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SUPERINTENDENTE DE INDUSTRIA V COMERCIO
E. S. D.

REF: EXPEDIENTE 06-076-505

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TITULO SOLICITADO: FORMAS DE SAL DE 4-(4-METILPIPERAZIN-1-
ILMETIL)-N-(4-METIL-3-(4-PIRIDIN-3-IL)PIRIMIDIN-2-ILAMINO)FENIL)-BENZAMIDA

PUBLICAcION: Gaceta 582 de 30 de noviembre de 2007

PRIORIDAD: US 60/541,817 de 04/0212004

SOLlCTANTE: NOVARTIS AG

APODERADO: CARLOS R. OLARTE

TRAMITE: REMISION DE INFORMACION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de la firma, abogado en ejerciclo, titular de la tarjeta profesional nümero 44655 del C.S.J, obrando en nombre y representaciôn de TECNOQUIMICAS S.A., sociedad comercial constituida y vigente de acuerdo con las leyes de la Repüblica de Colombia, con domicilio y sede principal en Cali, de manera respetuosa, y con el propOsito de coadyuvar en la decisiOn que sobre la solicitud de patente de la referencia deberÆ adoptarse, por este escrito me permito remitir informaciOn fundamentada que demuestra que la solicitud en mención no cumple los reguisitos de novedad y nivel inventivo exigidos por la DecisiOn 486 de 2000, y que por ello deberia el Despacho abstenerse de concederle el privilegio de patente

solicitado.

AdemÆs de la defensa del orden jurIdico vigente en materia de propiedad industrial, el presente escrito se fundamenta en la necesidad de evitar que la

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Carrera 17 No. 88-23 Of. 205 Tels.: +57 1 655 7795, +57 1621263 1, Fax: +57 1 621 2542 inforeyes-abogados.com - www.reyes-abogados.com - Bogota, Colombia.

concesión de la solicitud vulnere la libre competencia, y restrinja el mercado farmacØutico en perjuicio de los consumidores colombianos.

I. INCUMPLIMIENTO DE REQUISITOS DE PATENTABILIDAD

El solicitante pretende, en general, obtener privilegio de patente sobre sales de adición Æcidas de 4-[(4-metil-1 -piperazinil) metil]-N-[4-metil-3-[[4-(3-piridiflil)-2-pirimidinit]amino]fenH]-benzamida Imatinib, seleccionada a partir del grupo que consiste en la sal de tartrato, (D)(-)-tartrato, (L)(+)-tartrato, clorhidrato, citrato, malato, fumarato, succinato, benzoato, bencensulfonato, pamoato, formiato, malonato, I,5-naftalendisulfonato, silicato, ciclohexansulfamiato, lactato, mandelato, glutarato, adipato, escuarato, vanhlato, oxaloacetato, ascorbato, sulfato, entre otras, composiciones que las contienen y su uso en el tratamiento de una enfermedad tumoral, especialmente en el tratamiento de la leucemia.

1.1. ABSOLUTA CARENCIA DE NOVEDAD Y DE NIVEL INVENTIVO DE LAS SALES DE IMATINIB

En primer lugar, es importante mencionar que Imatinib es un fÆrmacoampliamente reconocido por su actividad antileuc6mica1 el cual fue identificado en 1990 por quImicos de Novartis y su actividad en leucemia mielOgena crOnica fue confirmada por Druker B.J. et al., aprobado como medicamento y especialmente en forma de su sal Mesilato (Gleevecfi) por Ia FDA en mayo de 20012.

Como se observa, la aprobación del fÆrmaco Imatinib ante la FDA se hizo sobre una sat de Imatinib, en este caso la sal de Mesilato, lo que demuestra el conocimiento y el empleo previo de sales de este fÆrmacono solo en el estado del arte sino en el campo farmacØutico.

Adicional a esto, es del caso necesario citar diversas publicaciones anteriores a la solicitud colombiana que hacen referenda a la obtenciOn de sales de adiciOn de imatinib, veamos:

Tyrosine kinase inhibitor, highly specific for BCR-ABL, the enzyme associated with chronic myelogenous leukemia (CIVIL) and certain forms of acute lymphoblastic leukemia (ALL). Prepn: J. Zimmermann, EP 564409; idem, US 5521184 (1993, 1996 both to Ciba-Geigy); idem et al., Bioorgan. Med. Chem. Letters 7, 187 (1997). Structural mechanism of ABL specificity: T. Schindler et al., Science 289, 1938 (2000). Clinical evaluation in CIVIL: B. J. Drucker et al., N. Engl. J. Med.

344, 1031 (2001); in blast crisis of CIVIL and ALL: eidem, ibid. 1038. 2 hftp://www.accessdata.fda.gov/scdpts/cder/ob/does/tempai.cfm
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o La publicaciOn intemacional WO 03/066613 publicada el 14 de agosto de 2003 y titulada "N-PHENYL-2-PYRIMIDINE-AMINE DERIVATIVES" revela compuestos tipo amida de formula (I), entre los que se encuentra Imatinib luego de las sustituciones pertinentes.

Adicionalmente, en Ia parte descriptiva se menciona que los compuestos de formula (I) (entre elios Imatinib) pueden formar diversas sales Æcidasde adición con Æcidos organicos oinorganicos, como sigue:

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I or IV with a basic nitrogen atom1 especially th pharmaceutically acceptable salts Suitable inorganic acids are, for example1 halogen acids, such as hydrochloric add, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxyllo, phosphonic, suitonlo or suitarnie acids, for example acetic acid, propionlc acid, actanoic acid, decanolo acid, dodocanok acid, glycolic acid, lactic acid, fumaric acid, succinlo acid, adiplo acid, pimelic acid, suberic acid, azelaic acid, malls acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic add, methyirnaleic acid, cyclohexanecarboxyllo acid, adamantanecarboxyftc acid, benzoic acid, oxalic acid, salicylic acid, 4-aminosalicyiic acid, phthalic acid, phenytacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonlc acid, ethane-1,2-dlsulfonio acid, benzenesulfonlc acid, 2-naphthalenesulfonic acid, I,5naphthaIene-disulfonic acid, 2-,3- or 4-rnethylbenzenesulfonic acid, methylsuifuric acid, ethyisufturic acid, dodacyisuifuric acid. N-cyclohexylsutfarnic acid, N-methyl-, N-ethyl or N-propyi-sulfamic acid, or other organic protonic acids, such as
ascorbic acid.

De igual manera, encontramos en este documento referenda expresa al compuesto imatinib, sus sales, formas cristalinas y composiciones que 10 contienen, ademÆs unejemplo de capsulas de Imatinib Metanosulfonato, veamos:

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The present invention particularly relates to pherrnaceu1ca1 compositions especially tablets comprising 4..(4.methytpiperazin-i-y1methyl)N.(4eth(4-pyridin-3-yUpyrimidin-2-yiamlna)phenyl]-benzamide or a pharrnaceutioaily acceptable salt or crystal form thereof.

Exarnnle A: Capsules with imatinib.(44(4.mthy!1 -pIperazlni yimethyN{4nethvi44F4-(3vrIdlnvfl-2-łvrlmldlnv11arnino1phenvflbenzwnkie.methanesulfonaie.of formula IV, 13 crystal form.
Capsules containing 1i95 mg of the compound named in the We (= SALT 1) corresponding to 100 mg of imatinib (free base) as active substance are prepared in the following composition. The composition containing also compounds of formula (wherein, P3 is (4 methyi-p(perazinyl)-rnethyl, R1, R2, R4, R5 and 1% are hydrogen, R is Br, Cl, NI-12, NO2, NHC(0)CF3, NHC(0)CH3, NHC(NH)NH2, and 137 is methyl
Composition
SALT 119.5 Mg
Compounds of formula 1 0.0005mg
Cellulose MK GA 92 mg
Crospovidone XL 15 mg
Aerosil 200 2 mg

En este punto se debe resaltar que, la menciOn de la sal de metanosulfonato de Imatinib no es limitante a esta sal exclusivamente, en la pÆgina anterior veIamos que, los compuestos de formula (I) estÆn en la capacidad de formar diversas sales como por ejemplo la sal de ÆcidoclorhIdrico, succinico, IÆctico, atIpico, mÆlico, cItrico, tartÆrico, mandØlico, entre otras, y que son algunas de las sales citadas en Ia solicitud colombiana en trÆmite, loque revela sin mÆs, la ausencia de novedad y nivel inventivo de la misma.

