

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

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REF: Expediente 02-079-431

TÍTULO SOLICITADO: "NUEVO SISTEMA AUTOEMULSIFICANTE PARA LIBERACIÓN DE MEDICAMENTO"

PUBLICACIÓN: Gaceta 531 de 29-08-2003, número de publicación 1533

SOLICITANTE: Astra Zeneca AB

APODERADO: José Antonio Lloreda

TRÁMITE: Sustentación de Oposición

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JOSÉ LUIS REYES VILLAMIZAR, identificado como aparece al pie de mi firma, reconocido apoderado del opositor en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito me permito ratificar y sustentar los argumentos del escrito principal de oposición, también radicado dentro del plazo de ley ante esa entidad.

I. RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentario para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que se exponen a continuación:

- En cuanto al sistema autoemulsificante, este carece de novedad y nivel inventivo por la publicación US 5.993.858 de 30 de noviembre de 1999, que revela como solución para mejorar la solubilidad y biodisponibilidad de fármacos en general, una formulación de excipientes en forma de sistema autoemulsificante, basada en una emulsión que contiene un aceite u otro lípido, un tensioactivo y un tensioactivo hidrofílico que es un alcohol.

Por tanto resulta obvia la posibilidad de aplicar tal principio técnico a un grupo de fármacos que según la literatura especializada y el propio solicitante,

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presenta conocidos problemas de solubilidad, para lo cual se plantea el empleo de una formulación de excipientes en forma de sistema autoemulsificante que mejore la biodisponibilidad de fármacos poco solubles

- En cuanto a la formación de sistemas autoemulsificantes en medio acuoso, la anterioridad PCT WO99/44584 de 10 de septiembre de 1999 revela el empleo de pre-concentrados para emulsión para lograr formulaciones biodisponibles sobre principios poco solubles, para este caso las ciclosporinas, en presencia de los mismos grupos de excipientes y transportadores empleados en la solicitud colombiana en curso.

De la misma forma, la patente US 5.980.939 de 9 de noviembre de 1999 revela una composición farmacéutica que contiene ciclosporina, un aceite y uno más tensioactivos, la cual presenta la propiedad de lograr la disolución de dicha formulación en medio acuoso, en particular en fluidos gastrointestinales artificiales para formar un autoemulsificante.

El efecto anteriormente descrito es el mismo pretendido por la solicitud que nos ocupa, en tanto una y otra pueden ejercer su acción en medio acuoso -en particular en los fluidos gastrointestinales dada la acción y el efecto de los excipientes en un sistema autoemulsificante, en consecuencia, la solicitud colombiana carece de nivel inventivo puesto que lo revelado en ella pertenece al estado del arte anterior.

- Si de hablar de la existencia de formulaciones para administración oral que comprenden NSAIDs y PPIs, en donde los PPIs están entéricamente recubiertos se trata, cito la PCT/WO97/25064, a través de la cual se revela una forma farmacéutica de dosificación oral preferida en forma de tabletas o cápsulas, que comprende un PPI sensible al ácido y uno o más NSAIDs, estando el primer componente y la formulación entéricamente recubiertos, y cuya utilidad es el tratamiento de los efectos gastrointestinales adversos ocasionados por tratamientos con NSAIDs.

Es obvio que esta publicación anticipa la posibilidad de formular composiciones farmacéuticas para administración oral, simultánea o secuencial de las mismas dos familias que se emplean en la solicitud que nos ocupa, esto es, de NSAIDs y PPIs, con el propósito de lograr el mismo efecto que ahora se presenta como novedoso. Por lo tanto, lo anteriormente transcrito lleva a concluir que lo

pretendido por la solicitud colombiana pertenece al estado de la técnica y carece de nivel inventivo.

