el: 20/09/2004

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1)217-9211 (57)(1) 310-4995

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cØdula de ciudadania No. 35.456.344 y Tarjeta Profesional N023.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artIculo 66 del CÆdigo de Procedimiento Civil.

Seæora Jefe,

EMILIO FERRERO
T.P.A. NO 31.929

C.C. NO 438.019 de UsaquØn

Acepto:

4; OcT

LIJZ CLEMENCIA DE PAE
T.P.A. No 23.555

C.C. No. 35.456.344 de UsaquØn

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DEPOSITANTE TIPO PASO BANCO CUENTA No. PASO FECHA P80 Vr. PASO

CAVELIER ABOADOS CONSISNACION BANCO DE BOGOTA 062754387 175527354 19/04/2010 56,517000.00

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CANT. RENTISTICO CONCEPTO TOTAL CONCEPTO

1 50005-01-08 PRORROBA DE TERNINOS

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RECIBO BE CAJA APLIC400 AL EXPEDIENTE No.

4** N.CREACION PRORROGA DE TERMINOS 0 TOTAL 4

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