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DIRECCIÓN DE NUEVAS CREACIONES**

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Abogado
CARLOS R. OLARTE
(Apoderado)

ASUNTO	Radicación	09057912
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	12600
	Folios	015

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/EP2007/010785

Fecha de Presentación Internacional 4/12/2007

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 le comunica:

1. Documentos estudiados:

1.1. Descripción: Folios: 53 a 103 4/06/2009

1.2. Reivindicaciones: Folios: 104 a 117 4/06/2009

1.3. Prioridad: US 60/872.830 04/12/2006

2. Análisis de la prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

Título de la solicitud: SAL DE POTASIO CRISTALINA DE ANÁLOGOS DE LIPOXINA A4.

El problema planteado en esta solicitud consiste en la necesidad de sales cristalinas de un análogo de lipoxina A4 para el tratamiento de enfermedades inflamatorias.

Para resolver este problema técnico la solicitud en estudio proporciona sal de potasio

cristalina de lipoxina A4 de fórmula I.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07C51/41, 59/70; A61K31/192; A61P29/00.

4. Excepciones de patentabilidad (artículo 20 D486 literal a)-d))

De acuerdo con lo anterior, la(s) reivindicación(es): 44 (Folio: 117), que se refiere(n) a un método de tratamiento de un estado patológico, no es (son) patentable(s) porque es un método para tratar una enfermedad por lo cual está exceptuado de patentabilidad.

5. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486)

La(s) reivindicación (es) 36 a 43 (folios: 114 a 116), que se refiere(n) al uso de una sal de potasio cristalina de un análogo de lipoxina A4 no se encuentra(n) dentro del campo de la patentabilidad (productos y procedimientos).

6. Análisis de la(s) oposición(es): (artículo 43 D. 486)

No se presentaron oposiciones al objeto reivindicado.

7. Determinación del estado de la técnica:

La fecha que se ha tenido en cuenta para determinar el estado de la técnica es:

Fecha de presentación de la solicitud prioritaria 4/12/2006

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontraron como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	WO03/040080	Lipoxin A4 analogs	15/05/2003
D2	Journal of Pharmaceutical Sciences	Pharmaceutical Salts ¹	Enero 1977

D1 (Fls. 167 a 171): menciona compuestos análogos de lipoxina A4 entre los cuales están compuestos específicos de los de la presente solicitud; además, enseña distintas sales farmacéuticamente aceptables que dichos compuestos pueden formar, entre las cuales están las de potasio.

D2 (Fls. 172 a 177): divulga generalidades sobre sales farmacéuticas, propiedades fisicoquímicas, estabilidad, biodisponibilidad, etc. Entre las sales más usadas están las de potasio.

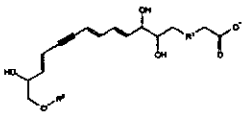
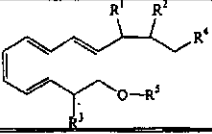
1 S. M. Berge, L. D. Bighley y D.C. Monkhouse. "Pharmaceutical Salts". Journal of Pharmaceutical Sciences. Volumen 66, número 1, enero de 1977.

8. Examen de patentabilidad (artículo 14 D486)

8.1. Nivel inventivo (artículo 18 D486)

La presente solicitud de patente reivindica lo siguiente: una sal de potasio cristalina de la fórmula (I), en donde el compuesto de fórmula (I) es un estereoisómero individual o cualquier mezcla de estereoisómeros.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características técnicas esenciales	D1	D2
		No menciona
Sal de potasio cristalina	Sales farmacéuticamente aceptables: potasio que son cristalinas	Generalidades sobre sales farmacéuticas entre ellas están las de potasio

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan el compuesto de fórmula (I) y sus sales (pág. 11, líneas 3 a 10, Fl. 168, reivindicación 9, compuestos 2 y 4, Fls. 170 y 171), así como aspectos generales sobre sales farmacéuticas (Fls. 172 a 177).

La diferencia entre la invención, definida en la reivindicación 1, y el compuesto del documento D1 consiste en que no se especifica la sal de potasio.

La diferencia entre la invención, definida en la reivindicación 1, y el documento D2 consiste en que no se especifica el principio activo.

El efecto que logra formar sales de potasio del compuesto de fórmula (I) es que mejora la estabilidad y propiedades farmacéuticas del compuesto base, pero este efecto no fue demostrado ni comparado con el arte anterior en la presente solicitud.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “¿cómo modificar el compuesto de lipoxina A4 conocido en el documento D1 para hacerlo más estable?”.

Sin embargo, la formación de sales farmacéuticas para mejorar la estabilidad y otras propiedades fisicoquímicas, ya está divulgada en el documento D2 que se refiere a los conceptos generales sobre sales farmacéuticas, (Fls. 173 a 176) tipos de sales como las de potasio (Fl. 173, tabla I), estabilidad de las sales y su influencia en la solubilidad y biodisponibilidad de los fármacos (Fls. 176 y 177).

La persona del oficio normalmente versada en la materia enfrentada con la tarea de proveer sales de potasio de un análogo de lipoxina A4 con la actividad deseada, puede darse cuenta que a partir de los documentos D1 y D2, dicho análogo puede estar en forma de sal de potasio y, que además, puede estar en forma cristalina, o en forma de hidrato o anhidra. Hay que tener en cuenta que los compuestos descritos en el documento D1 son intrínsecamente cristalinos y no es sorprendente que sus formas anhidras o hidratadas se puedan presentar.