- La patente US 5.417.980 de 23 de mayo de 1995, revela el empleo combinado de cantidades efectivas de NSAIDs e inhibidores de bombas de protones – PPIs-, en una misma combinación farmacéutica, para el tratamiento simultáneo del dolor y la indigestión ocasionadas por el exceso en la ingestión de comida y bebida. Por tanto, queda una vez más demostrado que la existencia de formulaciones combinadas de NSAIDs y PPIs para el tratamiento del dolor y desórdenes gastrointestinales carece de nivel inventivo si se tiene en cuenta los documentos anteriormente mencionados.

II. COMPLEMENTACIÓN DE LA INFORMACIÓN

Llamo la atención al despacho a lo revelado en el artículo "Self-Emulsifying Drug Delivery Systems (SEDDS)"¹, donde el autor hace una revisión que proporciona un breve resumen de las formulaciones de sistemas autoemulsificantes de liberación de fármacos, su composición, biodisponibilidad y mecanismos de auto-emulsificación.

Como es sabido, uno de los problemas más persistentes para los formuladores ha sido el encontrar métodos que mejoren la biodisponibilidad de fármacos pobremente solubles en agua ya que su escasa o nula solubilidad en ésta, pueden llevar a una incompleta y errática absorción. Es por esto que se han desarrollado distintos métodos cuyo fin es vencer estos problemas, entre ellos se encuentra la incorporación de compuestos activos lipofílicos pobremente solubles en agua dentro de vehículos de lípidos inertes tal como aceites, dispersiones surfactantes, formulaciones autoemulsificantes y liposomas.

Entre estos se destaca el método de incorporación del fármaco dentro de un líquido autoemulsificante con lo cual la emulsificación para formar la emulsión aceite en agua (o/w) ocurre espontáneamente cuando se mezcla con agua. La formulación de fármacos de la manera descrita anteriormente, representa una

¹ Review Article "Self-Emulsifying Drug Delivery Systems (SEDDS): A Review. Sojan Jose and P. K. Kulkarni. J.S.S. College of Pharmacy, S. S. Nagar, Mysore -15. Aceptado el 12 de junio de 2002. Aunque el artículo fue aceptado después de la fecha de prioridad de la solicitud Colombiana 02-079-431, la mayoría de los documentos citados como bibliografía fueron publicados con anterioridad a ella.

posible alternativa a las tabletas y cápsulas ya que el sistema puede autoemulsificarse con el contenido del estómago, y consecuentemente, el fármaco puede ser rápidamente desalojado del estómago y distribuido en finas gotitas por todo el tracto Gastrointestinal.

De otro lado, la publicación internacional WO 00/16744 del 30 de marzo de 2000 y con prioridades anteriores a la fecha de prioridad de la presente solicitud, revela una nueva preparación en solución que contiene Prostaglandina E1 para el tratamiento de la disfunción eréctil, la cual es preparada a partir de una forma de Preconcentrado para emulsión, que tiene la propiedad de ser fácilmente emulsificada o dispersada por ella misma y cuyo sistema se llama SEDDS o Sistema autoemulsificante de liberación de fármacos, el cual es preparado por dispersión o disolución de un fármaco en una mezcla de aceite, surfactante y co-surfactante.

En consecuencia, la composición farmacéutica para administración oral en forma de un pre-concentrado en emulsión que comprende: i) uno o más AINE (s) liberadores de ON; ii) uno o más tensioactivos; iii) y opcionalmente un aceite o grasa semi-sólida adicional que forma una emulsión aceite en agua (o/w) in-situ al entrar en contacto con los fluidos gastrointestinales revelada en la solicitud colombiana 02-079-431 carece de nivel inventivo y no se traduce en ningún avance sorprendente puesto que el desarrollo de este tipo de formulaciones es ampliamente divulgado en la literatura científica desde los años ochenta -como consta en la bibliografía correspondiente al artículo "Self-Emulsifying Drug Delivery Systems (SEDDS)- y en el contenido del mismo, y en lo revelado en la publicación internacional WO00/16744.