> La publicaciOn internacional WO 99/03854 publicada el 28 de enero de 1999 y titulada "CRYSTAL MODIFICATION OF A N-PHENYL-2-PYRIM [DIN EAMINE DERIVATIVE, PROCESSES FOR ITS MANUFACTURE AND ITS USE" revela:

The Invention relates to a particular form of the methanesulfonic acid addition salt of 44-methyipiperazin-1
benzamide,, comprising certain crystals, processes for the preparation thereof, pharma-ceutical compositions containing this crystal form, and their use In diagnostic methods or preferably for the therapeutic treatment of warm-blooded animals, especially humans or their use for the preparation of pharmaceutical preparations for use in diagnostic methods or preferably for the therapeutic treatment of warm-blooded animals, especially humans.

The invention relates especially to a particular, essentially pure crystal form preferably that which is referred to hereinafter as the crystal form, of the methanesuUonic acid addition salt of 4-(4’rnethylpiperazin-i ylmethyl-N-4m.ethyt-3(4-pyiid-3-yl)pyrirnidin-2-ylamino)phenyljbenzamide methanesulfonate of formula I,

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Esta segunda referencia aniquila al menos el nivel inventivo de la solicitud colombiana en trÆmite ya que como vimos, se refiere a la sal de adiciOn del Æcido metanosulfónico de Imatinib en forma cristalina, 10 que sin lugar a dudas demuestra que, el compuesto imatinib puede a debe ser preparado en forma de alguna sal para proporcionar por 10 menos una solubilidad mejorada; en consecuencia, y si bien es cierto que este documento no cita alguna otra sal, no es menos que, desde 1999 se plantea la necesitad o tiene la finalidad de formular a este principio activo en forma de una sal adecuada que permitirÆpar obvias razones, mejorar sus caracteristicas fisicoqulmicas y biofarmacØuticas.

> La publicaciôn internacional WO/ 02/22597 publicada el 21 de marzo de 2002 y titulada "N-PH ENYL-2-PYRIM I DINE-AMINE DERITIVES" revela compuestos de fOrmula (I) que luego de las sustituciones pertinentes podria tratarse de imatinib y sus sales Æcidas deadición, pero, en la Rv I se hace la exclusiOn del compuesto en donde R10= (4-methyl-piperazinyl)methylphenyl), Ia que llevarIa a pensar que se excluye de este documento al compuesto imatinib; sin embargo, vemos que este tipo de compuestos "similares" a imatinib puede

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formar sales de adición con Æcidos orgÆnicos o inorgÆnicos como los que se mencionan en la solicitud colombiana en trÆmite, lo que demostrarla una vez mÆs la ausencia de nivel inventivode la misma, si se tiene en cuenta tanto 10 revelado a lo largo de este documento, como que los compuestos aqul revelados pertenecen a la misma familia y tienen la misma estructura qulmica

bÆsica del imatinib.

The invention relates to N-phenyl-2-pyrimidina-amine derivatives of formula I

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Salt-forming groups in a compound of formula I are groups or radicals having basic or acidic properties. Compounds having at least one basic group or at least one basic radical, for example a free amino group, a pylnyl radical or a pyddyf radical, may form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sutiwic acid or a phosphoric acid, or with suitable organic carboxyllo or suitordc adds, for example aliphatic mono- or di-carboxylic acids, such as trlfluoroacetic acid, acetic acid, proplonic acid, glycolic acid, succinic acid, maloic acid, fumaric acid, hydroxymaleic acid, maRc acid, tartaric acid, Citric acid or oxalic acid, or amino acids such as arginine or lysine, aromatic carboxylic acids, such as benzoic add, 2-phenoxy-benzoic acid, 2-acetoxy-benzotc acid, salicylto acid, 4-aminosalicytic acid, aromaticallphatic carboxylic acids, such as mandelie acid or cinnamic acid, hetercaromatic carboxyflo acids, such as nicotinic acid or lsonicotinic acid, aliphatic sulfonic adds, such as methane-, ethane- or 2-hydroxyethane-sulfonlc acid, or aromatic suifonto acids, for example benzene-, p-toluone- or naphthalene-2-suIfonIc acid. When several basic groups are present mono- or poly-acid addition -salts may be formed.

> De otro lado, y si tenemos en cuenta que la solicitud colombiana de manera general se refiere a diversas formas de sales del compuesto farmacØuticamente activo de 4-[(4-meti I-I -piperazinil) metil]-N-[4-metiI-3-[[4-(3-piridinil)-2-pirimidinil]amino]fenil]-benzamida Imatinib, consideramos que dicha solicitud incumple los requisitos de patentabilidad si se tiene en cuenta

que la preparaciOn de sales de fÆrmacos y su aplicación en Ia industria farmacØutica, corresponden a aspectos cotidianos de los ensayos de preformulación y formulación, especialmente en lo relacionado con aspectos fIsicos y biofarmacØuticos, en donde Ia formación 0 selección de la sal de un fÆrmaco puede intervenir directamente sobre la solubilidad, estabHidad, eficacia, efectividad, biodisponibilidad, entre otras, del medicamento.

Para cualquier persona medianamente versada en la materia es obvio que las caracterIsticas a tener en cuenta en el momento de preparar formas de sales de fÆrmacos y/o en la selección de las mismas para una determinada formulaciôn, son relevantes ya que pueden influir directamente, por ejemplo, en la solubilidad, en la absorción del fÆrmaco, en la estabilidad (higroscopicidad), en la cristalinidad y polimorfismo, e inclusive en la compresibilidad y compactibilidad en el caso de formulaciones sólidas; de esta manera, el criterio de selección de la sal de fÆrmaco a utilizarse debe basarse en la descripciOn y comportamiento fisicoqulmicos de dicha sal, tanto en el contexto de la formulación como en el del media dentro del organismo al cual se vera

expuesto3.

Par consiguiente, las sales reivindicadas por la solicitud colombiana en trÆmiteno son mÆsque el resultado de la aplicación del conocimiento previamente adquirido’ y sobre todo del hecho que, una sal puede mejorar las propiedades fisicas y farmacØuticas de un determinado compuesto, Ia que hace evidente que, cualquier persona medianamente versada en el arte estØ en capacidad de buscar la sal mÆs adecuada que permita una mejorada solubilidad y biodisponibilidad y en consecuencia, el fÆrmaco ejerzasu efecto biológico, luego de ser transportado por los fluidos biológicos, atravesar membranas, distribuirse, penetrar en una concentraciOn adecuada a los sitios de acción y ejercer su efecto en dicho sitio.

Del mismo modo, es importante tener en cuenta y tal como lo admite el mismo solicitante, que la obtención a preparaciOn de tales sales no son mÆs que el resultado de la aplicaciOn de mØtodos conocidos en el estado de la tØcnica y se resume simplemente a Ia reacciOn Æcido-base, comün y reconocida por cualquier persona medianamente versada en la materia, entre imatinib y los diversos tipos de Æcidos organicos y/oinorgÆnicosque en dicha solicitud se mencionan.

Remington. The science and practice of pharmacy. 20th ed. Paginas 104 a 720.

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12. EL USO DE LAS SALES DE IMATINIB EN EL TRATAMIENTO DE LA ENFERMEDAD TUMORAL INCLUMPLE EL ARTICULO 20 d) DE LA DECISION 486.

Por ültimo y no menos importante, es necesario resaltar que la solicitud colombiana en trÆmite incurre en una clara improcedencia de patentabilidad, especIficamente en lo contenido en su reivindicación nümero 7, al exponer el uso
de una sal de adjción de Æcido de imatinib en una composiciOn farmacØutica Para
el tratamiento de una enfermedad tumoral, ya que par lo explIcitamente dispuesto
por la Comunidad Andina De Naciones en la decisiOn 486 de 2000, especIficamente en su articulo 20 literal d) "No serÆnpatentables: Los mØtodos

S terapØuticos o quirUrgicos para el tratamiento humano o animal, asI como los

mØtodos de diagnostico aplicados a los seres humanos o animales"

En conclusion, la solicitud colombiana en tramite carece de novedad y de nivel
inventivo, ya que reivindica Ia formaciôn de sales de un compuesto farmacológico ampliamente reconocido, en donde dicha estrategia (formaciOn de sales) es ampliamente reconocida en la industria farmacØutica y porque ademÆs, la
formaciOn de dichas sales par adiciOn de algunos âcidos organicos y/o inorgÆnicos mencionados por dicha solicitud en trÆmite se encuentran expuestas en publicaciones anteriores.