La preparación de compuestos anhidros y la determinación de su tendencia a pasar

de forma anhidra a forma hidratada son de conocimiento general y es una práctica rutinaria en investigación la obtención de una u otra forma dependiendo de los requerimientos del investigador, por lo cual carecen de nivel inventivo las formas anhidras e hidratadas de las sales de potasio del compuesto de fórmula (I).

En ausencia de un efecto inesperado mostrado por las sales de potasio reivindicadas en relación con lo conocido en el arte anterior, la solución al problema técnico parece ser obvia a la luz de los documentos D1 y D2.

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

9. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO03/040080	1 a 35	Nivel Inventivo
D2	Journal of Pharmaceutical Sciences	1 a 35	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 días contados a partir de la fecha de la 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 N° 10 de 2001.


JESUS FERNEL GARCÍA G.
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 19 8 JUL. 2012

Elaborado por: Lina Patricia Forero T. 
Revisado por: Ana Delia Pinzón 

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(74) Agents: ZELANO, Anthony, J. et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza 1, 2200 Clarendon Boulevard, Suite 1400, Arlington, VA 22201 (US).

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(71) Applicant (for all designated States except US): SCHERING AKTIENGESELLSCHAFT [DE/DE]; 13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BAUMAN, John, G. [US/US]; 5466 Deer Run Drive, El Sobrante, CA 94803 (US). GUILFORD, William, J. [US/US]; 1881 Robin Whipple Way, Belmont, CA 94002 (US). PARKINSON, John, F. [GB/US]; 6727 Waverly Road, Martinez, CA 94553 (US). SKUBALLA, Werner [DE/DE]; Mattersburger Weg 12, 13465 Berlin (DE). SUBRAMANYAM, Babu [IN/US]; 497 McCall Drive, Benicia, CA 94510 (US).

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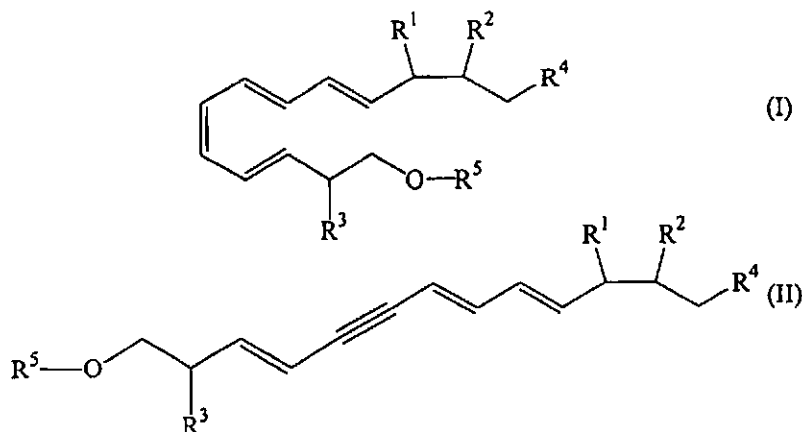
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LIPOXIN A₄ ANALOGS



(57) Abstract: This invention is directed to lipoxin A₄ analogs of the following formulas (I) and (II), wherein R¹, R², R³, R⁴ and R⁵ are described herein. These analogs are useful in treating inflammatory and autoimmune disorders in humans. These analogs are also useful in treating pulmonary or respiratory tract inflammation in humans.



WO 03/040080 A2

methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

“Pharmaceutically acceptable base addition salt” refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

“Prodrugs” is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term “prodrug” refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted *in vivo* to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

A discussion of prodrugs is provided in Higuchi, T., *et al.*, “Pro-drugs as Novel Delivery Systems,” *A.C.S. Symposium Series*, Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

The term “prodrug” is also meant to include any covalently bonded carriers which release the active compound of the invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the invention may

The compounds of the invention, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, e.g., polyoxyethylene glycols and polyethylene glycols (PEG), e.g., PEG 1000 (96%) and PEG 4000 (4%).

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., a compound(s) of the invention (about 0.5% to about 20%), as a single stereoisomer, a mixture of stereoisomers, or as a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof, and optional pharmaceutical acceptable adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, as a single stereoisomer, a mixture of stereoisomers, or as a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof, for treatment of a disease-state characterized by inflammation in accordance with the teachings of this invention.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disease-states; and the host undergoing therapy. Generally, a therapeutically effective daily dose is from about 0.14 mg to about 14.3 mg/kg of body weight per day of a compound of the invention, as a single stereoisomer, a mixture of stereoisomers, or as a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof; preferably, from about 0.7 mg to about 10 mg/kg of body weight per day; and most preferably, from about 1.4 mg to about 7.2 mg/kg of body

R^{13} is a branched alkylene chain, a straight or branched alkenylene chain or a cycloalkylene.

7. The compound of Claim 6 wherein:

R^1 , R^2 and R^3 are each independently halo, $-OR^6$, or $-SR^6$;
 R^4 is $-R^9-O-R^{10}-R^{11}$;

R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy) or aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aryl, or aralkyl;
 each R^7 is independently hydrogen, alkyl, aryl, or aralkyl;

R^9 is a direct bond or a straight or branched alkylene chain;

R^{10} is an straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene; and

R^{11} is $-C(O)OR^7$ or $-C(O)N(R^7)_2$.