Por lo tanto, ruego sea negada la solicitud en cuestión y como consecuencia de ello, se ordene el archivo del expediente debido al evidente incumplimiento de lo dispuesto en los artículos 14, 15, 16, 18 y 20 de la Decisión 486 de 2000.

III. PRUEBAS

Además de las solicitadas en el escrito de oposición, y de aquellas que oficiosamente considere el despacho, ruego que se tengan como tales las siguientes:

- 3.1. Copia del artículo "Self-Emulsifying Drug Delivery Systems (SEDDS): A Review. Sojan Jose and P. K. Kulkarni. J.S.S. College of Pharmacy, S. S. Nagar, Mysore -15. IJPE - Indian Journal of Pharmaceutical Education. Aceptado el 12 de junio de 2002.
- 3.2. Primera página de la publicación internacional WO 00/16744.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

Indian Journal of Pharmaceutical Education(I.J.P.E)

The Official Journal of A.P.T.I
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ISSN-0019-5484

Indian Journal of Pharmaceutical Education(I.J.P.E) is the official journal of APTI. It is been published from past 33 years (since-1966). It mainly covers the articles of special interest, covering the areas of teaching and learning, laboratory innovations, education technology, curriculum design, examination reforms, training and other related issues. It encourages debates and discussions on the issues of vital importance to Pharmaceutical Education. It is read by about 8000 teachers, about 40,000 students and about 1000 professionals work in Pharma industries, Drug control department, hospitals etc. Few copies of journal are also sent to countries outside India. It also publishes the abstract of research work pertaining to Ph.D.

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OBJECTIVE:

- To serve as a major for publishing papers on pharmacy Education for the academic community.
- To encourage papers that include lab and class room demonstrations, faculty generated educational software, new applications of established computer programmes to the teaching process, curriculum, design, examination reforms and ethics.
- To publish information that impacts of Pharmacy Education from individuals outside the teaching fraternity.
- To publish news about institutions and persons related to profession, debate, continuing education series, technical reviews, obituary, etc.

INSTRUCTIONS TO THE AUTHORS:

Two copies of the manuscript along with passport size photos of authors, should be sent to the editor. The author should certify that the article is not under consideration for publication elsewhere. This is not applicable to news items.

Authors are requested to send their articles in print as well as floppy Disc version. Written in Word Star-4, Microsoft word 97 or higher version. The articles should be typed double spaced and should not exceed eight pages of A4 size. Articles can also be sent through E-mail (ijpeindia@mailcity.com). The editors reserve the right to revise all manuscripts submitted if necessary. Letter to the editor should not exceed one page. The reports for news section should be brief and not exceed half page. For guidance on style, nomenclature, symbols and references, authors should follow the current volume of Indian Journal of Pharmaceutical Education.

All materials submitted for publication is subject to peer-review. Invited editorial, technical reviews, continuing Pharmaceutical Education articles and book reviews are commissioned by the editor. However, new ideas are welcome. All manuscripts must be sent to the editor, Indian Journal of Pharmaceutical Education, JSS College of Pharmacy, SS. Nagar, Mysore-570015, Karnataka, India.

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Review Article

Self - Emulsifying Drug Delivery Systems (SEDDS) : A Review

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ABSTRACT

Several methods are used to improve the bio-availability of water-soluble drugs using inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations and liposomes. The purpose of this review is to provide a brief outline of the formulation of self-emulsifying drug delivery system, which upon dilution forms emulsions of oil in water type. The biopharmaceutical aspects of SEDDS upon ingestion into the GIT are considered. The ease of emulsification could be associated with the ease by which water penetrates into the various liquid crystalline or gel phases formed on the surface of the droplet. Physical characterization of SEDDS should be carried out with particle size analysis and spontaneity of emulsification. This review describes SEDDS as one of the important approaches to overcome the formulation difficulties of potent lipophilic drugs.

