

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

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Abogado
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ASUNTO	Radicación	10-001885
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	12 - 18308
	Folios	12

Patente de Invención	☐	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☐	Cap. I	☐
		Cap. II	☒

No. Solicitud Internacional PCT/US2008/069301
Fecha de Presentación Internacional 07/julio/2008

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 21 a 33	08/enero/2010
Reivindicaciones:	Folios 34 a 79	08/enero/2010
	Folios 111 a 112	08/Abril/2010
Prioridad:	US 60/949,268	12/julio/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida" modificado Fl. 70 a 71.

El problema planteado en esta solicitud consiste en la necesidad de suministrar una composición farmacéutica estable a la conversión quiral de N-{4-(2,2-dimetil-

propionil)-(5R)-5-(2-etilamino-etanosulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il]-2,2-dimetilpropionamida para una mayor estabilidad de almacenamiento a término largo.

Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica de N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etano sulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il]-2,2-dimetilpropionamida y buffer pH 2 - 4.2.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K9/19, A61K31/433.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 1 y 6 define a la composición farmacéutica porque no contiene más de 2.0% de N-{4-(2,2-dimetil-propionil)-(5S)-5-(2-etilamino-etano sulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il]-2,2-dimetilpropionamida, pero esta no es una característica esencial de una composición, sino es el resultado a alcanzar de la conversión quiral de la forma enantiomérica R. La reivindicación no se puede definir por el resultado a alcanzar, porque no sólo incluye la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere al señor solicitante escribir la reivindicación de composición solo en términos de componentes y proporciones.

Las reivindicaciones 1, 5, 6 y 10 define a la composición farmacéutica por el pH (menor que 4.2 y mayor que 2.0), pero esta no es una característica esencial de una composición, sino es el resultado a alcanzar del proceso de preparación de la composición. La reivindicación no se puede definir por el resultado a alcanzar, porque no sólo incluye la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere al señor solicitante escribir la reivindicación de composición solo en términos de componentes y proporciones.

Las reivindicaciones 6 y 9 no son claras porque reclaman el pH de una composición liofilizada pero no es posible determinar el pH a un sólido porque el pH es la medida de la concentración de iones H+ de una solución. Se sugiere al señor solicitante hacer las correcciones respectivas.

5. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de prioridad (12/julio/2007) y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	CA2602397	Agent for treatment of solid tumor	28/septiembre/2006
D2	US20040014994	Method for resolving chiral (2S) and (2R) chromanes	22/enero/2004

D1.http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=CA&NR=2602397A1&KC=A1&FT=D&ND=&date=20060928&DB=&locale=en_EP

Divulga composiciones farmacéuticas inyectables de una solución de N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonil-amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida e isómero R o mezcla racémica (R/S), con excipientes como agua destilada, manitol y cloruro de sodio a pH 7 (Pág. 35, 60 y 61).

D2. <http://www.google.com/patents/US20040014994?printsec=abstract&dq=lyophilized+formulations+buffer+chiral+conversion+and+stability&ei=6GZbUPXJKYW68AS6l4CgDw#v=onepage&q=lyophilized%20formulations%20buffer%20chiral%20conversion%20and%20stability&f=false>

Divulga composiciones farmacéuticas liofilizadas para solución inyectable de (2S)(2R) benzopirano, buffer fosfato, citrato y otras sales de ácidos orgánicos donde el pH es menor que 8 y mayor que 2.0 para tener un enantiómero puro (Pág. 5 y 6).

6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en una composición farmacéutica caracterizada porque comprende *N*-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida, un buffer y/o sal seleccionada entre tartrato, fosfato, citrato, mesilato, fosfato de sodio, sulfato de sodio, y un vehículo, diluyente o excipiente en solución acuosa en donde el pH de dicha composición es menor que 5.4 y mayor que 2.0 y contiene no más de 2.0% de *N*-{4-(2,2-dimetil-propionil)-(5S)-5-(2-etilamino-etano sulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida. (SIC)