8. The compound of Claim 7 wherein:

R^1 , R^2 and R^3 are each $-OR^6$;

R^4 is $-R^9-O-R^{10}-R^{11}$;

R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy);

R^6 is hydrogen, alkyl, aryl, or aralkyl;

each R^7 is independently hydrogen, alkyl, aryl, or aralkyl;
 R^9 is a direct bond;

R^{10} is a straight or branched alkylene chain; a straight or branched alkenylene chain, or a straight or branched alkynylene chain; and

R^{11} is $-C(O)OR^7$ or $-C(O)N(R^7)_2$.

9. The compound of Claim 8 selected from the group consisting of the following:

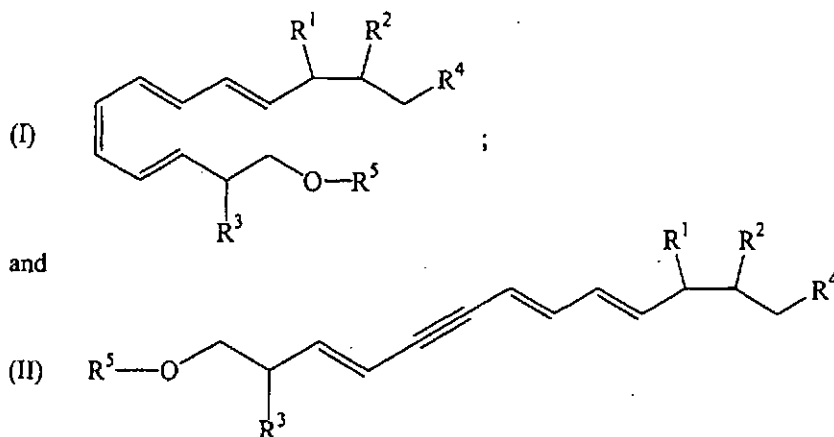
(5*S*,6*R*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid, methyl ester;

(5*S*,6*R*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid;

(5*S*,6*S*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid, methyl ester, and

(5*S*,6*S*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid.

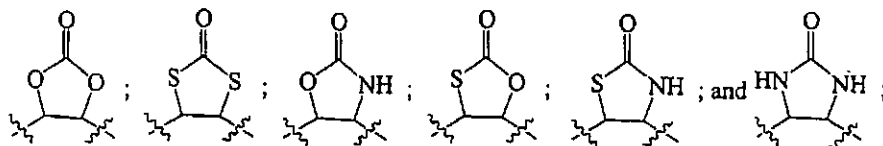
10. A pharmaceutical composition useful in treating an inflammatory or autoimmune disorder in a mammal, which composition comprises one or more pharmaceutically acceptable excipient(s) and a therapeutically effective amount of a compound of formula (I) or formula (II):



wherein:

each R^1 , R^2 and R^3 are independently halo, $-OR^6$, $-SR^6$, $-S(O)_tR^7$ (where t is 1 or 2) or $-N(R^7)R^8$;

or R^1 and R^2 together with the carbons to which they are attached form a monocyclic heterocyclic structure selected from the following:



or R^1 and R^2 together with the carbons to which they are attached form the following bicyclic heterocyclic structure:

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REVIEW ARTICLE

Pharmaceutical Salts

STEPHEN M. BERGE^{*,†}, LYLE D. BIGHLEY^{*}, and
DONALD C. MONKHOUSE^{*}

Keyphrases □ Pharmaceutical salts—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Salts, pharmaceutical—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Physicochemical properties—dissolution, solubility, stability, and organoleptic properties of pharmaceutical salts, review □ Bioavailability—formulation effects, absorption alteration and pharmacokinetics of pharmaceutical salts, review □ Toxicology—pharmaceutical salts, review

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The chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form. Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to

Salt-forming agents are often chosen empirically. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis: cost of raw materials, ease of crystallization, and percent yield. Other basic considerations include stability, hygroscopicity, and flowability of the resulting bulk drug. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles.

Some decision-making models have, however, been developed to help predict salt performance. For example, Walking and Appino (1) described two techniques, "decision analysis" and "potential problem analysis," and applied them to the selection of the most suitable derivative of an organic acid for development as a tablet. The derivatives considered were the free acid and the potassium, sodium, and calcium salts. Both techniques are based on the chemical, physical, and biological properties of these specific derivatives and offer a promising avenue for developing optimal salt forms.