INTRODUCTION

The oral route is the preferred route for chronic drug therapy. One of the most persistent problems faced by the formulation scientists has been to find methods of improving the bioavailability of poorly water-soluble drugs. As a drug must almost invariably be in solution within the gastrointestinal tract before it can cross the GI mucosa, poor water solubility may lead to incomplete and erratic absorption. Several methods are used to overcome these problems, such as incorporation of the lipophilic, poorly water-soluble active component into inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations¹⁻⁴ and liposomes. Among these, an important method is to incorporate the drug into a self-emulsifying liquid, whereby emulsification to form oil in water (o/w) emulsion occurs spontaneously on mixing with water. Formulation of drugs in this manner represents a possible alternative to tablets and capsules as the system may be expected to self emulsify in the

contents of the stomach. Consequently, the drug may be rapidly emptied from the stomach and distributed in fine droplet form throughout the GI tract. Usually, these droplets are negatively charged. This would theoretically confer the advantage of a large surface area from which dissolution may occur as well as a reduction in the irritation caused by prolonged direct contact between drugs in conventional dosage forms and the gut wall². Recently, it is proved that the absorptive cells, as well as the other cells in the body are negatively charged with respect to the mucosal solution in the lumen⁵. It was shown by Gershanik and Benita that positively charged emulsion droplets formed by appropriate SEDDS dilution undergo electrostatic interaction with the caco-2- monolayer and the mucosal surface of the everted rat intestine. Positively charged formulations differ from negatively charged formulations with respect to their interaction with biological component in the GI environment⁶⁻⁷. Positively charged droplets should be attracted to the negatively charged physiological compounds naturally occurring in the lumen.

Larger droplets (few microns in size range) are less neutralized by mucin solutions of different concentrations than smaller droplets (sub micron size range). A similar behavior was observed in different SEDDS which, upon aqueous dilution, resulted in positively charged coarse or fine emulsions, or microemulsions. Thus the droplets size/ bioavailability correlation is much more complex in positively charged formulations.

SEDDS comprises of an oil component and a surfactant, (the oil component comprises an oily carrier and optionally, a lipophilic oily fatty alcohol) the oil in water emulsion which forms upon dilution of the SEDDS with GI contents have oily droplets, which are either negatively or positively charged.

The formulation of SEDDS is simple; involving incorporation of the drug into a suitable oil surfactant mix until a clear solution is formed. This solution can be filled into soft or hard gelatin capsules.

* Corresponding Author

Composition of SEDDS

Pouton revealed that the self-emulsification process is specific^{1,8,9} to the nature of the oil - surfactant pair. The process depends on

1. Oils
2. The surfactant concentration and oil/surfactant ratio
3. The temperature at which self-emulsification occurs

A SEDDS consists of

I. OILS

Both long and medium - chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduced their use in SEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages¹⁰. Now a days, MCTs are replaced by novel semi-synthetic MCT which can be defined as amphiphilic compounds exhibiting surfactant properties¹⁰.

II. SURFACTANTS

Non-ionic surfactants with relatively high HLB values are used in the design of SEDDS. Eg: Ethoxylated polyglycolysed glycerides, Tween-80¹⁰. They are considerably less toxic compared to ionic surfactants, but they may cause moderate reversible changes in intestinal wall permeability.¹ The usual surfactant concentration in SEDDS required to form and maintain an emulsion state in the GIT ranged from 30 - 60% w/w of the formulation. The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self-emulsifying performance. The surfactants are amphiphilic in nature, and they are usually able to dissolve and solubilize even relatively high quantities of the hydrophobic drug. The latter is of prime importance in preventing precipitation within the GI lumen and for the prolonged existence

of the drug molecules in the soluble form, which is vital for effective absorption.^{3, 11}

iii. CO- SOLVENTS

Relatively high surfactant concentration (usually more than 30% w/w) is needed in order to produce an effective SEDDS. Organic solvents suitable for oral administration (ethanol, propylene glycol, poly ethylene glycol) may help to dissolve large amounts of hydrophilic surfactant or the drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the microemulsion systems, although alcohol-free self-emulsifying micro emulsions have also been described in the literature.¹⁰