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D2
Composición farmacéutica que comprende	Composición farmacéutica (solución inyectable) que comprende	Composición farmacéutica (liofilizada para solución inyectable) que comprende
N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida contiene no más de 2.0% de N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etano sulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida	N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida contiene no más de 2.0% de N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etano sulfonil amino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida	(2S)(2R) benzopirano
Buffer y/o sal seleccionada entre tartrato, fosfato, citrato, mesilato, fosfato de sodio, sulfato de sodio donde el pH es menor que 5,4 y mayor que 2.0	Cloruro de sodio donde el pH es 7	Buffer y/o sal seleccionada entre fosfato, citrato y otras sales de ácidos orgánicos donde el pH es menor que 8 y mayor que 2.0
Un vehículo, diluyente o excipiente en solución acuosa	Agua como diluyente en solución acuosa	No menciona

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la
Primer Artículo 45- Expediente 09-125378

invención definida en la reivindicación 1 porque divulgan composiciones farmacéuticas para administración inyectable.

El documento D1 da a conocer composiciones farmacéuticas inyectables de una solución de N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida e isómero R o mezcla racémica (R/S), con excipientes como agua destilada, manitol y cloruro de sodio a pH 7 (Pág. 35, 60 y 61).

El documento D2 divulga composiciones farmacéuticas liofilizadas para solución inyectable de (2S)(2R) benzopirano, buffer fosfato, citrato y otras sales de ácidos orgánicos donde el pH es menor que 8 y mayor que 2.0 para tener un enantiómero puro (Pág. 5 y 6).

La diferencia entre la invención, definida en la reivindicación 1 y las composiciones farmacéuticas del documento D1 consiste en que la invención menciona un buffer y/o sal seleccionada entre tartrato, fosfato, citrato, mesilato, fosfato de sodio, sulfato de sodio donde el pH es menor que 5.4 y mayor que 2.0.

La diferencia entre la invención, definida en la reivindicación 1 y las composiciones farmacéuticas del documento D2 consiste en que la invención tiene como fármaco la N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida.

No se evidencia que por el hecho de emplear un buffer y/o sal seleccionada entre tartrato, fosfato, citrato, mesilato, fosfato de sodio, sulfato de sodio donde el pH es menor que 5.4 y mayor que 2.0, se tenga una mejor estabilidad de almacenamiento a término largo.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar las composiciones farmacéuticas conocidas en el documento D1 para conseguir composiciones farmacéuticas alternativas".

Sin embargo, es conocido en el documento D2 un buffer y/o sal seleccionada entre tartrato, fosfato, citrato, mesilato, fosfato de sodio, sulfato de sodio donde el pH es menor que 5.4 y mayor que 2.0 para tener un enantiómero puro. Adicionalmente es conocido para una persona versada en la materia, la aplicación de un medio ácido para resolver una mezcla racémica (R/S) de los derivados de aminas para obtener un enantiómero puro.¹ Por otra parte, son actividades rutinarias en el área de desarrollo galénico de las empresas farmacéuticas hacer ensayos que evalúen la influencia del pH, con el objetivo de determinar la composición farmacéutica que evite la conversión quiral al enantiómero indeseable y así tener una mayor estabilidad de almacenamiento a término largo.²

En consecuencia, la persona del oficio normalmente versada en la materia, estaría motivada a usar un buffer y/o sal seleccionada entre tartrato, fosfato, citrato, mesilato, fosfato de sodio, sulfato de sodio donde el pH es menor que 5.4 y mayor que 2 para tener un enantiómero puro y evitar la conversión quiral al enantiómero S de composiciones farmacéuticas para administración inyectable que contienen el fármaco N-{4-(2,2-dimetil-propionil)-(5R)-5-(2-etilamino-etanosulfonilamino)-

¹ Sadri A. Said. Stereoselective Transformations of Chiral Amines. Norwegian University of Science and Technology Department of Chemistry. January 2002. Pág. 15.

² Mukesh C. Gohel. Overview on Chirality and Applications of Stereo-selective Dissolution testing in the Formulation and Development Work. Pág. 15 a 20.

metil]-5-fenil-4,5-dihidro-[1,3,4] tiadiazol-2-il}-2,2-dimetilpropionamida. Por lo cual se considera obvia.