. Por todo lo anterior, le solicito Seæor Superintendente,que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, ademÆs de la
negaciOn de Ia solicitud en comento, el archivo del citado expediente.

II. PRUEBAS

Ruego que se tengan como tales las siguientes, sin perjuicio de aquellas que el Despacho considere oficiosamente, las siguientes:

> Remington. The science and practice of pharmacy. 20th ed. PÆginas 704 a

720.

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> La publicaciOn intemacional WO 03/066613 publicada el 14 de agosto de 2003
y titulada "N-PHENYL-2-PYRIMIDINE-AMINE DERIVATIVES" paginas 1, 2 y

14.

> La publicación internacional WO 99/03854 publicada el 28 de enero de 1999 y

titulada "CRYSTAL MODIFICATION OF A N-PHENYL-2-PYRIMIDINEAMINE DERIVATIVE, PROCESSES FOR ITS MANUFACTURE AND ITS USE" paginas I y 3.
> La publicación internacional WO/ 02/22597 publicada el 21 de marzo de 2002 y
titulada "N-PHENYL-2-PYRIMIDINE-AMINE DERIVATIVES" paginas I y 4.

III. NOTIFICACIONES

Mi representada y el suscrito las recibiremos en la secretaria de su Despacho, 0 en ml oficina de abogado, ubicada en Ia Carrera 17 No. 88-23, Oficina 205 de Bogota, Fax (1)621.25.42.

SeæorSuperintendente,

JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473 (Usaquen)
T.P. No. 44655 del C. S. J.

704 CHAPTER 38 ./ 055

(I) Library Expansion

k(2) Series Selection

1111111 1iiII1 IlfilTi (3) Analog Expansion
(4) Analog Selection

11 111 (5) Salt Expansion
(6) Salt Selection
(7) API Specifications
(8) Compressibility &
Compactibility
(9) Excipient Selection

Figure 38-4. Typical API sequential decision-making: selection and expansion cycles.

4, the remainder of this section will deal with how solid-state properties affect absorption and consistency, the two major development issues for an API. Salt selection, which deter-mines the character ofJA" is the first critical solid-state deci-sion for preformulation in the developmental arena.

Salt Expansion: Exploring the Molecular Possibilities of A’

The un-ionized (free) form ofweak,acids and bases, AO, may not
be the ideal molecular form for development. During the salt expansion Step 5 of Figure 38-4, salts are prepared to explore

S whether one ofthem would make a more suitable API. Salts are

formed by reacting An with an: appropriate counter-acid or counter-base. In this discussion, HAn is used to represent a counter-acid that forms an anion An-. Common counter-acids
like HCI and maleic acid are listed in Table 38-2. Similarly, CnOH is used to represent a mineral base of counter cation
Cut Common mineral bases like NaOH and KOH are also shown in Table 38-2 along with organic counter-bases. -

When An is a weak base, the salt, (A°H) An’, is composed ofthe protonated form ofthe base, (A°H)’ and the ionized form of the counter-acid HAn, An. For salt formation, An must be sufficiently basic to remove the proton from HAn (see Salt-Forming Reactivity Potential, page 705).
Salts have different physical properties than their free forms. Salt selection explores whether a particular salt might have properties that are more appropriate for an API than its parent form. Improving oral absorption by in-creasing the dissolution rate is often a goal of the salt ex-pansion step. Salts generally dissolve faster in water than their free forms because dissolution is enhanced by the rapid hydration of the ionized salt species with water. Salts of weak bases generally lower the pH of water; salts of weak acids elevate it. For the salt of a weak base in water, the
initial dissociation of the salt into the two ions, A°H and
An- is relatively complete. On the other hand, the deproto-nation ofA°H depends on the pK, ofAn, as shown by these
reactions:

A°WAn - A°H+An d A°HA°+H (11)
high pK.

It is the release ofthe H in the second reaction by the salt that lowers the pH and increases the solubility (see pH-Solubility Profiles, page 717). Hydrochlorides are the most common salts of weak bases.
When A° is a weak acid, the salt that forms from a reaction with CnOH is A’Cn’ W represents An minus a proton). The most common salts for weak acids are the’ sodium salts.

Even though salts increase aqueous solubility, they only alter the pH of the solution so that more ofthe ionized form is present in solution. Salts do not change the ionizable character
ofthe free form; this is an intrinsic property ofthe free acid or
free base and their associated pK(s). pH-solubility profiles
show the solubility relationship between salts and their free
forms.

Table 38-2. Molecular Forms Marketed Worldwide Between 1983-1996

SALT FORM FREQ. GROUP’ PKa clogP MW
No salt form 390 0
Hydrobromide 1 1 -8 0.45 80.91 Hydrochloride 102 1 -6.1 0.24 36.46 Sulfate 5 1 -3 -1.58 98.08 Nitrate 6 1 -1.44 2.09 63.01 Phosphate 2 1 2.15 -1.95 96.99 Glucuronate 1 1 322b -3.74 194.14
Acetate 8 1 4.76 -0.36 59.05 Maleate 3 2 1.92 -0.18 116.07 Fumarate 8 2 3.02 -0.18 116.07 Tartrate 1 2 3.03 -2.21 150.09
SCitrate 1 2 3.13 -2.11 189.10
Succinate 2 2 4.21 -0.62 118.09 Mesylate 8 3 -1.20 -1.31 96.11 Acis’trate 1 3 4.91 7.98 284.49

Besylate 2 4 _280b 0.23 157.17 Tosylate 3 4 -1.34 0.88 171.20 Xinafoate 1 4 2.66k’ 3.00 188.18
Potassium 1 1 16 39.10
Sodium 37 1 14.77 23.00
Tromethamine 2 1 8.07c -3.17 121.14
Bismuth 1 1 1.58 208.98
Bromide 6 5 79.90
Chloride 2 5 35.45

’Groups: 0 No salt, 1 Polar, 2 Multifunctional, 3 Flexible aliphatics, 4 Planar aromatics, 5 Quartenary. ’ Calculated pK,. -- CCRC Handbook of Basic-Tables for Analysis, page 469.

Source: Serajucidin ATM, Sheen P, Augustine MA. To market, to market. In: Bristol J, ed. Annu Rep Chem. New York: Academic, 1983-1996.

PH-SOLUBILITY PROFILES

For a weak base, a plot of solubility versus pH will show the highest solubility at low pH and the lowest solubility at high PH; for weak acids, the opposite is true. Such plots give a graphic view of the impact of ionization on solubility for an NCE. The pH range of the small intestine, where oral absorp-tion generally occurs, is approximately 6.5 to 8. It is undesir-able to have a compound totally charged or uncharged in this region. Ifit is entirely charged, there are no un-ionized species that can be transported across the GI membrane. Ifit is totally uncharged, there are no charged species to enhance solubility. For a monoprotic NCE, the pK denotes the pH where the number of charged and uncharged species in solution are equal. On the ionized side of the the solubility of the salt limits the maximum solubility. The solubility decline at very low pHs is due to activity and solubilitroduct effects.5 On the un-ionized side, the solubility ofA (the intrinsic solubility) marks the lowest solubility. Salts promote a saturated solution to be formed at a pH that is on the ionized side of the They cannot alter the or the intrinsic solubility. Using these parameters, a qualitative pH-solubility profile can be con-structed. Figure 38-5 shows pH-solubility profiles for different counter-acid salts.

The synthesis ofsalts depends on

1. A proton-exchange reactivity between A° and the counter-acid/base
2. A long-range order that permits crystal formation.

The discussion that follows will focus on forming salts from weak bases, because they comprise ’the majority of the new drug candidates. Weak acids would be treated analogously.

SALT-FORMING REACTIVITY POTENTIAL

In order for a salt to form, both the weak base, A°, and the counter-acid, HAn, must have sufficiently different p1,,, values

0

0
0
Acid

Methanesuitonic Acid

0

Phosphoric Acid

pH

Figure 38-5. pH solubility profile of a weak base.’