Drug Incorporation into SEDDS

The addition of drugs to SEDDS is very critical since the drug interferes with the process of self-emulsification to an extent usually by changing the optimal oil/surfactant ratio. SEDDS performance alteration can be caused either by blocking charge movement through the system, via the direct complexation of the drug with some mixture components through its interaction with the liquid crystalline phase,^{4,12} or by penetration into the surfactant interfacial monolayer.^{2, 4,13}

FORMULATION OF SEDDS.

One method of formulating SEDDS is to liquid fill soft gelatin capsules, as this presents a simple method of incorporating the surfactant-oil mixture. Alternatively, hard gelatin capsules may be used if a gelatin band is included to prevent leakage. However, in addition to considering the most suitable oil-surfactant combination in terms of emulsion formation, it is also necessary to consider the acceptability of the components. Due to their favorable oral toxicity profiles, non-ionic surfactants such as Tweens and glyceride-based oils such as Miglyol and Labrafil (polyoxyethylated oleic glycerides) have been studied. A major consideration in the choice of vehicle is the solubility of the drug; and the efficiency of self-emulsification may have to be compromised in order to allow the use of a soft gelatin capsule, which is of a realistic size. Furthermore, problems such as the hygroscopicity of the contents causing dehydration of the gelatin shell or solute migration into the shell must also be considered.

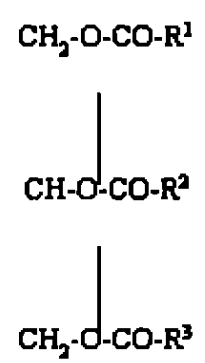
For example, Craig et al¹⁴ studied the incorporation of a poorly soluble benzodiazepine derivative containing Labrafil M 2125 CS, propylene glycol, Tween 80 and the drug in various ratios. These systems produced droplets in the μm range rather than the nm range, but were nevertheless chosen for study as more efficient emulsifying systems could not incorporate the drug in suitable quantities.¹⁴

BIOAVAILABILITY OF DRUGS FROM SEDDS

While the considerations relating to the formulation of SEDDS are of clear importance in developing these systems as viable dosage forms, it is equally important to have some understanding of what happens to these systems on ingestion. As most SEDDS are based on triglycerides, it is helpful to consider the mechanisms by which these materials are absorbed from the GI tract.

1. The absorption of fats from the gastrointestinal tract

Triglyceride molecules are fatty acid esters of glycerol and have the general structure



where R¹⁻³ are saturated or unsaturated alkyl groups. The saturated fatty acids commonly found in the diet are long chain, mainly palmitic and stearic (C16, C18), while the most common unsaturated acid is oleic (C18, 1 double bond) and linoleic (C18, 2 double bonds). A much smaller quantity of medium chain triglycerides may also be present (C8-12). The ester groups of the triglycerides are prone to hydrolysis and this represents the major initial route of metabolism within the GI tract. On ingestion of the triglycerides, the lipids enter the stomach. Some hydrolysis of the triglycerides may occur in the stomach due to the presence of gastric lipase, but the reaction is not extensive and the major role of

the stomach in the digestion of fats is believed to be one of emulsification of the fats via mechanical agitation. On entering the upper section of the small intestine, two processes occur. The fat droplets are further emulsified by the bile salts, monoglycerides, cholesterol, lecithin and lysolecithin to produce droplets with a diameter of approximately 0.5-1 μm . Bile is released from the gall bladder under the influence of the enzyme cholecystokinin (CCK) and contains bile salts, bile pigments, phospholipids and cholesterol. The triglyceride droplets are then metabolized by pancreatic lipase, an enzyme with a molecular weight of approximately 40,000. The enzyme is specific to the 1- and 3-ester linkages of the triglyceride molecule, producing diglycerides (which are further metabolised), free fatty acids and 2-monoglycerides, the last two contributing to the digestion process as they themselves are emulsifying agents.