Conclusión:

La reivindicación 1 no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 2 a 10 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	CA2602397	1 a 10	Nivel inventivo
D2	US20040014994	1 a 10	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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 No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ

Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 16 OCT. 2012

Elaborado por: Ruth Angélica Lizarazo Pedraza 
 Revisado por: Consuelo Leguizamón Leguizamón
 Aprobado por: José Luis Salazar López

Stereoselective Transformations of Chiral Amines

Sadri A. Said



January 2002

Norwegian University of Science and Technology
Department of Chemistry

A thesis submitted in partial fulfillment of the requirements for the
Dr.ing. degree

1.4.5 Deracemization techniques

As described earlier, resolution methodologies are among the effective means for the production of enantiomerically pure compounds. However, these methods are obstructed by some disadvantages for practical applications. The most obvious limitation of resolution methodologies is that the theoretical yield can not exceed the maximum of 50%. Therefore, any procedure that can directly convert a racemate to a single enantiomer is highly advantageous. These processes are generally known as 'deracemization' and are divided in three general categories⁸³: a) repeated racemizations and resolutions, b) dynamic kinetic resolution and c) enantioselective stereoinversion.

1.4.5.1 Repeated racemization and resolutions

The loss of half of the substrate in resolution processes could be avoided by / racemization of the unwanted isomer after separation from the desired enantiomer and subjecting it again to resolution in the next cycle. This process can be repeated until all of the racemic material has virtually been converted to a single enantiomer. The overall yield of the desired isomer can reach a value of more than 95% after only few cycles when both racemization and resolution processes proceed without loss of the material⁸³. Racemization can be achieved by several methods, but the most important industrial methods are acid- or base-catalyzed and thermal racemizations⁸⁴ (Scheme 1.5).

The base catalyzed procedure is the most widely used process for racemization of secondary chiral amines and alcohols. It is applicable to all compounds bearing an acidic hydrogen at the stereogenic center and is achieved via achiral enolate type intermediates (Scheme 1.5). On the contrary, the acid catalyzed process is limited to only few substrates due to its restriction to compounds capable of keto-enol tautomerism. Heat labile chiral compounds such as those possessing axial chirality, for example DABN (**32**) (Scheme 1.5), can be racemized through rotation around a σ -bond and are viable substrates for thermal racemization.

Most of the racemization techniques suffer from the disadvantage that they require harsh reaction conditions leading to side reactions and loss of materials.

Overview on Chirality and Applications of Stereo-selective Dissolution testing in the Formulation and Development Work

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Abstract

The importance of chirality is considered in various areas such as purchasing of active pharmaceutical ingredient, selection of adjuvants in dosage form development, in vitro dissolution studies, stability studies, in vitro/ in vivo correlation (IVIVC), dossier preparation for technology transfer, ANDA/NDA applications and in scale up and post approval changes (SUPAC). The use of chiral selective dissolution testing is recommended for certain drugs that exist in racemic form in order to assess the performance of a product, both *in vitro* and *in vivo*. An extension of the Biopharmaceutics Classification System (BCS) is suggested for drugs that undergo chiral conversion after permeation through gastrointestinal wall, taking into account that the amount of active form of the drug reaching the receptor site is more important. It is suggested that the shelf life for chiral drugs shall be determined by considering the amount of degradation of the active form (R or S) of the drug. This paper also gives a brief overview of work done on chirality from the viewpoint of formulation of dosage forms.

Introduction

Chiral molecules exist in a pair of stereoisomers (enantiomers). If a plane of polarized light is passed through a sample of each enantiomer, one will rotate the light to the left (levorotatory or (-)-enantiomer or R-form), and the other will rotate the light to the right (dextrorotatory or (+)-enantiomer or S-form). Rotation of light will not be observed if the light is passed through an equimolar mixture (racemic mixture). Scientists have started using prefixes such as lev- (e.g. levibupropfen), dex- (e.g. dexmethylphenidate), ar- (e.g. arbupivacaine) and es- (e.g. esomeprazole) to describe enantiomerically pure active pharmaceutical ingredients (API). A glossary of the selective terms related to stereochemistry is given in Table 1¹. Rentsch² reported that about 56% of the synthetic drugs currently in use are chiral compounds, and 88% of these chiral synthetic drugs are used therapeutically as racemates. However, the recent trend in industry is to market the drugs in a pure enantiomeric form to give new life to old drugs by patenting the pure enantiomer. Stephen³ reported that a worldwide sale of chiral drugs in single enantiomer was \$133 billion in 2000. Forty percent of all dosage form drug sales in 2000 were of a single enantiomer. In 1999, the share was only one third. The advantages of marketing the drug in pure enantiomeric form are shown in Table 2⁴. Racemic switch or chiral switch means that racemic mixtures are redeveloped as single enantiomers³.

