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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 06-042-169

TÍTULO SOLICITADO: “UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE.”

PUBLICACIÓN:

GACETA No. 576 de 31 de Mayo de 2007, número de publicación 71.

SOLICITANTE:

PROCAPS S.A.

APODERADO:

REINALDO PINILLA MORENO

TRÁMITE:

REMISIÓN DE INFORMACIÓN.

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, dentro del trámite de la referencia, por medio del presente escrito, procedo a presentar argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario:

I. REMISION DE INFORMACIÓN.

En primer lugar, es importante señalar que la modificación en el capítulo reivindicatorio, presentada el 27 de Julio de 2010, corresponde a un cambio de

forma, que por esa condición, no logra superar los argumentos planteados en contra por el suscrito, ni aquellos formulados por el examinador técnico. Es así como al revisar dicho nuevo capítulo reivindicatorio, persiste la carencia de nivel inventivo, al mantenerse en esencia las mismas características técnicas (obtención de una composición farmacéutica en solución transparente que contiene Ritonavir para ser incluida en una cápsula de gelatina blanda).

Entrando en materia, y teniendo en cuenta que en dicha respuesta a requerimiento de información, el solicitante expresa que *“Ritonavir, es un activo hidrofóbico y de baja biodisponibilidad oral, que logra mediante la adición del solvente que comprende alcohol tetrahidrofurfurílico polietilenglicol éter, un elevador de la absorción, un antioxidante y una cantidad controlada de agua para formar un sistema básico cuya finalidad es la de originar una fina combinación aceite/agua en micro emulsión tipo SMEDDS, la cual una vez administrada por vía oral y por la motilidad del estómago y del intestino, provee la agitación requerida para la autoemulsificación en vivo, dando como resultado una perfecta distribución de partículas para su absorción en un rango entre 0.02 y 2000 micrones. Por lo tanto, un sistema SMEDDS es una formulación, se usa como alternativa respecto a formulaciones orales convencionales, para asegurar biodisponibilidad.”* es relevante mencionar, que como toda persona medianamente versada en la materia debe reconocer, el concepto de micro emulsión fue introducido por primera vez por Hoar y Schulman en 1943¹; quienes prepararon dicha primera micro emulsión por dispersión de aceite en una solución acuosa de surfactante y agregando un alcohol como co-surfactante, obteniendo así una solución estable y transparente. Así mismo debe reconocer que por sus propiedades de solubilización únicas, estas micro emulsiones son una alternativa atractiva para el diseño de sistemas de entrega de fármacos, como vehículos para aplicaciones tópicas o como mejoradores de la biodisponibilidad de principios activos poco solubles en agua². También se debe tener en cuenta que estos sistemas de micro emulsiones denominados SMEDDS fueron patentados por Gattefossé en la década de los 90³ y aplicados en productos farmacéuticos reconocidos en el

¹ Hoar T.P. and Schulman J. H. “Transparent water in oil dispersions: the oleopathic hydromicelle”. Nature 152: 102 – 103, 1943.

² <http://www.vetcontact.com/presentations/midler1/abstracts/midler.pdf>

³ Farah N. and Denis J. “Orally administrable composition capable of forming a microemulsion”, French Patent FR-B-2 710 535

estado de la técnica tal como lo es el producto ZOCOR® de Merck que contiene Simvastatina.

Muestra de la versatilidad de este tipo de sistemas SMEDDS se puede evidenciar a través de algunas publicaciones de carácter científico que exponen la inclusión de diferentes principios activos en dichos sistemas, veamos:

Examination Of Oral Absorption And Lymphatic Transport Of Halofantrine In A Triple-Cannulated Canine Model After Administration In Self-Microemulsifying Drug Delivery Systems (SMEDDS) Containing Structured Triglycerides⁴.