The fatty acids are distributed between the aqueous solution, the emulsion droplet and the micelles, while the monoglycerides are incorporated into the micelles and are believed to swell the structure, allowing incorporation of other water-insoluble components such as certain vitamins. The micelles then diffuse through the gut contents to the intestinal mucosa, adjacent to which is an unstirred water layer. Incorporation into micelles facilitates this diffusion process compared to the much larger oil droplets. Once in the intestinal mucosa, the monoglycerides are resynthesised into triglycerides and covered with a layer of lipoprotein, cholesterol and phospholipid. The resulting particles (known as chylomicrons) are released into lymphatic system. A smaller proportion may also be incorporated into very low-density lipoproteins (VLDL). Short chain fatty acids may diffuse directly into the portal supply, while longer chain acids (<12C) are resynthesised into triglycerides in the intestinal mucosa.

2. Bioavailability of drugs from oily vehicles

Given the processes described above, it is perhaps questionable whether drug absorption from SEDDS is simply a function of increased dissolution from the large surface area afforded by the emulsion. Bates and Sequeira¹⁵ compared the absorption of griseofulvin from commercial tablets, a corn oil emulsion (equivalent to 12g oil) and an

aqueous suspension in humans. The authors found that the emulsion gave a much more rapid excretion of the griseofulvin metabolite, desmethylgriseofulvin. The authors also reported that the absorption enhancement was considerably greater in emulsified oil than in a comparable dose unemulsified oil. The authors suggested that factors such as the inhibition of gastric motility caused by the presence of the lipid might have allowed more time for dissolution and absorption of the drug. Alternatively, the presence of the emulsified oil may have stimulated bile secretion, which, for the reasons described above, may have improved bioavailability. Both hypotheses were supported by the observation that increasing the dose of oil to 12g caused an increase in the maximum excretion rate and the cumulative total excreted up to 6g oil. Similar dose-response profiles have been reported for decreases in intestinal motility and gall bladder emptying¹⁶. Later hypotheses have included increased mucosal permeability via incorporation of lipids from mixed micelles¹⁸ and enhanced mesenteric lymph flow.¹⁷

3. Drug absorption from SEDDS

A number of studies have investigated the effects of drug incorporation into SEDDS, on bioavailability of drugs, particularly cyclosporin. This drug is available in oil-based formulation [SandimmuneR]²⁰ which is composed of olive oil, alcohol and Labrafil in the ratios 40:18:42 and cyclosporin, in a concentration of 100mg/ml. This formulation may be described as self-emulsifying in that an emulsion may be formed by mild agitation. Administration involves gently mixing the drug-containing oil with several millilitres of a non-carbonated liquid prior to administration, although this is largely to disguise the taste of the medication.¹⁹ Using conventional dosage forms, absorption is slow and erratic, while the system described earlier showed considerably enhanced absorption.²⁰

Tarr and Yalkowski showed the importance of the emulsion particle size using stirred and homogenised SandimmuneR. By reducing the particle size from 4 mm to 2 mm, the whole blood concentration taken 2 hours after perfusion increased from 0.906 mg/L to 1.51 mg/L. Furthermore, increasing the length of intestinal tissue over which perfusion took place had little effect on drug

absorption, implying the presence of an absorption window along the intestine.

In a study by Charman et al,² a SEDDS was compared to PEG 600. While the average percentage bioavailability was similar in both cases, the reproducibility and C_{max} value was found to be higher for the SEDDS formulation. The authors suggested that as the oil phase was a medium chain triglyceride (Neobee M5), lymphatic uptake was unlikely to be enhanced, hence the drug absorption may simply be a function of the increased surface area for dissolution provided by the emulsion. The authors also suggested that the presence of the surfactant in the formulation (Tagat TO) might play a role in increasing the absorption of the drug. This is a consideration that has received comparatively little attention within this field and may be of considerable relevance to the uptake process.