Table 1: Glossary of Selective Terms in Stereochemistry¹

Chiral inversion	Conversion of one enantiomer into its mirror image /
Distomer	Refers to the enantiomer with lower pharmacological affinity or activity
Enantiomer	Stereoisomer whose mirror images cannot be superimposed
Eutomer	Refers to the enantiomer with higher pharmacological affinity or activity
Isomers	Compounds that have identical molecular formulae but differ in nature or sequence of bonding of their atoms or in the arrangement of their atoms in space
Racemate	A mixture of equimolar amounts of enantiomers
Racemization	Conversion of an enantiomer to its racemate

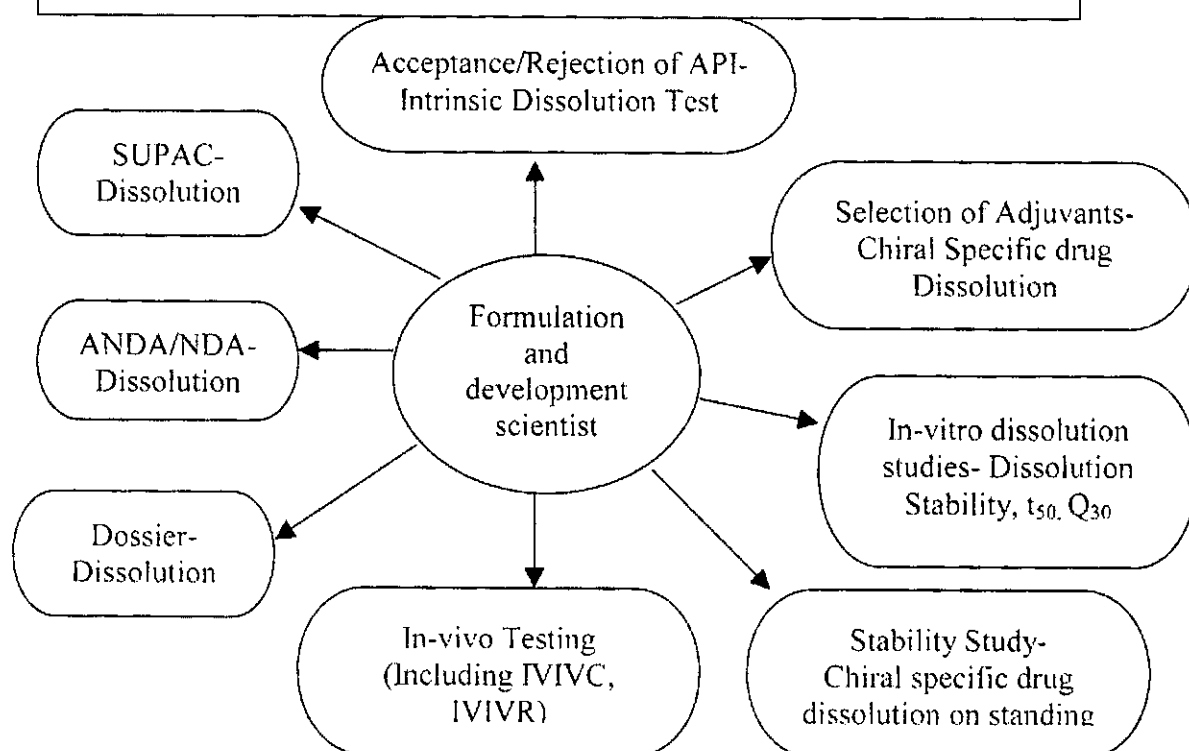
Table 2: Advantages of using more active isomer of a drug⁴

It leads to opportunities for "racemic switching"
Increase in production capacity
Less waste (API manufacturer viewpoint)
Dose will be halved
Less likelihood of side effects

Table 3: In Vivo Effect of Enantiomers

Both enantiomers exhibit similar therapeutic properties (e.g. Promethazine, Flecainide) ⁶
Only one isomer shows pharmacological activity (S-propranolol is a beta blocker) while the other one is inactive (R-propranolol) ⁵
One type of isomer may show one type of pharmacological activity (S-penicillamine) and the other one shows toxicity (R-penicillamine) ⁴
One type of isomer may show one type of pharmacological activity (R- methylphenylpropyl barbituric acid – anesthetic) and the other type shows convulsant effect ⁵ .