Information on salts is widely dispersed throughout the pharmaceutical literature, much of which addresses the use of salt formation to prolong the release of the active component, thereby eliminating various undesirable drug properties (2-6). This review surveys literature of the last 25 years, emphasizing comparisons between the properties of different salt forms of the same compound. Included also is a discussion of potentially useful salt forms. Our purpose is twofold: to present an overview of the many different

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Table I—FDA-Approved Commercially Marketed Salts

Anion	Percent ^a	Anion	Percent ^a
Acetate	1.26	Iodide	2.02
Benzenesulfonate	0.26	Iserthionate ¹	0.96
Benzoate	0.51	Lactate	0.76
Bicarbonate	0.13	Lactobionate	0.13
Bitartrate	0.63	Malate	0.13
Bromide	4.66	Maleate	3.03
Calcium edetate	0.25	Mandelate	0.36
Carbamate ²	0.25	Mesylate	2.02
Carbonate	0.36	Methylbromide	0.76
Chloride	4.17	Methylnitrate	0.36
Citrate	3.03	Methylsulfate	0.86
Dihydrochloride	0.51	Mucate	0.13
Edetate	0.25	Napsylate	0.25
Edisylate ³	0.32	Nitrate	0.64
Estolate ⁴	0.13	Pantoate (Embonate)	1.01
Erylate ⁵	0.15	Pantothenate	0.25
Fumarate	0.25	Phosphate/diphosphate	3.16
Glucaptate ⁶	0.13	Polygalacturonate	0.13
Glucuronate	0.51	Salicylate	0.83
Glutamate	0.25	Stearate	0.25
Glycylglycylsarcosinate ⁷	0.13	Subacetate	0.38
Hexylresorcinate	0.13	Succinate	0.32
Hydrobamine ⁸	0.25	Sulfate	7.46
Hydrobromide	1.00	Tannate	0.58
Hydrochloride	42.92	Tartrate	3.54
Hydroxynaphthoate	0.25	Teoclate ⁹	0.13
		Triethiodide	0.13
Cation	Percent ^a	Cation	Percent ^a
Organic:		Metallic:	
Benzathine ¹⁰	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.93	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.32
Meglumine ¹¹	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

^a Percent is based on total number of anionic or cationic salts in use through 1974. ¹ Camptorsulfonate. ² 1,2-Ethanedithiolate. ³ Lauryl sulfate. ⁴ Ethanesulfonate. ⁵ Glucoheptonate. ⁶ *p*-Glycylamidophenylarsionate. ⁷ *N,N'*-Di[(dehydroxyethyl)ethyl]ethylenediamine. ⁸ 2-Hydroxyethanesulfonate. ⁹ 5-Chlorotheophyllinate. ¹⁰ *N,N'*-Dibenzylethylenediamine. ¹¹ *N*-Methylglucamine.

to assemble data that will provide, for the student and practitioner alike, a rational basis for selecting a suitable salt form.

POTENTIALLY USEFUL SALTS

Salt formation is an acid-base reaction involving either a proton-transfer or neutralization reaction and is therefore controlled by factors influencing such reactions. Theoretically, every compound that exhibits acid or base characteristics can participate in salt formation. Particularly important is the relative strength of the acid or base—the acidity and basicity constants of the chemical species involved. These factors determine whether or not formation occurs and are a measure of the stability of the resulting salt.⁷

The number of salt forms available to a chemist is large; surveys of patent literature show numerous new salts being synthesized annually. Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. For example, a salt's hydrophobicity and high crystal lattice energy can affect dissolution rate and, hence, bioavailability. Ideally, it would be desirable if one could predict how a pharmaceutical agent's properties would be affected by salt formation.

Tables I and II list all salts that were commercially marketed through 1974. The list was compiled from all agents listed in "Martindale The Extra Pharmacopoeia,"

26th ed. (7). Table I categorizes all salt forms approved by the Food and Drug Administration (FDA), while Table II lists those not approved by the FDA but in use in other countries. (Only salts of organic compounds are considered because most drugs are organic substances.) The relative frequency with which each salt type has been used is calculated as a percentage, based on the total number of anionic or cationic salts in use through 1974. Because of simple availability and physiological reasons, the monoprotic hydrochlorides have been by far the most frequent choice of the available anionic salt-forming radicals, outnumbering the sulfates nearly six to one. For similar reasons, sodium has been the most predominant cation.

Knowledge that one salt form imparts greater water solubility, is less toxic, or slows dissolution rate would greatly benefit chemists and formulators. In some cases, such generalizations can be made. Miller and Heller (8) discussed some properties associated with specific classes of salt forms. They stated that, in general, salt combinations with monocarboxylic acids are insoluble in water and lend themselves to repository preparations, while those of dicarboxylic acids confer water solubility if one carboxylic group is left free. Pantoic acid, an aromatic dicarboxylic acid, is an exception since it is used as a means of obtaining prolonged action by forming slightly soluble salts with certain basic drugs. Salas *et al.* (9) reviewed the use of this salt form in preparing sustained-release preparations. More recently, Isentiation of dihydrostreptomycin (10)

decrease but had the opposite effect on phenobarbital. Therefore, as a tablet dosage form, the dissolution rate of the sodium salt was slower than that of the free acid. These results were attributed to differences in the disintegrating properties of the tablets; in some instances, rapid dissolution may in fact be a problem for very soluble drugs.

Others have illustrated a phenomenon that decreases the dissolution rate of a salt below that of its nonionized form. Lin *et al.* (112) studied the relationship between salts and biological activity by dissolving three salts and the free base of an experimental antihypertensive in water, 0.1 N HCl, and pH 7.2 phosphate buffer. The dissolution rate of the monohydrochloride salt was lower than that of the free base in 0.1 N HCl and higher than the free base in both water and phosphate buffer. These authors ascribed this variation to the common ion effect and substantiated it experimentally. Although the biological activity of the monohydrochloride was greater than that of the free base, the implications of altered absorption characteristics on the activity of any other hydrochloride salt in GI fluids must be considered. Similar results also were reported for hydrochloride salts of some tetracyclines (113).