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such that a Bronsted-Lowry proton transfer from HAn to A° 11-1 can take place. Table 38-2 gives potential counter-ions and their pK,, values from a listing of all drugs approved worldwide from 1983 to 1996. An acidbase proton transfer should be possible as long as the pK of HAn is less than that ofthe weak base A° (recall that the pI(ofA° is referenced to its protonated form A°H; see Solid-State Character, page 702). If ApK. is
defined as

pK, = pK, (weak base) - pK,, (HAn) (12)

a salt-forming reaction should be possible as long as ApK, is positive. For example, a succinate salt. (p 4.2) with doxyl-amine (pK. 4.4) is possible’ where the ApK,, is 0.2. Neverthe-less, the greater the ApK,, the greater the probability that a salt can be formed. Because the pK., values in Table 38-2 are calculated for an aqueous environment, this rule must be used only as a guide for salt-forming reactivity in oranic solvents. In an organic solvent in which the dielectric constant is lower than water, the ionization equilibria would be shifted:

low dielectric,otv,, -

HAn’ H+An . (.3)

AH low dielectric,ol,neo H* + A° (14)

For acridine bases, 50:50 ethanol:water weakens the aqueous plC by 1.41 pH units. For the counter-acid, HAn, pK., weaken-ing is greater than for the protonated base, A°H, because of the greater solubility of HAn in the organic phase and the production of two charges upon ionization. The net effect of organic solvent weakening is to reduce the p1r,. difference be-tween the counter-acid and the weak base. This lowers the salt-forming reactive potential. Therefore, in a given organic solvent, ifsalt formation fails to occur for a particular aqueous ipK, it is unlikely that salts can be formed in this organic solvent with a smaller aqueous ApK.

VARYING SALT PROPERTIES

USING COUNTER-ACID GROUPINGS

For weak bases, salt-forming counter-acids can be used to alter an APrs solubility, dissolution, hygroscopicity, stability, and processing.’ Table 38-2 shows counter-acids organized into dif-ferent functional groups. For each counter-acid, both the plC and the log P is given where appropriate. A starting point for salt expansion must begin with the properties of A°. If, for a weak base, ipKa = Plc A - counter-acid. HAn > 0, then aqueous salts may be possible. Use of this table and the influ-ence ofdifferent counter-acids are covered under Decision-Tree, Goal-Oriented Approach, page 712.

CRYSTAL FORMATION REQUIREMENTS

In general, crystalline solids, including salts, make the most promising APIs. The amorphous form of the solid state is usu-ally not as stable as crystals, either physically or chemically. Crystal formation is a special characteristic of a solid in which the molecules self-organize into regular, repeating, molecular patterns. Solvents play at least three roles in crystallization.

1. They provide some solubilizing capacity so that concentrated solu-tions can be formed.

2. They promote the nucleation process. Nucleation may be from a pure solution (homogeneous nucleation) or from a seed crystal (het-erogeneous nucleation). If a solvent binds too strongly to the mo-lecular organizing functionalities of the salt or seed crystal, crys-tallization will be impeded. Finding appropriate solvents for crystal formation is a very important step in salt expansion. Failure to adequately explore and find solvents that can crystallize salts could mean that very usable salts would not be evaluated in the salt-selection step because they were not synthesized.

T

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3. Solvents, temperature, and cooling rate can impact the crystal- packing pattern of crystals. Stable polymorphic forms usually are desired for APIs. Metastable forms are normally avoided in an API

because they are prone to physical and chemical instability. Solvent conditions that promote metastable and stable crystal formations will be explored under Metastable Polymorph Formation, page 710.

Salt Selection: Choosing the "Best" API

Salt selection is the first important API decision from the de-velopment perspective. Once a salt is chosen, time-consuming and lengthy toxicological studies are initiated that would have to be repeated ifthe salt form is changed. This decision involves choosing a solid-state phase, A, which balances potentially conflicting needs: increasing absorption versus maintaining an API that is consistent and can be manufactured in a market-

image dosage form (see Compressibility and Compactibil-ity, page 712). Figure 38-6 shows some ofthe factors involved in this decision.

Permeability, solubility (C5), and pK.a are intrinsic proper-ties of A° that have been already determined in the analog selection phase (see Fig 38-4). The major dependent variables, absorption and consistency ofthe API, can be manipulated and balanced in salt selection. In the following sections, the impact of dissolution and particle size on absorption will be explored. In addition, the consistency of the API solid state under the influence of environmental destabilizing factorssuch as expo-sure time (t), ultraviolet light (UV), pH, moisture (H20), tem-perature (T), and pharmaceutical processing operations like milling, compression, and compaction.will be considered.

OBSORPTION ASSESSMENT

Oral absorption is generally viewed as two-step, sequential process:

dissolution permeation

A 50 >aGI ta z-a4 (15)

tuv 1120 11c’tcdi DestabRizing Factors

State of the Solid Phose4 RecivstaWzlng Particle Size 1A(a, 411, W2,b,s’A’)

Permeability C5 Dissolution

Absarption Consistent AN

Figure 38-6.’API salt selection decision a balance between absorp-tion and consistency.

Either dissolution of solid drug, A,01d, after the dosage form disintegrates in the GI tract, or the permeation ofthe dissolved drug, aGI trect’ through the GI membrane could be the slowest process. The slower of these two steps determines the overall rate of absorption and is thus rate-limiting. Dissolution-limited absorption occurs when the rate of ap-pearance in the GI tract by dissolution (aGI) is slower than the rate of appearance in the systemic system (abl,,,); permeation-limited absorption occurs when the abl,,,,, appearance is the slowest process. The impact of these two rate processes on in vitro-in vivo (IVIV) correlations will be discussed in the section Biopharmaceutical Classification ofAPI, page 714. Dissolution-limited absorption will now be considered.
The rate of dissolution of a particle is given by the Noyes-Whitney equation,

dAldt = kdS, [C3 - C,,01j (non-sink conditions) (16)

where

A is the amount of drug dissolved.

dAldt is the rate of dissolution (Q sometimes is used for this rate). kd is the intrinsic dissolution constant for the drug.
S. is the total surface area of the dissolvthg particle.
Cs is the saturation solubility ofthe drug at the surface ofthe particle. Cb0,, is the concentration of the drug in the bulk solution.

Because the rate of dissolution depends on the concentration difference between C5 and CbU&, the maximum rate of disso-lution would occur if Cbulk = 0 (ie, if drug was removed from solution as fast as it dissolved). This would be analogous to a sink that could drain the water coming out of a water faucet as fast as it comes in so that the water level never built up. This analogy is the basis for referring to Equation 16 as nonsink conditions for dissolution, because drug does build up in the solution and the rate of dissolution is correspondingly reduced. The expression for the maximum dissolution rate is found by setting Cbk equal to O:

dAldt = kaS5 C (sink conditions) (17)

This initial rate ofthe Noyes-Whitney equation is termed sink conditions for the dissolution rate.
Particle-Size EffectsFor a spherical drug particle ofradius r, amount m, and of density p, Equation 17 can be rewritten as

- dAldt = (3kdm/p) (1/r) C3 (18)

This expression emphasizes the inverse relationship between the dissolution rate, dAldt, and the particle size r, assuming no dissolution rate-reducing factors are present such as adsorbed air bubbles or aggregated particles.
Smaller particles dissolve faster than larger particles. Thus milling, a pharmaceutical unit-operation, increases dissolution because the API particle size is reduced. On the other hand, when drug particles are suspended in an aqueous solution, particles can increase in size due to recrystallization growth8 (Fig 38-7). Dosing such suspension orally would be expected to reduce absorption because of a reduction in the dissolution
rate.

Reactive Media 1: Implications for Salts of Weak Acids and Weak BasesWhen a drug reacts with gastric fluids, its disso-lution deviates from Equation 17. For dissolution in 0.1 NHC1, acid-base reactivity is most important for salts of weak acids and for free bases. It has been found that the low pH environ-ment of the stomach dissolves a salt of a weak acid 10 to 100 times faster than the weak acid itself? On the other hand, it is the free base, and not its HC1 salt, that dissolves faster in this same environment.° These deviations from Equation 17 have been shown to be due to differences between bulk-solution pHs and the pH at the surface of the drug particle. Thus, Equation 17 becomes

dAldt = k,S0 C3,,, -

FORM I

INITIAL SUSPENSION

FORM I

SUSPENSION AFTER 6 HOURS.