MECHANISM OF SELF-EMULSIFICATION

According to Reiss, self emulsification occurs, when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion.¹⁴ The free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation $\Delta G = 4\pi N r^2 \sigma$ where ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and σ represents the interfacial energy. With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to coalescence.²¹

A method of quantitatively assessing the ease of emulsification by monitoring the turbidity of the oil surfactant systems in a water stream, using phosphated nonylphenoxylate (PNE) and phosphated fatty alcohol ethoxylate (PFF) in n-hexane was developed. The authors related emulsification (expressed as the equilibration time) to the phase behaviour, and indicated that these

mixtures exists in liquid crystal and gel phases in water, depending on the composition and consequently they related phase behaviour to the spontaneity of emulsification, with liquid crystal forming compositions tending to form emulsions more readily and on this basis they suggested that, the emulsification process may be associated with the ease with which water penetrates the oil-water interface. With the formation of liquid crystalline phases resulting in swelling at the interface, thereby resulting in greater ease of emulsification.²²

The correlation between the ease of emulsification and the phase behaviour of oil-surfactant water systems; using a range of pharmaceutically relevant mixtures was investigated, and the correlation was found to hold for some but not all systems. For example, liquid paraffin, tween-80, and span-80 mixtures showed reasonable correlation between liquid crystal formation and emulsion formation, while benzyl alcohol mixed with the same surfactants showed little relationship between the two parameters.

The involvement of the liquid crystal phase in the emulsion formation process was studied and concluded that the specificity of surfactant combinations required to allow spontaneous emulsification may be associated with a minimization of the phase inversion temperature, thereby increasing the ease of emulsification, which may also explain the empirical observation by Lin et al. that there is an inverse relationship between the ability of span-20/tween-20 mixes of varying ratios to solubilize water and the particle size of emulsions formed containing mineral oil i.e., those combinations of surfactants that showed the greatest water solubilization also resulted in emulsions with the lowest particle size.²³

In case of self-emulsifying systems, the free energy required to form the emulsion is either very low, and positive, or negative (then, the emulsification process occurs spontaneously.)⁴ Emulsification requires very little input energy, involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing.²⁴ In earlier work it was suggested

that the ease of emulsification could be associated with the ease by which water penetrates into the various liquid crystal or gel phases formed on the surface of the droplet¹.

The addition of a binary mixture (oil/ non-ionic surfactant) to water results in interface formation between the oil and the aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilization limit is reached close to the interface.⁸ Further aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self emulsification process, causes interface disruption and droplet formation. The high stability of these self-emulsified systems to coalescence is considered to be due to the liquid crystal interface surrounding the oil droplets.

A combination of particle size analysis and low frequency dielectric spectroscopy was used to examine the self emulsifying properties of a series of Imwitor 742 (a mixture of mono- and di-glycerides of capric and caprylic acids/tween 80) systems which provided evidence that the formation of the emulsions may be associated with liquid crystal formation, although the relationship was clearly complex.⁴ The presence of the drug may alter the emulsion characteristics, possibly by interacting with the liquid crystalline phase.

The mechanism of self-emulsification is still a complex one but provides a useful basis for further study and debate.