Some consideration must be given to the influence of salt formation on oral toxicity, which often reflects the relationship between the *in vivo* dissolution rate and the appearance of drug in the circulation (114, 115). Morozowich *et al.* (114) showed that the relative toxicities of a series of salts of a drug reflect the rate of absorption, providing the salt-forming agents themselves are relatively nontoxic. They stated that "when absorption is rate-limited by dissolution of the salt in the gastrointestinal tract, as will be the case with slowly soluble salts, the toxicity of a slowly dissolving salt will most probably be lower than that of a more rapidly dissolving salt." The implications of salt formation on toxicology will be discussed under *Toxicological Considerations*.

Several reviews dealt with the influence of the dissolution rate on drug availability and, in particular, salt effects (116, 117). Other reports illustrating the influence of salts and salt form on dissolution rate are listed in Table IV.

Solubility—Knowledge of the solubility characteristics of a pharmaceutical agent is essential, because solubility is usually an important factor in the pharmacokinetic profile, the chemical stability, and, ultimately, the formulation of the drug. As discussed previously, it is certainly a primary factor in controlling dissolution rates. The solubility of a compound depends basically upon the physical and chemical properties of the solute; e.g., a lower melting point for a compound within a series reflects a decreased lattice energy, which would suggest a higher solubility. Solubility depends as well upon such elements as temperature, pressure, solvent properties (such as resulting pH), and, to a lesser extent, the state of subdivision of the solute.

An important solvent property which is often overlooked involves the common ion effect; in particular, hydrochloride salts of drugs often exhibit less than desirable solubility in gastric juice because of the abundance of chloride ions. The equilibrium involved is shown in Scheme I.

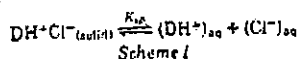


Table IV—Additional References on Salt Form and Dissolution Rate

Topic	Reference
Dissolution rate of mixtures of weak acids and tribasic sodium phosphate	118
Physiological availability and <i>in vitro</i> dissolution characteristics of some solid dosage formulations of aminosalicylic acid and its salts	119
Biopharmaceutics, rate of dissolution: chronological bibliography	120
Biopharmaceutics: rate of dissolution <i>in vitro</i> and <i>in vivo</i>	121
Dissolution tests and interpretation of anomalies observed in the dissolution process of sulfaquinolone based on salt formation	122
Influence of the dissolution rate of lithium tablets on side effects	123
Dissolution kinetics of drugs in human gastric juice	124
Comparison of dissolution and absorption rates of different commercial aspirin tablets	125
<i>In vitro</i> dissolution rates of aminorex dosage forms and their correlation with <i>in vitro</i> availability	126

considered as a means of increasing a compound's water solubility. As with dissolution rates, however, salt formation does not always confer greater solubility. Liberally dispersed throughout the pharmaceutical literature are studies that compare the solubilities of different salt forms of the same compound with those of its free acid or base (Table IV). Selection of the salt form exhibiting the desired solubility properties is critical, since these properties often dictate the formulation characteristics of the drug.

Phase solubility techniques were used to study the formation of complex salts of triamterene (127). The results indicated that the organic acid salts of basic drugs, such as amines, were more soluble in water than the corresponding inorganic (halide) salts. This consideration is important in the synthesis and selection of a salt form that will exhibit enhanced bioavailability and desirable formulation characteristics.

The hydrogen-ion concentration can significantly affect the solubility of a salt. Anderson (128) discussed the influence of pH on the solubility of pharmaceuticals. Mathematical relationships between pH and solubility of therapeutically useful weak acids and bases and their salts were given along with some considerations in the formulation of solutions of these particular agents.

An extensive study on the solubility interrelationships of the hydrochloride and free base of two pharmaceutically useful amines was reported (129). Mathematical equations describing the total solubility at an arbitrary pH in terms of the independent solubilities of the hydrochloride and free base species and the dissociation constant of the salt were derived and fitted to experimental data with good results. This report elucidated the point that, while the solubility of the amine hydrochloride generally sets the maximum obtainable concentration for a given amine, the solubility of the free base and the pKa determine the maximum pH at which formulation as a solution is possible (assuming that the desired concentration exceeds the free base solubility). Shifting the pH-solubility profile to higher pH values for formulation purposes may require increasing the solubility of the free base. This increase might be accomplished by using an appropriate cosolvent. Since the dissociation characteristics of carboxylic acids and other acidic organic species are similar to those of organic hydrochlorides, it is expected that the pH-solubility profiles

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of these organic acids, although reversed, can be characterized theoretically using the same treatment.

Several reports showed that the structure of an organic salt-forming radical influences the solubility of the resulting salt. The water solubilities of 16 salts (carboxylates, sulfates, sulfamates, and phosphates) of the weak base erythromycin were dependent on the size of the alkyl group of the acid (130). In a study with *N*-alkylsulfamates of lincomycin (86), a similar phenomenon was observed: solubility of these salts decreased as the size of the alkyl group attached to the acidic function increased.