Figure 38-7. Photomicrographs showing change in crystal size for a suspension of Form I of an experimental drug.

where Csh = 0 is the saturation solubility at the surface of the API.
Forweak acid salts, the surface pH has been calculated to be 6.2 to 6.5 for sodium salicylate (pK 3.0) and 10.3 for sodium theophylline (pK 8.4) in bulk solutions having pHs of 1.10 and 2.1, resective1y. On the other hand, the weak base phenazo-pyridine 5.2) sees a surface H of 3.3 to 3.6, while its HC1 salt sees a surface pH of 1.2 for abulk-solution pH of 1.10. Ifthe

Cs(11) dA5Idt P

PREFORMULATION

1120 > 1A

I I

Cs(I) dA/dt P

Absorption (11) Absorption (I)

707

Figure 38-8. Absorption changes due to aqueous-phase trans-formations.

solubility due to surface pH and not the pH of the bulk is considered, deviations from Equation 17 become understand-able. For the HC1 salt, the common-ion effect reduces its solu-bility from the maximum solubility’of the pH-solubility profile at 3.45. Thus, the nonaggregated fi’e base, in this situation, has a surface pH that is optimized to give the highest dissolu-tion rate because it has the highest surface solubility. Reactive Media 2: Implications forAnhydrates and Metasta-ble PolymorphsAqueous-phase transformations are solid-state changes in which water acts as a mediator. During the transition from one form to another, dissolution behavior will reflect the switch from the dissolution rate of the initial solid state to that of the more stable state. Two types of aqueous-phase transformations were introduced in Equations 7 and 9:
(1) a transformation from Polymorph II to Polyxnorph I and (2) a transformation from an anhydrous Form II to a hydrated form h." In Figure 38-8, the transformation of Equation 7 is shown.

Because the permeability (F) of the dissolved drug is the same for the different crystalline forms, the impact on absorp-tion will be due to differences in their solubilities (C5) as defined in Equation 17 and thus will be reflected in the disso-lution rates, d.A1/dt and dA11Idt, being different.
When a solvent-mediated transformation like that shown in Equation 9 occurs, dissolution profiles become more complex. Figure 38-9 shows the biphasic dissolution characteristics for Equation 9. In this situation, an anhydrous substance, ohA,

0

I
b

dAldt = kdSaCSfl

\ OhA (no ph se change)
ohA (phase change)

dA /dt = kdSaCsh

b = kd (C811 - CSh)/kr

Time

Figure 38-9. Biphasic dissolution of anhydrous to hydrous forms.1’

5.

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becomes hydrated as it dissolves and fom6 a surface layer of AA. It is this latter layer that controls subsequent dissolution. The concentration versus time plot for the net reaction is 01,A (phase change). Note that initially the slope for 01,A (phase change) approaches that of the very steep slope 01,A (no phase change), and that the terminal slope approaches that of,,A (no phase change), the hydrated form. Modifications ofEquation 17 to take into account surface recrystallization of/,A on 01,A. give the biphasic dissolution behavior,

dA/dt = k,jS,{C57e -kt + C51[1 e1"11 (20)

where k, is the recrystallization rate constant for the second phase, kd is the intrinsic dissolution constant, C11 is the sat-uration concentration for the first phase, and C51, is the satu-ration concentration for the second hydrate phase. 12 Enhanced. and Retarded Dissolution Due to Sinks and PlugsThe increase in dissolution due to the particle-size re-duction of an uncharged API, A°, can be estimated from Equa-tion 18. Equation 21 shows the resulting surface area increase, t, and the corresponding dissolution enhancement.

(21)

This enhancement, however, is assumed to be under sink con-ditions and is driven by C5 = aso in Equation 17. Ifthe concen-tration of drug does build up, dissolution is reduced by and is given by Equation 16. This slower dissolution is diagramed in Equation 22 where akul 1’ indicates the buildup of the drug in the bulk solution.

A° ’ a,,, (22)

10 An ionizable drug, on the other land, reduces which is

indicated by. in Equation 23 because it is rapidly converted to

the ionized form. Thus, the ionized form (a = acts as a sink to remove ab°, and promotes the dissolution of
A° by driving the reaction to the right:

A°+ Wt very f,,,, - - aL.1. a,,a (sink)’ (23)

Reduction of dissolution, on the other hand, can occur for an anhydrous API when the hydrated form recrystallizes on the surface as in Figure 38-9. This effect is the opposite ofthe sink concept, hence the term plugging. Equation 24 show the species involved in plugging. The subscript X emphasizes that this is a surface phenomenon.

relh,,Io,,

OhAI abulk 1 As ab,,&.1. (plug) (24)

Acceptance Criteria GuidanceA simple model to assess the impact of particle size on dissolution and absorption of a non-ionized drug considers the intestine as a single compartment. 12 Ifthe number of particles of uniform size at time t is

N(t) = N1e0‘ (25)

where No is the initial number of particles, Q is the flow rate out of the intestine, and V is the intestinal volume, then the surface area for spherical particles of uniform size, r, as a function of time can be given by

S,,’=4’jrr2(t)N(t) (26)

This expression can then be used in the non-sink dissolution expression ofEquation 16, with certain assumptions including linear intestinal absorption, to approximate the fraction ab-sorbed as

kXd. Foe (27)

where ha is the absorption rate constant, X0 is the administered dose, Xd is the amount of drug dissolved in the GI tract at i,., and t, is the GI transit time. Further refinements to this model include accounting for polydispersed spherical powders and comparing cylindrical with spherical shape factors, with and without time-dependent diffusion layer thickness.
Finally, for poorly soluble drugs, simulated dose absorption studies have been carried out over different ranges of solubil-ity, absorption rate constants, doses, and particle sizes. Table 38-3 shows the percent of drug absorbed for a drug that has a solubility of 10 g/mL with a of 0.01 min-’. Note that, even though particle-size reduction from 100 to 10 pm increases the percent absorbed, as the dose increases, the impact of this reduction decreases dramatically.

CONSISTENCY ASSESSMENT

Polymorphic Stability: Importance of the Transition Point Polymorphic systems, in which different crystalline forms of the same molecular composition can exist, vary in their ability to interconvez-t at different temperatures. The enantiotropic/monotropic classification is based on the observation that some systems can reversibly interconvert and some cannot. In enan-tiotropic systems, reversible interconversion between the dif-ferent forms is possible. For monotropic polymorphic systems, interconversion is only possible in one direction, from a meta-stable form to a more stable form.
For enantiotropic systems, a critical temperature exists, the transition point, TP, at which the rate of conversion from one form to another is equal. At temperatures below T, one form is more stable; at temperatures above T, another form is more stable (see the section Solid-State CIaracter, page 702; the convention ofdesignating Form I as the most stable polymorph breaks down for such systems because Form I cannot be the most stable form both above and below Ta).
Figure 38-10 shows a solubility versus temperature dia-gram for an enantiotropic polymorphic system. 13,14 For the enantiotropic system on the left, at constant pressure, there are three solubility versus temperature curves: Form ii is the lowest, Form I is the next higher, and the melting curve is M. The critical temperature, T, occurs at the intersection of the Form II and I curves. At this point the solubilities of Form II and Form I are equal and the interconversion rate in any direction is zeiO.14 Below the T, Form I interconverts to Form U; above the 7’,,, Form II converts to Form I. The melting point ofForm I occurs at the intersection ofthe Form I curve and the melting curve M.
Because enantiotropic forms show a change in relative phys-ical stability as temperature is changed, it is important to anticipate the impact of temperature on stability. An early warning sign that one is dealing with an enantiotropic system can be found by relating solubilities with thermal parameters. The higher melting Form I has a smaller heat offusion. Equa-tion 28 gives the relationship between the solubilities,

In 1S1(2’)lfAH0R111T,,,T1
= (RT 7’,,, (28)
where S1 and S1, are the solubilities and 1H1 and AH11 are the heats of fusion of Forms I and U, respectively.’5 The more

Table 38-3. Reduced Absorption with Increasing Particle
Size for a Poorly Soluble Drug
PERCENT OF DOSE ABSORBED

DOSE 10 Imn 25 14m 50 PM 100 AM
1 913 66.9 38.5 17.5
10 70.0 50.0 30.7 15.4
100 9.0 8.7 8.0 63 -- 250 3.6 3.6 3.4 3.1

Source: Johnson KC, Swindell AC. Pharm Res 1996; 13: 1795.