Figure 1. Applications of Chirality in Formulation and Development



Enantiomeric forms of a drug can produce different therapeutic or adverse effects. Table 3 shows the different possibilities⁴⁻⁶.

Applications of Chirality from the viewpoint of Formulation Development:

Many reports are found in literature on the applications of chirality in manufacturing of API and chiral separation. However, there are only few reports from the perspective of formulation and development (F&D). Pharmaceutical companies around the world have registered significant success in racemic switching. Therefore, F&D scientists now have to focus their attention on chirality. The applications of chirality from the viewpoint of F&D are schematically shown in Figure 1.

Acceptance/ Rejection of API:

The analytical chemist generally carries out routine tests on drug purity (assay) and related impurities at the time of purchasing API. The chirally pure drugs should be quantitatively analyzed for the presence or absence of chiral impurities besides the routine determination of related impurities. Tao and Cooks⁷ recently reported that quantitative chiral analysis could be done by tandem MS. The method is rapid and requires very little sample. Lou⁸

recently reported that it would be useful to determine enantiomers and other structurally similar drug impurities using one rather than two analytical methods.

The pharmaceutical companies should accept or reject a sample of API based on the ratio of the active/inactive enantiomers in the non-racemic mixtures. This ratio may change from one vendor to another. Most pharmaceutical companies do not consider this fact at the time of purchase. The success or failure of the formulation and development team may depend upon this ratio. The *in-vitro* dissolution test and *in-vitro/in-vivo* correlation (IVIVC) are the two major areas where the differences may be observed if an eye is not kept on chirality when API is purchased. The intrinsic dissolution rate of chirally pure API may prove to be a useful quality control parameter.

Selection of Adjuvants:

Formulation and development scientists add a number of adjuvants with diversified purposes in pharmaceutical formulations. Adjuvants are added to facilitate manufacturing, for functionality improvement, and to improve appearance and stability. The adjuvants may be either chiral or non-chiral in nature. The type and amount of the adjuvant may determine the functionality of the dosage form, especially the drug release rate. The characteristics of

Overview on Chirality and Applications ... continued

adjuvant such as solubility, compressibility, surface area, porosity, etc. are considered today in F&D. However, very little attention is given to the nature of adjuvant from the viewpoint of chirality.

A few references are cited below to show the effect of adjuvant type on drug release.

Solinis et al.⁹ studied the release of salbutamol and ketoprofen enantiomers from hydroxypropylmethylcellulose (HPMC) K100M matrices containing two types of cellulose derivatives. The authors concluded that stereoselectivity is dependent on the amount of chiral excipient in the formulation.

Srichana and Suede¹⁰ examined the *in vitro* dissolution of salbutamol from matrix tablets containing various chiral excipients such as gamma cyclodextrin, heptakis (2,6 di-O-methyl) -beta cyclodextrin, sulfobutyl-beta-cyclodextrin, HPMC and egg albumin. The formulation containing gamma cyclodextrin provided significant stereoselectivity throughout the dissolution profile. The release of eutomer R-salbutamol was higher than that of the distomer S-salbutamol from the gamma cyclodextrin tablets.

Suede et al.¹¹ monitored enantioselective *in vitro* release of propranolol. The influence of the method of polymer synthesis, drug to polymer ratio, pH, and temperature on the release of two enantiomers was determined. The study revealed that release of eutomer can be controlled via means of formulation. The distomer was retained in the dosage form.

Stereoselective interaction of ibuprofen was evaluated with chiral excipients such as HP-beta-cyclodextrin, tartaric acid, sucrose, HPMC, methylcellulose and a non-chiral excipient citric acid. The coprecipitates showed higher dissolution rate. The presence of chiral excipients did not cause stereoselective release of the drug¹².

An area which can be tapped by the F&D chemist is to control the drug release in the initial phase of drug dissolution by using a chiral adjuvant that exhibits binding affinity for the drug. This is sometimes necessary in real practice to match the *in-vitro* dissolution profile of the test product with that of the innovator's product. The objective may be achieved by preparing a bi-layer tablet. Applications of interaction between API and chiral excipient may be explored in the areas of sustained release buccal dosage form and colon drug delivery system. Teamwork between an expert analyst in chiral science and an F&D scientist may open up many avenues in formulation development work.