Senior (131), in a study on the formulation and properties of the antibacterial chlorhexidine, determined the water solubilities of 35 salts and the free base. He found that inorganic salts had remarkably low solubilities while those of the lower aliphatic acids proved to be somewhat more soluble. Hydroxylation of the acid increased solubility, since salt formation with polyhydroxy acids, particularly the sugar acids, conferred extensive water solubility to the molecule.

Several investigators reported the influence of the solubility of a drug on its formulation and subsequent availability from the dosage form. In a discussion of the preparation and formulation of epinephrine salts in an aerosol system using liquefied gas propellants, Sciarra *et al.* (132) pointed out that the solubility characteristics of the agent are important in two respects. First, the solubility of the therapeutically active ingredient in the various propellants is an important consideration if the product is to be used for either local action in the lungs or systemic therapy. Second, the solubility of the drug in extracellular fluids plays an important role in selection of the compound. The bitartrate, malate, maleate, and fumarate salts of epinephrine were prepared and subjected to solubility and stability studies. While all salts had similar partition coefficients, the solubility of the maleate in several propellants and its stability in formulated aerosols made it the drug form of choice.

Ephedrine hydrochloride was more rapidly released than the free base from theobroma oil suppositories containing different surfactants (133). This enhanced rate of release (dialysis) was ascribed primarily to the greater aqueous solubility of the hydrochloride, which solubilized faster from the oil-in-water emulsion, whereas the ephedrine alkaloid base tended to remain behind in the oil phase.

The solubility of the active ingredient in ointment bases can dramatically influence its diffusion properties. A study of salicylic acid and its sodium salt showed that the diffusion of both was very low from hydrophobic bases, whereas the solubility of the drug significantly affected the diffusion from hydrophilic bases. The more soluble sodium salicylate diffused much faster from these latter bases than did salicylic acid (134).

Additional references on the relationship of salt form and solubility are listed in Table V.

Organoleptic Properties—Modern medicine requires that a pharmaceutical formulation be efficacious, safe, stable, and acceptable to the patient. Of primary importance in the development of oral dosage forms is taste acceptability. This factor presents no major problems when the drug is to be administered as a tablet or a capsule and swallowed as a unit but is clearly a prominent factor in

Table V—Additional References on Salt Form and Solubility

Topic	Reference
Influence of solubility on the rate of GI absorption of aspirin	135
Effect of dosage form upon the GI absorption rate of salicylates	136
Physical-chemical properties of polyene macrolide esters and their water-soluble salts	137
Isolation and reaction products of orotic acid and amines and their solubility in water	138
Solubility and stability of erythromycin salts	139
Studies on pharmaceutical preparations of orotic acid: water-soluble properties of orotic acid salts	140
Solubility of antibiotics in 24 solvents	141, 142
Solubility of antibiotics in 26 solvents	143

patient acceptability when it is to be administered as a liquid, chewable tablet, or lozenge.

Since taste is a chemical sense, a substance must be dissolved if it is to elicit a taste sensation—either by taking it as a solution or by its dissolving in the saliva. Therefore, one method used to minimize undesirable organoleptic properties of pharmaceuticals involves the preparation of a poorly soluble salt form of the drug such that the saturation concentration is less than the taste threshold.

Erythromycin estolate (lauryl sulfate) has approximately one-twelfth the solubility of the free base, is tasteless, and is useful in the formulation of oral suspensions (144). A study on erythromycin salts showed that the bitterness level was dependent on two properties: (a) the water solubility of the salt, which is dependent on the size of the alkyl group attached to the acid function; and (b) the strength of the acid used to form the salt, *i.e.*, the stability of the salt (130). The stearyl sulfamate salt possessed the most desirable organoleptic properties.

Many problems concerned with formulation and stability of topical and oral pharmaceuticals containing bacitracin have been overcome by incorporating bacitracin into the formulation as its zinc salt. One distinct advantage over the parent compound is its lack of taste, caused by its relative insolubility. Thus, it is the preferred drug form for preparations where taste is a factor (145). Taste panel evaluations of the comparative bitterness of bacitracin zinc and bacitracin indicate that the taste of the zinc salt is more easily masked and that the presence of a bitterness-masking adjuvant, such as sucrose, increases the bitterness threshold ratio differences between the two compounds even further (146).

Propoxyphene napsylate, nearly water insoluble, is only slightly bitter to the taste as compared to the highly water-soluble hydrochloride (147) and can be readily formulated into a flavored aqueous suspension. The taste of these suspensions can be improved significantly by the addition of a common ion (sodium or calcium napsylate) to depress solubility further.

A newer approach to the improvement of drug palatability has been to form insoluble salts with ion-exchange resins. Several investigators described and tested the practical application of this method (148–150). Spross *et al.* (149) outlined the conditions necessary for improving the palatability of a drug by adsorbing it onto an ion-exchange resin without appreciably modifying its pharmacological effects. They found that: (a) the degree of drug release from the ion-exchange adsorbate depends on the

equivalent quotient between the electrolytes in the surrounding fluid and the ionic drugs, (b) the amount of ions is far less in the saliva than in the gastric juice (the temporary electrolyte contents can be estimated at 0.05 mEq in the saliva and at 10 mEq in the gastric juice), and (c) the exchange rates should allow the equilibria to be attained within a fairly short period. Insoluble drug resins formed between dextran gel² cation exchangers and several basic drugs were in many cases much more pleasant tasting than their parent compounds. Furthermore, release of the drug from the ion-exchange adsorbate was quite rapid and complete under conditions prevailing in the GI tract.