. 0

Enantiotropic System

114-i ll-+1

Temperature

CI

MouotropkSstem

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CA

Figure 38-10. Thermal stability of polymorphic Temperature systems. 13.14

stable form at a given temperature will have lower solubility at that temperature.
Enantiotropicity exists only when the transition point is below the melting point of Form I (see Fig 38-10). However, if a transition point is not found below the melting point ofForm I, it does not mean that the system is monotropic.’4 The tran-sition point, for example, could be below the lowest tempera-ture studied.

For monotropic systems, interconversion is always from the metastable Form II to Form I. The solubility curve ofForm Ills always above that of Form I, and a transition point does not exist because a crystal cannot be heated above its melting point (see Fig 38-10). Oswald’s Law of Stages dictates that if a system is supersaturated with respect to Form II at concentra-tion Ci and T, the metastable Phase II will be the first solid phase that appears.’6 As Form II continues to crystallize, the supersaturation is reduced until it reaches its solubility. At this point, although there Is no longer driving force to crystallize more Form U, the solution continues to be supersaturated with respect to Form I. Thus, crystallization of Form I occurs at the expense of the dissolution of Form U.
Polymorphic Solubility: Difference Between Equilibrium and Dissolution-Based SolubilityAssume Polymorphs I and U are possible for an NCE. Oswald’s Law ofStages tells us that a supersaturated solution will first crystallizout as Form H and then ultimately Form I. Thus, the thermodynamic equilib-rium solubility will be limited by the solubility of Form I. However, because the rate ofnucleation ofU and I is a function of a wide variety of variables, equilibrium solubility is not an especially useful parameter in estimating the impact of a poly-morph form on the absorption of drug from a dosage form. A dissolution-based solubility definition is more useful in this regard. How might such a solubility be defined?
Because the metastable state Form II has a faster dissolu-tion rate, dA/dt,, > dAldt,, where it is assumed that dissolution is carried out under sink conditions of Equation 17. Because d.AJdt = kdSaCS, we can conclude that Cs(H) > C(I) if we assume that Sa and kd are the same for both polyniorphs. Thus, Equation 17 provides a working definition for the solubility differences between Polymorph II and Polymorph I, and it provides.a method for measuring them from dissolution exper-iments. More precisely, it provides the solubility at the surface of the API, which is the solubility that is most relevant for dissolution (see the section Reactive Media 1, page 706). Polymorph Characterization TechniquesAt a given tem-perature, a fluid-phase transformation can cause a metastable polymorph to change into a more stable, less soluble poly-morph. Using a hot-stage microscope, fluid-phase transforma-tions as a function of temperature can be observed.’4 As the temperature is varied, the more soluble polymorph dissolves and the less soluble one grows. Ifa temperature can be found at which both polymorphs have the same solubility, then the system is enantiotropic, and the temperature is the transition point, T. Plots similar to Figure 38-10 can be constructed qualitatively in which the intersection is-the measured transi-tion point. These plots are important because they tell which

form is most stable at low temperatures, and whether the system is enantiotropic.
Differential scanning calorimetry (DSC) is another charac-terization tool that is commonly used. It can measure heat changes that occur when a solid undergoes phase transitions. Melting of a solid into a fluid, for example, requires an influx of heat into the crystal. Two techniques are useful for detecting polymorphic systems using DSC: scanning-rate variation and temperature cycling.
Scanning-rate variation has been shown to detect some re-versible polymorphic systems. In Figure 38-11, crystallization of the more stable polymorph shows up as exothermic depres-sions as the scanning-rate increases.17 Hot-stage microscopy can be used to confirm these thermal changes.

2.5°/mm

5°/mm

- 20°/mm

40°/mm

120 ISO 240

Temperature (°)

Figure 38-11. Detection of polymorphs by varyingthe DSC scanning rate. 17

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Temperature cycling using DSC also can be used to study the relative intercon’iertabffity of crystalline forms. A loss of the metastable, lower melting point polymorph of metoclopra- mide base was found after heating, cooling, and then reheat-ing.’8 The more stable polymorph can often be observed as exotherms due to crystallization after heat-cool cycles.’9 In

addition, storage of a metastable polymorph below the melting point of either polymorph can result in the formation of the more stable polymorph. For gepirone hydrochloride, this oc- curred after a heat treatment of 3 hours at 15O°.’

Powder X-ray diffraction, is the most powerful method for detecting polymorphs. Because different polymorphs have dif-

ferent crystal structures, the packing patterns of their atoms are different. Powder X-ray diffraction detects these packing differences as differences in diffraction patterns. Comparisons of diffraction scans between different polymorphs show char-

acteristic differences that can be used for identification (finger- printing) purposes.
Single-crystal X-ray diffraction is the most definitive char-acterization tool because the exact relative locations ofatoms in the molecular crystal can be determined. However, most often, high-quality crystals for this type of analysis are not available

from the bulk API (especially if the material was milled). Re- crystallization of suitable crystals from saturated solutions may be possible. Ifthe single-crystal X-ray diffraction problem can be solved, programs are now available that can convert
single-crystal diffraction data to a powder X-ray diffraction pattern. This is necessary to ensure that the recrystallization process has not grown a new polymorph.

Solid-state nuclear magnetic’resonance (NMR) is also a powerful technique for studying polymorphic systems. In this
technique, a powder sample must be rotated at a special angle
. (the magic angle) with respect to the magnetic field so that

preferential orientations ofthe powder particles are averaged. Microcalorimetry also has been used to characterize the ther-
modynamic properties of different polymorphs. Finally, diffuse

reflectance infrared Fourier-transform spectroscopy recently has been used to quantify binary mixtures ofpolymorphs using the partial least-squares method for spectral analysis.2°
Metastable Polymorph FormationExpjQring the poten- tial that a given salt has for polymorph formation is a very

important aspect of salt selection. It is important that the choice of the final molecular form be based on as much information as possible. Other factors being equal, a molec-ular entity that forms polymorphs is generally not as desir-able as one that does not, because of the potential intercon-version of polymorphs and a change in an API’s dissolution. This could cause consistency problems both in the API and in the dosage forms. Special techniques are used to attempt to synthesize metastable polymorphs. Preparation of metasta-ble polymorphs requires:

1. Supersaturating conditions for the metastable form, uA.

2. Crystallization ofthe metastable state before the stable polymorph forms.
3. Stable conditions for the metastable polymorph so that conversion
. tothe stable 1A form is prevented.
These steps are shown in Figure 38-12.

For a monotropic system, the metastable state can only change to the stable state; for an enantiotropic system, the

transition point is critical for interconversion. Therefore, the formation temperature should be as far above the transition point as practical.
The ideal solution conditions to prevent 11A from convert-ing to,A are such that the solution phase, a, should be highly supersaturated, of a small volume, and in a relatively poor solvent. Rapid cooling is the method of choice for main-

taining supersaturation with respect to 11A. To help ensure that the rate of metastable crystallization is much greater than the rate ofthermodynamic, equilibration, small volumes

and poor solvents for,A are used. The use of dry ice for rapid

41

Stable

NNThermod,u*mieEqUIIthT*tiOQ

0A Metastable

Figure 38-12. Formation of a metastable polymorph in a mono- tropic system)4

cooling with alcohol or acetone is common for these purposes. Once crystallization from the saturated solution phase, a,

has occurred, it is important to filter and dry the precipitate as quickly as possible to prevent a fluid-phase transformation to the
stable polymorph. Alternatively, if 1A can be melted without deg-

radation, complete melting and rapid cooling of the melt is an another method of forming metastable forms. This avoids two
major problems of solution-phase metastable polymorph forma-tionfiltration and drying, both of which can promote intercon-
version.

Hydrate Stability: Importance ofthe Critical Relative Hu-midity Relative humidity (RH) is the percentage of the maximum amount ofmoisture that air can hold. A substance

is, hygroscopic when it takes up this moisture from air. For a drug substance, the RH that is in equilibrium with a satu-
rated aqueous solution of a solute is termed the critical

relative humidity (CRH).2’ It is a key parameter that can influence the physical stability of solid-state hydrates. A
number ofstudies have shown that the gain or loss ofwater from a hydrate can center on the CRH. Because water in organic crystals is never a passive entity (see Hydrate For-mation, page 711), solid-state changes in the crystal are very likely to follow.