Abstract: *The potential for lipidic self-microemulsifying drug delivery systems (SMEDDS) containing triglycerides with a defined structure, where the different fatty acids on the glycerol backbone exhibit different metabolic fate, to improve the lymphatic transport and the portal absorption of a poorly water-soluble drug, halofantrine, were investigated in fasted lymph cannulated canines. Two different structured triglycerides were incorporated into the SMEDDS; 1,3-dioctanoyl-2-linoleyl-sn-glycerol (C8:0-C18:2-C8:0) (MLM) and 1,3-dilinoyl-2-octanoyl-sn-glycerol (C18:2-C8:0-C18:2) (LML). A previously optimised SMEDDS formulation for halofantrine, comprising of triglyceride, Cremophor EL, Maisine 35-1 and ethanol was selected for bioavailability assessment. The extent of lymphatic transport via the thoracic duct was 17.9% of the dose for the animals dosed with the MLM SMEDDS and 27.4% for LML. Also the plasma availability was affected by the triglyceride incorporated into the multi-component delivery system and availabilities of 56.9% (MLM) and 37.2% (LML) were found. These data indicate that the pharmaceutical scientist can use the structure of the lipid to affect the relative contribution of the two absorption pathways. The MLM formulation produced a total bioavailability of 74.9%, which is higher than the total absorption previously observed after post-prandial administration. This could indicate the utility of disperse lipid-base formulations based on structured triglycerides for the oral delivery of halofantrine, and potentially other lipophilic drugs.*

Development Of Self-Microemulsifying Drug Delivery Systems (SMEDDS) For Oral Bioavailability Enhancement Of Simvastatin In Beagle Dogs⁵.

Abstract: *The main purpose of this work is to prepare self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability enhancement of a poorly water soluble drug, simvastatin. Solubility of simvastatin was determined in various vehicles. SMEDDS is mixture of oils, surfactants, and cosurfactants, which are*

⁴ Holm R, Porter CJ, Edwards GA, Müllertz A, Kristensen HG, Charman WN. Eur J Pharm Sci. 2003 Sep;20(1):91-7.

⁵ Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH. Int J Pharm. 2004 Apr 15;274(1-2):65-73.

emulsified in aqueous media under conditions of gentle agitation and digestive motility that would be encountered in the gastro-intestinal (GI) tract. Pseudo-ternary phase diagrams were constructed to identify the efficient self-emulsification region and particle size distributions of the resultant microemulsions were determined using a laser diffraction sizer. Optimized formulations for in vitro dissolution and bioavailability assessment were Carprylol 90 (37%), Cremophor EL (28%), and Carbitol (28%). The release rate of simvastatin from SMEDDS was significantly higher than the conventional tablet. The prepared SMEDDS was compared with the conventional tablet (Zocor) by administering the prefilled hard capsules to fasted beagle dogs. The absorption of simvastatin acid from SMEDDS form resulted in about 1.5-fold increase in bioavailability compared with the conventional tablet. Our studies illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds, such as simvastatin by the oral route.

Preparation And Evaluation Of SEDDS And SMEDDS Containing Carvedilol⁶.

Abstract: *A new self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS) have been developed to increase the solubility, dissolution rate, and, ultimately, oral bioavailability of a poorly water soluble drug, carvedilol. Ternary phase diagrams were used to evaluate the self-emulsification and self-microemulsification domains. The self-emulsification time following introduction into an aqueous medium under gentle agitation was evaluated. The minimum self-emulsification time was found at a Tween 80 content of 40%. The particle size distribution and zeta-potential were determined. Benzoic acid had a dual function, it improved the self-emulsification performance of SEDDS and SMEDDS in 0.1 N HCl and lead to a positively charged emulsion. The in vitro dissolution rate of carvedilol from SEDDS and SMEDDS was more than two-fold faster compared with that from tablets. The developed SEDDS formulations significantly improved the oral bioavailability of carvedilol significantly, and the relative oral bioavailability of SEDDS compared with commercially available tablets was 413%.*

Expuesto lo anterior, sólo resta indicar que incluir dichos sistemas dentro de una cápsula de gelatina blanda, tampoco puede sustentar de algún modo una invención, puesto que la tecnología y los procedimientos mediante los cuales se pueden incluir diversos tipos de composiciones líquidas dentro de esta formulaciones son reconocidas con anterioridad y por cualquier persona medianamente versada en la materia⁷.