Similar findings were reported using a polymethacrylic acid ion-exchange resin (150). In addition, coating the adsorbate particles with a 4:1 ethylcellulose-hydroxypropyl methylcellulose mixture further reduced bitterness. While *in vitro* release from the uncoated resinate was rapid and complete, release from coated adsorbates varied with the extent of coating.

Another approach to improving the taste properties of pharmaceutical agents is to prepare a pleasant-tasting soluble salt of a poor-tasting parent drug. This approach often can be very difficult, however, since solubilization of the parent compound usually imparts its unpleasant taste to the preparation. Nevertheless, some success has been reported using the artificial sweeteners cyclamate sodium and saccharin.

As described earlier, formation of *N*-cyclohexylsulfamate salts of several drug substances has produced better tasting derivatives with enhanced solubility properties (31, 32). The physicochemical and toxicological properties of benzalkonium saccharinate and a series of saccharinates of other quaternary ammonium compounds were reported (151). While conventional quaternary ammonium compounds have a very bitter taste, their saccharin analogs are sweet.

Potassium salts frequently possess an unpleasant taste and a metallic aftertaste. The palatability of some potassium salts in flavored vehicles was reported (152); while the salts had similar taste thresholds at effective therapeutic levels, all potassium salts exhibited inferior palatability.

Table III includes several samples of other salts that exhibit an improved taste relative to their free acid or base forms.

Stability.—The chemical and physical stability of a pharmaceutical must be known, because it can influence the choice of dosage form, the manufacturing and packaging, and the therapeutic efficacy of the final preparation. Systematic determination of the thermal stability, solution stability (at various pH's), and light sensitivity of a drug and its derivatives, both alone and in the presence of common additives, provides essential input toward selecting the most suitable derivative and dosage form.

Depending on the route of degradation, different salt forms impart different stability characteristics to the parent drug by various mechanisms. Most commonly used are sparingly soluble salts which, when used in the formulation of suspensions, reduce the amount of drug in solution and, hence, its degradation. Differences in hygroscopicity of several salts influence the stability of the

drug in the dry state. In some cases, the salt-forming radical itself enhances the stability of the parent agent.

The stability of penicillin G and its salts has been widely studied due to the drug's therapeutic importance and its characteristic instability. Schwartz and Buckwalter (153) described some of the stability characteristics of this antibiotic, stating that, with present techniques, a solution of penicillin cannot be made stable for more than 2 weeks, even at refrigerator temperatures. They also discussed the use of suspensions of sparingly soluble amine salts in aqueous vehicles as a means of "allowing marketing of a 'ready-made' penicillin product." Procaine, benzathine, and hydrabamine salts are marketed, and their acceptable stability as aqueous suspensions is based mainly on their insolubility and the minimization of degradation in solution.

A theoretical treatment of the solubility of these salts was presented in which equations were derived for calculating the solubility as a function of pH and the pH of minimum solubility (154, 155). These equations are based on the mass action law and its relationship to the ionization constants of the amine and the penicillin and the solubility of the salt in water. Since the salt in solution is partially dissociated, further suppression of the solubility may be achieved by the common ion effect. Swintosky *et al.* (156) demonstrated this effect with penicillin G procaine by adding procaine hydrochloride to the preparation and further enhancing its stability. The 8-chlorotheophylline salt (or complex) of penicillin G was reported to be water soluble, yet stable in solution (157). Since 8-chlorotheophylline is acidic, it has been postulated that a buffer effect could account for the stabilization of this "salt."

While penicillin G procaine is more stable in aqueous vehicles, it is less thermally stable than the sodium or potassium salts, decomposing if heated much above 60°. The sodium and potassium salts are known to withstand heating up to 100° for 4 days with little loss in potency (158). This behavior might well be due to differences in melting points—*viz.*, 106° for penicillin G procaine and ~215° dec. for the potassium salt.

Since hydrolysis of penicillin is dependent on moisture content, preparations in which moisture is rigorously excluded are quite stable in the dry state. A study on the effect of moisture on penicillin salts found the calcium salt to be less hygroscopic than the sodium salt and, hence, more stable in moist atmospheres (159). Similarly, penicillin G potassium is also much less hygroscopic than penicillin G sodium and has become the preferred form for marketing in the dry state (160).

Several studies reported the relative stabilities of thiamine salts, particularly the hydrochloride and the mononitrate (161–163). The mononitrate is observed to be less hygroscopic and is accordingly much less water soluble than the hydrochloride. Investigations of various preparations including compressed tablets, multivitamin capsules, and dry-filled vitamin B complex capsules at various temperatures showed that the mononitrate was more stable than the hydrochloride (164, 165). The stabilities of numerous thiamine salts were studied in aqueous solution and in dry powder preparations with various excipients (166, 167). In aqueous solution, the resulting pH was the chief factor controlling hydrolysis and oxidative decomposition of thiamine salts; their stability as powder

² Sephadex.

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preparations was related to their aqueous solubility, with the sparingly soluble salts being more stable (and presumably less hygroscopic).