For the tetrahydrate sodium salt of a tetrazolate derivative, a number of different solid-state forms are possible.
above CRH

Z

KI -H20 hAx

4

below CRH
)’ Oh,A
-H20 (29)

The conversion of4hA to hA requires elevated temperature and a RH above the CRH. Water’s plasticizing action in reducing
the intermolecular H-bonding between adjacent molecules is believed to be the mechanism that facilitates the solid-state transformation to the more stable hA crystal form.23 Similarly, elevation ofboth temperature and RH were required to convert the ohA form ofparoxetine HC1 to the oshA form.24 Water also promoted a solid-state transformation ofthe A form to the 0A form of a disodium leukotriene antagonist. The amorphous form initially picked up a small amount ofwater (2%) and then slowly released this water as the anhydrous form was formed. Conversely, the humidity-mediated conversion from 11A to aA has been observed for another leukotriene antagonist.tm Diffi-cult hydrate situations have been dealt with by carefully de-fining the RH ranges of different species and setting specifica-tions consistent with typical manufacturing environments.26

In general, hydrates that are more closely packed tend to be more physically stable with respect to moisture loss. The ideal
solid state is one that is stable over a wide range ofRH, such as the 05hA form of paroxetine HCL24 For the sodium salt of the tetrazole derivative shown in Equations 29 and 30, the denser

 A structure is physically more stable than the 41,A structure. The latter loses four water molecules from crystal channels at a significantly lower temperature than the one water molecule ofthe,, A form, which is integrated into the crystal structure in a more cohesive manner.22 In the sections H-Bonding Networks (page 717), and Hydrate Formation (page 717), hydrate forma-tion is discussed from a molecular point of view. Crystal for-mation involves two mutually opposing principles: (1) satisfy-ing the molecule’s intermolecular H-bonding needs and (2) packing the atoms in the crystal as closely as possible. Hemi-(/i/2) and inonohydrates (h) evidently satisfy both close packing and H-bonding needs more efficiently than hydrates that con-tain water in channels.
Hysteresis is a general term that is used when a material’s response to a second exposure of a stress differs from a-prior response. This has been observed in the moisture uptake of an API as a function of RH. A number of instruments are now

available that can monitor a sample’s weight as RH is cycled from 0% to 95%. The noncoincidence of the weight as the sample is back cycled from 95% to 0% indicates hysteresis. One explanation of this type of behavior is that surface-initiated changes occurred in the solid state below or above the sample’s CRH. Dehydration of the surface below the CRH, as in Equa-

tion 29, with the formation of an amorphous coat of ohA, means that any subsequent water vapor will encounter a more
hygroscopic surface than 4hA.s and thus a different hydration kinetic behavior. On the other hand, conversion of 4hA to,,A above the CRH, as in Equation 30, will produce a different kinetic behavior upon rehydration. Thus, RH hysteresis may result from changes in both the kinetic and equilibrium behav-ior of the surface of the particle.
. Chemical Stability: Common Degradation Sequences

LOW CRH

Sorption/Desorption ofSurfaceWaterIfan anhydrous form of

A is exposed to an RH below the CRH, water molecules will slowly adsorb onto the surface of the drug particle (denoted as >Oh). Adsorp-
tion of up to a monolayer of water has been shown to provide partial

protection from’ oxidation. Dehydrated foods, for example, are more stable when moisture coats reactive sites. For the anhydrous phenyl-
butazone, the oxidation rate has been shown to be. Ipwer below the CRH. For a hydrate, however, the loss ofsurface w’ter of hydration (denoted as <h) at RHs below the CRH has been shown to increase reactivity. Equations 30 and 31 show both of these possibilities.

blov CRH

OhAz > >0h2 (partial oxidation protection) (30)

I,,!,, CRH A A (increased chemical reactivity) (31)

Formation of an Amorphous (a) SurfaceA water enriched/depleted surface, (>h/<h), is prone to furthersolid-state changes shown in Equations 32 and 33. For the water-enriched surface, a chemical reaction is shown in which the crystalline form ofA (j = I) reacts to form the product,,B., which is amorphous. This type of surface hydro-lysis at RHs below the CRH was shown to occur for meclofenoxate HC1 decomposition and for propantheline bromide hydrolysis. For the latter, a lag time occurred that was attributed to the amount of time

at was necessary to form a monolayer. For the water-depleted by- ate (j = h), the loss ofwater initiated the formation of an amorphous surface layer, A.. The consequences of these amorphous surfaces will now be explored.
- 11,0

8 r.>hA2 +,,B2 (32)

 11,0

hA- <hA2 8,A2 (33)

Transformation of Amorphous SurfacesBecause amorphous layers are more prone to be hygroscopic than crystalline solids, the chemical transformation of 1A. to,,B in Equation 32 is significant

because the latter can attract more water to the surface. Dissolution of,,B2 shown in the first downward reaction ofEquation 34 will then form a surface coated with b.c, as shown in Figure 38-3. The reaction of

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meclofenoxate HCl below the CRH to form amorphous dinthylami-noethanol HC1 (see Eq 32) is a good example of this. Next, the water adsorbed to the surface due to the dissolved form ofB on the surface, b.., promotes the dissolution ofthe surface ofA,A, to form a surface coated also with a., the dissolved form of A on the surface, which then undergoes further decomposition to b. This is shown in the horizontal and final downward reactions of Equation 34.

rB1

A, 8 a + b,

(34)

In Equation 35, two possible solid-state changes for A, are shown. First, the reactive amorphous surface can undergo a degradation reaction to form C. Second, the surface can con-tinue to lose water below the CR11 (50 that the subsurface,,A undergoes a solid phase transformation to a crystalline phase, 1A. The dehydration changes for cefixime trihydrate are exam-ples ofthese reactions.3’ The partially dehydrated form ofthis compound was more unstable than the fully hydrated or the completely dehydrated crystalline forms.

T C,

 H20, T 1A (35) 5’

ABOVE CRH

When water is adsorbed to the surface of the particle above the CRH, the drug particle becomes coated with a dissolved drug layer, a, which
is assumed to be saturated:’

,xces, 11,0

A, a2 (36)

Degradation under these conditions is assumed to occur solely in the dissolved layer. This situation has been extensively discussed.’ For the Maillard reaction, in which primary amines react with carbohydrates, adsorbed water initially increases the reaction rate to a maximum due to the enhancement of reactant mobility. Greater amounts of water then decrease the reaction rate due to dilution of the reactive species. Similarly, for free-radical auto-oxidation of unsaturated groups, reac-tivity increases above the CRH because of accelerated reactant mobil-ity. Below the CRH, oxidation decreases due to the immobilization of hydrogen peroxides and trace metal catalysts and the protective effects ofa monolayer ofwater that isinsufficient to increase reactant mobility.

Influence ofSalt Form on Hygroscopicity Table 38-2 shows that the non-salt forms, including free bases, free acids, and nonelectrolytes, are the most popular molecular forms on the market. In general, these forms would be expected to be less hygroscopic than salt forms due to their un-ionized character. Although the sodium salt is the most popular weak acid form, this form has a tendency to be hygroscopic. Alternative salts that have proven useful in overcoming hygroscopicity are hy-drogen sulfate" and tromethane.’34
Hygroscopic tendencies for weak bases might he overcome by using aromatic counter-ions. Aryl sulfonic acids were shown to provide moisture protection without decreasing dissolution for the sparingly soluble weak base, Xioban,.35 The free-base form ofthis drug (pK, 6.1) was hydrolyzed at 40C/80% RH. On the other hand, one weak base (pK.a 3.67) was chosen for de-velopment because it was less reactive to moisture exposureovelopment than the HC1 salt. The latter showed chemical instability with moisture and heat and was the only salt that could be formed.36 Stronger bases like peirinone (pK 4.71) can form stable and nonhygroscopic HC1 salts.3°