In Vitro Dissolution Studies and In Vivo Studies

The industrial pharmacist considers dissolution testing an invaluable tool since it provides useful information throughout the formulation development work, i.e. from preparing the first trial formulation to the final marketed product. The dissolution profile of an innovator product and

any limits prescribed by the health regulatory agencies are kept in mind while carrying out the developmental work.

Yonemochi et al.¹³ reported that the molecular arrangement in a crystal of enantiomers is different than that for racemic compound. If the difference in crystal structure results in a change in the melting point and heat of fusion, then the solubility of the pure enantiomers may be different from that of the racemic compound. The authors reported that the initial dissolution rate of racemic propranolol HCl was three times greater than that of enantiomers in distilled water.

For the drugs that exist in the racemic form where activity of the drug is attributed to one of the forms (R or S), we should not talk about the cumulative amount of drug (R plus S) released from the dosage form but about the percentage of the active enantiomer released with respect to time. This is now very much possible with the advancements made in analytical techniques such as capillary electrophoresis, simulated moving bed chromatography, etc.

A single point dissolution specification such as t_{50} (time required for 50% API dissolution) or Q_{30} (amount of API dissolved in 30 min) is routinely employed as a quality control release test and it is also used for establishing dissolution stability on storage. For the drugs where only one of the forms (R or S) is active, the use of a stereoselective dissolution test is recommended for the calculation of t_{50} or Q_{30} .

The results of chiral specific drug dissolution in a biorelevant dissolution medium or compendia media may be used for the selection of an appropriate formulation for *in vivo* studies or for convolution-deconvolution studies. Data may also be submitted to regulatory agency to obtain bio-waiver or for SUPAC for immediate release formulations.

After establishing the similarity of *in vitro* dissolution testing between a reference and a test product in different dissolution media, *in vivo* testing in man (bioequivalence testing) is ordered. It is a hard fact that many experimental formulations fail to establish an IVIVC. In such cases, reverse engineering is ordered. The major concern for any pharmaceutical company is the loss of time and money due to such failures. There may be multiple reasons for the failure of bioequivalence studies. In establishing Level A IVIVC for the products with significantly dissolution rate-limited absorption (and essentially complete absorption), one should consider the fraction of dose of active isomer dissolved versus the fraction of active isomer dose absorbed. The same approach may be used for calculation of parameters such as mean dissolution time (MDT) or mean residence time (MRT). We must also remember that the living body is a highly chiral environment. It is worthwhile to note here that optical isomers exhibit significant differences in their affinities for the receptor site, protein binding and biotransformation.

Bui et al.¹⁴ assessed *in vitro* dissolution testing and bioequivalence of two formulations of chlorpheniramine tablets. Dissolution tests showed that both formulations were equivalent. A nonstereoselective, but not a stereoselective, approach indicated bioequivalence between the formulations.

A pure enantiomer may be converted to another form after absorption or it may remain in its original form. The S- form of ibuprofen is the active form but significant R to S inversion takes place in the body. Therefore, even when ibuprofen is administered in racemic form, the drug exhibits 75% of the activity of the esibuprofen at the same dose level⁵. The use of stereoselective assay method is recommended in selected cases. The two enantiomers of thalidomide are inter-converted far too quickly (8 hr) in the liver⁵. S-thalidomide exhibits teratogenic effect whereas R thalidomide is sedative. For thalidomide there is no point in giving pure enantiomer because of inter-conversion. It is worthwhile to note here that some drugs may not undergo *in-vivo* conversion (R to S or S to R). In such cases, enantioselective determination in bioequivalence testing is not the absolute requirement.

The biopharmaceutics classification system (BCS) guidance of US FDA classifies the drugs in four classes considering the solubility and permeability of drugs. Once the drug meant for oral use dissolves in gastro-intestinal fluid and subsequently permeates through the membrane, it enters into general circulation. One should remember that some drugs may undergo chiral conversion in blood. In such cases, the pharmacological action will depend upon the amount of unchanged active enantiomers reaching the receptors. Enantioselective analysis should be adopted in cases where there is the possibility of chiral conversion in blood. The third dimension can be added to BCS, i.e. chiral conversion for the drugs where only one form (R or S) is active and the other form is inactive (Table 4). The drugs that fall under Class 1B will show superior action as compared to Class 1A. Each area shown in Table 3 may be explored in this way.