An orally administered drug must be stable in acidic solution because it generally must pass intact through the acidic environment of the stomach if it is to exhibit therapeutic blood levels. The advantage of erythromycin estolate over the free base lies in its low solubility in gastric juice, which enables it to be administered with food without any decrease in attained blood levels. The salt is more stable in the stomach because it remains undissolved. Therefore, it retains its potency even when exposed to acidic environments for extended periods (144).

In a study on the preparation and characterization of lincomycin cyclamate (33), it was noted that the cyclamate salt had an enhanced thermal stability over the hydrochloride. In a subsequent report (163), differential thermal analysis and thermogravimetric analysis showed that while the hydrochloride easily undergoes thermal degradation, the cyclamate anion confers a considerably greater thermal stability on the lincomycin moiety.

Mullins and Macek (169) showed that the physical and chemical stability of the calcium salt of novobiocin makes it the form of choice for the formulation of a liquid preparation of the antibiotic. The amorphous calcium novobiocin salt proved to be tasteless, yet fully biologically active and perfectly stable in aqueous suspension. Neither the sodium salt nor the free acid is suitable; the sodium salt cannot be formulated in a liquid due to its chemical instability, while the crystalline free acid is not absorbed from the GI tract. Amorphous novobiocin is absorbed, but is metastable in solution and slowly converts to the unabsorbed crystalline form.

Other reports of alterations in stability characteristics due to salt formation are listed in Table VI.

Miscellaneous Properties—The salt form has been reported to influence other physicochemical properties of a drug substance. Studies illustrating the effect of the salt-forming radical on surface tension, deaggregation behavior, and ion-pair extraction have appeared.

The influence of the anion on the absorption processes of two charged species, dextromethorphan and tetracycline, was studied in the rat stomach (186, 187). A linear relationship existed between the rate of absorption from buffer solutions of the anions under investigation and their surface tensions. Thus, the absorption process was related to the surface activity of the various salts and not to their lipid solubilities. This change of surface activity with the buffer (or salt) species is similar to the results reported in a study of the surface activity of various phenothiazine salts (188).

The antibacterial chlorhexidine possesses surface activity. A study of the colloidal properties of some chlorhexidine salts showed that the counterion can affect the critical micelle concentration of a surface-active agent, and this effect was usually associated with a change in micellar size (189).

The deaggregation behavior of a relatively insoluble acid and its sodium salt was studied, and deaggregation was postulated to be a possible rate-limiting step in the absorption of a drug from a dosage form (190). While no direct comparisons of the two forms were made, inspection of the data shows that the deaggregation rate of the salt

Table VI—Additional References on Salt Form and Stability

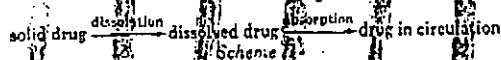
Topic	Reference
Stability of chlorhexidine solutions	170
Stability of chlorhexidine when autoclaved	171
Anhydrotetracycline and 4-epianhydrotetracycline in marketed tetracycline and aged tetracycline products	172
Solid-state stability of some crystalline vitamin A compounds	173
Physicochemical studies on the stability of penicillin salts	174
Light sensitivity of tetracyclines	175
Hygroscopic properties, thermostability, and solubility of oleandomycin salts	176
Stability of orotic acid and its amine salts in aqueous solution	177
Some factors influencing the stability of tablets (aspirin)	178
Stability of aqueous solutions of sodium aminosalicylate	179
Hygroscopic properties of various preparations of erythromycin	180
Physicochemical studies on the decomposition of aminosalicylic acid and its salts	181
Stabilities of aqueous solutions of 2-diethylaminoethyl-3-methyl-2-phenylvalerate hydrochloride and its methobromide	182
Investigation of some properties of penicillin G salts	183
Stability of ferrous iron tablets on storage	184
Stability of aspirin aluminum compounded with antacids	185

was considerably more rapid than that of the free acid in equivalent dosage forms. Therefore, if absorption is dependent on the dissolution rate, which in turn is dependent on the deaggregation rate, the salt should produce the highest and earliest blood levels. On the other hand, it is possible that hygroscopic (and deliquescent) salts can absorb atmospheric moisture, cause a sticky surface, and inhibit deaggregation.

Higuchi and coworkers presented an extensive study on the physicochemical basis of the ion-pair extraction of pharmaceutical amines. Distribution ratios of dextromethorphan (191) and chlorpheniramine (192) between an organic layer and water were highly dependent on the concentration and nature of the anion present. Less hydrophilic anions yielded more readily extractable ion-pairs. A study of the thermodynamic properties, enthalpy, free energy, and entropy, involved in the extraction equilibria of dextromethorphan ion-pairs indicated that the entropy change associated with transfer of the different anions between phases is the main controlling factor in the extraction process (193).

BIOAVAILABILITY

Most drugs prescribed in the United States are administered in solid and polyphasic dosage forms. Consequently, dissolution of the drug must precede the absorption process. The simplest model that adequately describes this process is shown in Scheme II.



Since the dissolution rate is generally slow for drugs with poor solubility, Step 1 is frequently rate limiting in the overall absorption process. As a result, the onset, intensity, duration of pharmacological activity, and, hence, bioavailability are affected by changes in dissolution rate. As discussed previously, administering a salt of the parent drug often proves to be an effective means of altering dissolution rate and absorption.