En conclusión, todos los argumentos expuestos en su momento en el respectivo escrito de oposición presentado por parte nuestra, continúan vigentes en cuanto a sustentar la carencia de nivel inventivo de la solicitud en cuestión, y en complemento, los argumentos expuestos aquí, ratifican que todo lo reivindicado

⁶ Wei L, Sun P, Nie S, Pan W. Drug Dev Ind Pharm. 2005 Sep;31(8):785-94.

⁷ Vila Jato J.L. Tecnología Farmacéutica. Volumen II. Paginas 62 a 67.

por la solicitud colombiana en trámite corresponde a la suma de dos principales tecnologías muy versátiles y aplicadas con anterioridad, como lo son los sistemas de micro emulsiones SMEDDS y las capsulas de gelatina blanda.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS.

- ❖ Copia de todas las publicaciones mencionadas en el acápite de Remisión de información.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

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Microemulsions as drug delivery systems

Olivier Midler
Marketing Director
Gattefossé group

The concept of microemulsion was first introduced by Hoar and Schulman in 1943 (1) ; they prepared the first microemulsions by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co-surfactant, leading to a transparent, stable formulation.

The existence of this theoretical structure was later confirmed by use of various technologies, and we can today adopt the definition given by Attwood (2) : “a microemulsion is a system of water, oil, and amphiphilic compounds (surfactant and co-surfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid”.

The main difference between emulsions and microemulsions lies in the size — and shape — of the particles dispersed in the continuous phase : these are at least an order of magnitude smaller in the case of microemulsions (10 – 200 nm) than those of conventional emulsions (1 – 20 µm). Also, whereas emulsions consist of roughly spherical droplets of one phase dispersed into the other, microemulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bicontinuous structures, making the usual “oil in water” and “water in oil” distinction sometimes irrelevant (3).

Microemulsions are formed when and only when (i) the interfacial tension at the oil/water interface is brought to a very low level and (ii) the interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions, and by the use of a “co-surfactant” which brings flexibility to the oil/water interface.

These conditions lead to a thermodynamically optimised structure, which is stable — as opposed to conventional emulsions — and does not require high input of energy (i.e. through agitation) to be formed.

Because the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent and their structure cannot be observed through an optical microscope.

Microemulsions have been used in a wide range of industries, starting with enhanced oil recovery in the 70's, expanding to a wide range of chemicals and entering the pharmaceutical and cosmetic formulation area a decade ago.

Because of their unique solubilization properties, microemulsions have attracted increasing attention as potential drug delivery systems, either as vehicles for topical applications or as bioavailability enhancers for poorly water soluble active pharmaceutical ingredients (API).

In topical formulations, microemulsions have been proved to increase the cutaneous absorption of both lipophilic and hydrophilic API's when compared to conventional vehicles (emulsions, pure oils, aqueous solutions, etc.). In an extensive review of this type of applications, Kreilgaard et. al. (3) attribute this performance to a generally higher solubility of the API's in microemulsions, generating an increased concentration gradient towards the skin. The role of penetration enhancers played by the amphiphilic components of the microemulsion and the internal mobility of the drug within the vehicle also contribute to the overall performance of microemulsions in dermal or transdermal drug delivery.

Many topical formulations currently marketed are based on microemulsions:

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The dog shampoo "Allermyl" marketed by Virbac is, to our knowledge, the first application of microemulsions to a therapeutic cleansing product ; the use of microemulsion allowed the addition of a higher content of essential fatty acids to the formula.

Solvium is a topical Ibuprofen gel marketed by Chefaro (Akzo). In this case, microemulsion has been used to formulate a poorly soluble active at a dose of 5% into a perfectly transparent gel.

But the most promising potential in microemulsions comes from the advantage they bring to oral route formulations.