Polli¹⁵ reported that one intent of *in vitro-in vivo* relationship (IVIVR) is to learn about the relative contribution of dissolution to a product's overall absorption kinetics. Here also, chiral-specific dissolution can be used.

Stability Study:

In the FDA's policy statement for the development of new stereomeric drugs, it is mentioned that the stability protocol for enantiomeric drug substances and drug products should include a method or methods capable of assessing the stereochemical integrity of the drug substance and drug product¹⁶. However, once it has been demonstrated that stereochemical conversion does not occur, stereoselective tests might not be needed.

The stability study program must address the issue of

Table : 4 Extension of Biopharmaceutics Drug Classification System

Class	Solubility	Permeability	Chiral Conversion*	
			A	B
I	High	High	A	High
			B	Low
II	Low	High	A	High
			B	Low
III	High	Low	A	High
			B	Low
IV	Low	Low	A	High
			B	Low

- *chiral conversion: An active form of drug is converted into an inactive form in bloodstream. For racemic drugs, the fraction of dose of active enantiomer reaching the receptor site is more relevant for pharmacological response.
- High: Higher amount of active enantiomer is converted to inactive form.
- Low: Lower amount of active enantiomer is converted to inactive form.

chiral inversion and racemization. Pomponio et al. carried out photostability studies on inclusion complexes of racemic nicardipine with beta-cyclodextrin and 2-hydroxypropyl beta-cyclodextrin. Beta-cyclodextrin showed photoprotective effect (UV-A and UV-B radiations); conversely 2-hydroxypropyl beta-cyclodextrin favoured the drug photodegradation. The photodegradation was found to follow apparent first-order kinetics and two different kinetic constants were obtained for the two different enantiomers¹⁷.

Interactions between enantiomers have also been described¹. Racemization, or action or process of changing from an optically active compound or an optically inactive mixture of corresponding dextro (d-) and levo forms is a major factor in pharmaceutical stability¹⁸.

Shelf life of pharmaceutical formulation is fixed after considering 90% or 95% drug degradation under stated conditions of drug storage. This could be the amount of inactive/active enantiomer. For the racemic drugs where the action is attributed to one form (R or S), the scientist should talk about the amount of active enantiomers (R or S) degraded. We should not be surprised if the FDA starts assigning shelf life on the basis of degradation of active enantiomers since that seems to be more realistic.

Besides chemical stability, dissolution stability is also an equally important issue for popular dosage forms such as tablets and capsules. Many tablets show protracted disintegration on standing and such a change will generally result in change in dissolution rate. In select cases, the use of enantioselective dissolution is recommended to ascertain dissolution stability.

Dossier for Technology Transfer

The responsibility of the F&D team is not only to develop a functional formulation but also to prepare a well-docu-

Overview on Chirality and Applications ... continued

mented dossier so that consistency from lot to lot is maintained in a marketed formulation. All the drugs that exist in racemic form and the drugs that are used in the pure enantiomer need special attention at the time of dossier preparation. The FDA and other applicable agencies' practices (ICH, Pharmacopoeia, etc.) shall be kept in mind while preparing the dossier. Good dossier preparation practice may prove to be useful at the time of inspection by the regulatory agencies.

NDA/ANDA Application

The current applicable guidance documents shall be kept in mind while preparing the applications. We should also keep in mind that increasing the desired activity should not be accompanied by a rise in the untoward effect. FDA requires toxicology testing on the racemate. The data of stereoselective dissolution testing should be submitted for the enantiomers that exhibit different action (e.g. methylphenylpropyl barbituric acid). There are endless opportunities and it is difficult to address all relevant issues in this communication. The current guidance documents should be consulted at the time of submitting an application.

Summary

Change in the formulation and development work may be reflected into change in drug dissolution and stability. The commonly used excipients such as beta-cyclodextrin, HPMC, maltodextrin, etc., may affect the drug release rate. The use of chiral selective dissolution testing or non-chiral dissolution testing should be considered on a case-by-case basis for chiral API. In the coming years, scientists will carry out research in arresting undesirable chiral conversion in the blood stream. The dose of API can be reduced if researchers are able to arrest conversion of an active form of a drug into an inactive form of a drug. Finally, it is concluded that chirality is going to be an important issue even in F&D work, and the use of stereoselective dissolution testing is going to find widespread applications.

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