EVALUATION OF SEDDS

Few methods have been proposed in the literature to characterize the self-emulsifying performance. Visual assessment may provide important information about the self-emulsifying properties of the mixture and about the resulting dispersion system^{14,25,26} although more objective criteria are required for efficient SEDDS evaluation and

comparison. Pouton proposed the estimation of the efficiency of self-emulsification by evaluation of the rate of emulsification and the particle size distribution.¹⁴ He used turbidity measurements to identify efficient self-emulsifying systems by establishing whether the dispersion reached equilibrium rapidly and in a reproducible time. Shah et al.,³ pointed out the role of emulsion droplet polarity, in addition to droplet size, as an important emulsion characteristic. The polarity of the oil droplets is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. Size of the emulsion droplet is considered to be a decisive factor in self-emulsification/dispersion performance, since it determines the rate and extent of drug release and absorption.³ Droplet/particle size is usually established by the photon correlation spectroscopy (PCS) method.^{3,25,27} Efficient emulsification was arbitrarily defined by Shah et al., as a system which produces mean emulsion droplet diameter values of less than 5 μ m. Further reduction of droplet size led to the development of SEDDS capable of forming thermodynamically stable, isotropic, clear o/w dispersions.

Positively charged SEDDS recently developed by Gershanik and Benita,²⁵ introduced a new parameter for SEDDS characterization: the charge of the resulting droplets. The emulsion droplets resulting from the aqueous dilution of conventional SEDDS formed by traditional oil/non-ionic surfactant blend carry some negative charge, possibly provided by free fatty acids present in the mixture. Incorporation of a small amount of a cationic lipid, oleylamine [2.5-3%] into such a system reversed the charge nature, leading to the formation of emulsion droplets, which exhibit a positive - potential value of about 35-45mV. This positive potential value was also preserved after the incorporation of the model drug.

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(21) International Application Number: PCT/KR99/00568 (22) International Filing Date: 21 September 1999 (21.09.99) (30) Priority Data: 1998/39462 23 September 1998 (23.09.98) KR 1999/34157 18 August 1999 (18.08.99) KR (71) Applicant (for all designated States except US): GUJU PHARM. CO., LTD. [KR/KR]; 341-1, Jegi-ri, Jungnam-myun, Hwasung-kun, 445-940 Kyunggi-do (KR). (72) Inventors; and (73) Inventors/Applicants (for US only): LEE, Sang, Soon [KR/KR]; 207-206, Daelim Apt., Paeungchou-dong, Dungan-gu, Anyang-city, 431-070 Kyunggi-do (KR). CHOI, Young, Wook [KR/KR]; 111-103, Banpo Apt., Banpo-dong, Seocho-gu, 137-040 Seoul (KR). LEE, Sang, Kil [KR/KR]; 3-102, Bugang Village, 758 3 Chwon-dong, Changan-gu, Suwon-city, 440-200 Kyonggi-do (KR). PARK, Goo, Bae [KR/KR]; 1175-4, Baekmok-dong, Iban-gu, Koyang-city, Kyonggi-do 411-360 (KR). (74) Agent: KIM, Joo, Cheon; Suite 306, Changlim Building, 816-3, Yoksam-dong, Kungnam-ku, Seoul 135-081 (KR).	(81) Designated States: CA, CN, DE, GB, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IL, IT, LU, MC, NL, PT, SI). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: A PHARMACEUTICAL SOLUTION FOR THE TREATMENT OF ERECTILE DYSFUNCTION, PREPARED BY SEDDS FORMULATION Legend: O : Oil only M : Microemulsion TL : Transparent Liquid E : Emulsion T : Turbid Liquid		
(57) Abstract The present invention relates to a new solution preparation containing prostaglandin E1 for the treatment of erectile dysfunction, which is prepared into a form of microemulsion preconcentrate. This preparation has a property, upon administration to a human body, of easily emulsifying or dispersing of itself and is of a system called a self-emulsifying drug delivery system (hereinafter to be referred to as "SEDDS"), which is prepared by dispersing or dissolving a drug into a liquid mixture of oil, surfactant and cosurfactant.		

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José Antonio Lloreda
Apoderado

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Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorios Legrand S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

12 MAR. 2004

El anterior requerimiento fue notificado por fijación en lista de fecha, _____.

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