Microemulsions enhance the bioavailability of poorly soluble drugs by maintaining them in molecular dispersion in the GI tract and extending the absorption window available in the GI lumen.

This lead to a faster absorption allowing a more rapid onset of drug action. But microemulsions also overcome food effect and reduce subject to subject variability by levelling the differences in digestive capabilities.

Many examples of microemulsion based formulations are now on the market ; Among them, the performances of microemulsions are well demonstrated in the reformulation of Cyclosporin A by Novartis into a microemulsion based formulation marketed under the trade mark Neoral® : this has increased the bioavailability nearly by a factor 2. In addition, Neoral shows a much faster onset of action than the earlier version Sandimmune®, a reduced inter/intra-subject variability and a much lower impact of food intake on cyclosporin pharmacokinetics.

Further promising development have been brought by Self Micro Emulsifying Drug Delivery Systems (SMEDDS), patented by Gattefossé in the 90's (5): these are "latent" microemulsions in the form of a stable, water-free combination of surfactants, co-surfactants and lipophilic phase, which creates a microemulsion when diluted in water or body fluids. Such systems combine the advantages of microemulsions with a water-free formulation protecting sensitive API from the chemical degradation they would undergo in an aqueous medium.

The performance of SMEDDS has been demonstrated by Gattefossé on Simvastatin, a well known anti-hyperlipidemic drug marketed by Merck (Zocor), which is subject to extensive hepatic first pass metabolism. The use of a SMEDDS formulation gives a spectacular (four fold) increase in bioavailability in dogs (6).

Microemulsions are powerful formulation tools for poorly soluble API's, both for the oral and topical administration routes. The availability of efficient, non toxic surfactants and co-

surfactant now makes them a very attractive and feasible option to overcome the bioavailability problems frequently encountered in the development of modern drugs.

1. Hoar T.P. and Schulman J. H. "Transparent water in oil dispersions: the oleopathic hydromicelle". Nature 152: 102 – 103, 1943.
2. Attwood D. Microemulsions in Colloidal drug delivery systems (J. Kreuter ed.), Marcel Dekker, New York 1994.
3. Kreilgaard M. "Influence of microemulsions on cutaneous drug delivery". in Bulletin Technique Gattefossé N°95 : 79 – 100, 2002
4. Meinzer A., Mueller E. and Vonderscher J. in Bulletin technique Gattefossé N°88 : 21 – 26
5. Farah N. and Denis J. "Orally administrable composition capable of forming a microemulsion", French Patent FR-B-2 710 535
6. Benameur H., Jannin V., and Roulot D. "Composition pharmaceutique à usage oral comprenant un principe actif susceptible de subir un important effet de premier passage intestinal", French patent application N° FR-A-2 827 770.

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Eur J Pharm Sci. 2003 Sep;20(1):91-7.

Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides.

Holm R, Porter CJ, Edwards GA, Müllertz A, Kristensen HG, Charman WN.

Department of Pharmaceutics, The Royal Danish School of Pharmacy, Universitetsparken 2, 2100, Copenhagen, Denmark.

Abstract

The potential for lipidic self-microemulsifying drug delivery systems (SMEDDS) containing triglycerides with a defined structure, where the different fatty acids on the glycerol backbone exhibit different metabolic fate, to improve the lymphatic transport and the portal absorption of a poorly water-soluble drug, halofantrine, were investigated in fasted lymph cannulated canines. Two different structured triglycerides were incorporated into the SMEDDS; 1,3-dioctanoyl-2-linoleyl-sn-glycerol (C8:0-C18:2-C8:0) (MLM) and 1,3-dilinoyl-2-octanoyl-sn-glycerol (C18:2-C8:0-C18:2) (LML). A previously optimised SMEDDS formulation for halofantrine, comprising of triglyceride, Cremophor EL, Maisine 35-1 and ethanol was selected for bioavailability assessment. The extent of lymphatic transport via the thoracic duct was 17.9% of the dose for the animals dosed with the MLM SMEDDS and 27.4% for LML. Also the plasma availability was affected by the triglyceride incorporated into the multi-component delivery system and availabilities of 56.9% (MLM) and 37.2% (LML) were found. These data indicate that the pharmaceutical scientist can use the structure of the lipid to affect the relative contribution of the two absorption pathways. The MLM formulation produced a total bioavailability of 74.9%, which is higher than the total absorption previously observed after post-prandial administration. This could indicate the utility of disperse lipid-base formulations based on structured triglycerides for the oral delivery of halofantrine, and potentially other lipophilic drugs.

PMID: 13678797 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

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Int J Pharm. 2004 Apr 15;274(1-2):65-73.

Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs.

Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH.

Department of Polymer Science and Engineering, Chonbuk National University, Duckjin Dong, Jeonju 561-756, South Korea.

Abstract

The main purpose of this work is to prepare self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability enhancement of a poorly water soluble drug, simvastatin. Solubility of simvastatin was determined in various vehicles. SMEDDS is mixture of oils, surfactants, and cosurfactants, which are emulsified in aqueous media under conditions of gentle agitation and digestive motility that would be encountered in the gastro-intestinal (GI) tract. Pseudo-ternary phase diagrams were constructed to identify the efficient self-emulsification region and particle size distributions of the resultant microemulsions were determined using a laser diffraction sizer. Optimized formulations for in vitro dissolution and bioavailability assessment were Carpyrol 90 (37%), Cremophor EL (28%), and Carbitol (28%). The release rate of simvastatin from SMEDDS was significantly higher than the conventional tablet. The prepared SMEDDS was compared with the conventional tablet (Zocor) by administering the prefilled hard capsules to fasted beagle dogs. The absorption of simvastatin acid from SMEDDS form resulted in about 1.5-fold increase in bioavailability compared with the conventional tablet. Our studies illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds, such as simvastatin by the oral route.

PMID: 15072783 [PubMed - indexed for MEDLINE]

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Drug Dev Ind Pharm. 2005 Sep;31(8):785-94.

Preparation and evaluation of SEDDS and SMEDDS containing carvedilol.

Wei L, Sun P, Nie S, Pan W.

Department of Pharmaceutics, Shen Yang Pharmaceutical University, Shen Yang, P.R. China.
weilanlanww@yahoo.com.cn

Abstract

A new self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS) have been developed to increase the solubility, dissolution rate, and, ultimately, oral bioavailability of a poorly water soluble drug, carvedilol. Ternary phase diagrams were used to evaluate the self-emulsification and self-microemulsification domains. The self-emulsification time following introduction into an aqueous medium under gentle agitation was evaluated. The minimum self-emulsification time was found at a Tween 80 content of 40%. The particle size distribution and zeta-potential were determined. Benzoic acid had a dual function, it improved the self-emulsification performance of SEDDS and SMEDDS in 0.1 N HCl and lead to a positively charged emulsion. The in vitro dissolution rate of carvedilol from SEDDS and SMEDDS was more than two-fold faster compared with that from tablets. The developed SEDDS formulations significantly improved the oral bioavailability of carvedilol significantly, and the relative oral bioavailability of SEDDS compared with commercially available tablets was 413%.

PMID: 16221613 [PubMed - indexed for MEDLINE]

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Publication Types:

Comparative Study

MeSH Terms:

Adrenergic alpha-Antagonists/administration & dosage

Adrenergic alpha-Antagonists/blood

Adrenergic alpha-Antagonists/pharmacokinetics

Adrenergic beta-Antagonists/administration & dosage

Adrenergic beta-Antagonists/blood

Adrenergic beta-Antagonists/pharmacokinetics

Animals

Antihypertensive Agents/administration & dosage

Antihypertensive Agents/blood

Antihypertensive Agents/pharmacokinetics

Benzoic Acid

Biological Availability

Carbazoles/administration & dosage*

Carbazoles/blood

Carbazoles/pharmacokinetics*

Chemistry, Pharmaceutical

Dogs

Drug Compounding

Drug Delivery Systems*

Emulsions

Ethylene Glycols



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