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Grinding ImpactProcessing of solids can have a major impact on dissolution due to solidsolid phase changes. Grind-ing is one process that has been shown to cause changes in both polymorphs and hydrates. For the 111A polymorph (Form C) of chioramphenicol palmitate,37

grinding m,,rr gr,ndlng /

(37)

grinding causes a successive change to the 31A polymorph (Form B) and finally to the 3A polymorph (Form A).38 Corre-spondingly, dissolution from the fastest to the slowest is in the order

ground 31A > ground 1A > 11A > 1A (38)

For hydrates, similar solid-state changes have been observed. When cefixime trihydrate is ground, a solid-phase transforma-tion takes place:

grinding

3hA- 0,OhA (39)

Water in this situation plays an essential role in crystal forma-tion. Its removal causes a collapse ofthe crystal lattice.39 Other pharmaceutical processing operations and their impact on crys-tals have been reviewed.40

SALT SELECTION DECISION-MAKING

The pressure to increase the productivity of the knowledge worker is readily apparent at the salt-selection stage. Because

ofincreased productivity in discovery, the cascading impact on development to choose rapidly-the best molecular form is

readily apparent; toxicological and bioavailability studies can- not proceed until the salt is chosen. Once these studies are initiated, it becomes very costly to change the molecular form

because many of these biological studies would have to he repeated. More importantly, precious time and a competitive advantage will be lost. However, if an unanticipated, unaccgpt-

able property emerges during the developulent of an API, the sooner the change is made the better. It is for these reasons that efficient paradigms are being sought for this stage of

development. Two approaches will be presented that attempt to optimize the probability of success with speed. Previous ap-proaches were criticized for excessive characterization of poor candidates and for a lack of clear go/no-go decision-making.41 As a practical consideration, it is essential that NCEs have high purity, and that salts be crystallized. In the following discussion, weak bases that are to be absorbed orally are used. Similar approaches can be developed for intravenous NCEs and for weak acids.

Multitiered SelectionApproachOne approach in which dif-ferent critical parameters are used to filter a salt candidate’s progression to the next stage has recently been proposed.41 Crystalline salts are successively sorted by a three-tier system in the following way:

Tier 1. Hygroscopicity
Tier 2. Thermal analysis and X-ray diffraction
Tier 3. Accelerated solid-state stability

Tier 1 eliminates any form with excessive moisture sorption/desorption characteristics. Only the survivors progress to Tier
2. In this second tier, changesin crystal structure are examined under extremes of moisture conditions by using thermal anal-ysis and powder X-ray diffraction to detect desolvation and aqueous-phase transformation problems. In addition, aqueous solubility is determined to address potential dissolution prob-

lems. The best candidates for formulation and manufacturing are considered here and survivors proceed onto Tier 3. In this
third tier, accelerated thermal and photo-stability testing is

carried out. This is considered to be the most time-consuming

stage.

step so

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excipient

the

Tier

limiting

2 eliminates

compatibility

of candidates
testing

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all ofthe candidates, additional salts or free acid/bases are considered before reevaluating any salt

that was dropped in an earlier tier.
Several comments can be made regarding this approach.

The HCI salt of ranitidine, due to its hygroscopicity,42 probably would not have been a final candidate in the multi-tiered approach. Yet this is one of the most successful drugs ever marketed. This

emphasizes a need for prioritizing the salt selection process so that as wide of a range of development issues are addressed as early as possible and that they all are put in perspective. If a hydrochloride salt has much better absorption properties than the free base but is hygroscopic, it would be very prudent for development to see if it can deal with this problem. Otherwise, bioavailability may be com- promised by a single-minded emphasis on API consistency. The free base is not considered in the multi-tiered approach unless

all alternatives have failed despite its potentially favorable disso-lution in gastric fluids and its sensitivity to particle size reduction with a reactive sink.

The decision-tree, goal-oriented approach discussed below ad-dresses some of these issues. -

Decision-Tree, Goal-Oriented ApproachAn alternative ap-proach to the multi-tiered go/no-go selection approach is onepproach based on a decision-tree using statistical probabilities and functional grouping of counter-ions to seek prioritized physical properties. In Figure 38-13, prioritized problems are shown, absorption being the highest priority.

The decision-tree considers the free base, the HC1 salt, as well as other options. Although this approach uses statisticalu
probabilities for molecular form consideration, ideally, a high-throughput, automated methodology would be available that could determine exhaustively which salts can form crystals and under which conditions. Feasible salts would then be synthe-sized and placed under accelerated stability and stressing con-ditions. This would allow for the maximum amount ofexposure to the sample before a decision has to be made. Degradant evaluation need not be carried out on these stressed samples immediately-, otherissues may eliminate a particular candidate and make this unnecessary. However, evaluation for crystal-Unity should be carried out early to ensure.that this does not impact physical or chemical stability. Physical property screens and absorption-dominated prioritization would then force a pharmaceutical evaluation to be made regarding the possibility of overcoming consistency and processing problems. By using functional groupings (see Table 38-2), salt forms would be considered that could address specific problems.’

Compressibility and Compactibdity

Because tablets remain the preferred oral dosage form due to high-speed manufacturing, information obtained during pre-formulation studies on the ability of powdered drugs to be compressed and compacted can be a valuable aid to market-
image formulators. Compressibility and compactibility relate
directly to tableting performance. Compressibility can be de- :2 fined as the ability of a powder to decrease in volume under pressure; compactibility can be defined as the ability of a pow-
der to be compressed into a tablet of a certain strength or hardness. Even though powdered drugs usually are formulated
with excipients to modify compression and compaction proper-
ties, the properties of the powdered drug alone may be the primary determinant of its ability to be manufactured into a tablet.. Significant differences in compression and compaction behavior often can be observed in different lots of the same

drug. For example, changes. in crystallization or milling proce-
dures may produce differences in behavior. rocedures

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1.__ Full

Eval

Prioritized Problems

1. Absorption 2. Consistency 3. Pro.

C5 dA/dt T 1›120 1w 1:1 Syn. Milling Other

llndicatoral ___

’up dA/dt Polar FlexA MultiF PlanarA Bulky

Ha

Syn

"P

’Full1 ill

I>Y
- < *

Y

Problems
Group Solve

Group(s)
S3.

m lFFval]
Figure 38-13. Absorption-dominated decision-tree.

Compression and compaction most often are evaluated by measuring the tensile strength and hardness of compacts. Tensile strength commonly is measured by radial compression of round tablets, where the analysis of strength accounts for the dimen-sions of the tablets. Transverse compression of square compacts between platens narrower than the compact is reported to provide more reproducible results on a wider variety of powders. Hardness can be defined as the resistance of a solid to local ermanent deformation. Static impression or dynamic methods ually measure deformation hardness tests. The static method involves the formation of a permanent indentation on a solid surface by a gradual and regularly increasing stress load. Hardness is determined by the load and size ofthe indentation and is expressed as force per unit area. In dynamic tests, the  solid surface is exposed to an abrupt impact such as a swinging pendulum or an indenter allowed to fall under gravity onto the surface. Hardness then is determined from the rebound height of the pendulum or the volume ofthe resulting indentation. Hiestand has used adaptations of a compression test and a hardness test to obtain measurements that are used to formulate three dimensionless parameters or th&ces. The indices are used to, characterize the relative tableting performance of individual componens.or mixtures. The Strain Index is the ratio of dynamic indentation hardness to reduced Young’s modulus. The Bonding

Index is the ratio oftensile strength to indentation hardness. The Brittle Fracture Index is obtained by comparing the tensile strengths of square compacts with and without a hole at their center. The indices themselves do not measure intrinsic proper-ties of a chemical compound, but rather the traits that influence the tableting performances of a specific lot of chemical. It is nec-essary to know the magnitude of all three indices to predict the variety of tableting properties that may be incurred. Such infor-mation can act as a guide in selecting excipients to overcome problem properties of a drug ingredient.

Excipient Selection:

Formulation Compatibilities

Excipients serve many roles and are the backbone of a formu-lation. They may be needed to stabilize the API by providing antioxidant, heavy-metal chelating, or light-protection proper-ties. They also may be used to enhance bioavailability and to control the release from dosage forms. For solid dosage forms, they provide suitable properties for dispensing the API in ac-curate dosage units that have reproducible release proper-ties. Diluents provide a flowable bulk, binders hold powders

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together after wet granulation, lubricants provide punch- releasing properties, and disintegrants help to disperse dosage

forms in the GI tract. On the other hand, judicious choices must be made to prevent incompatibilities between the API and excipients.
Screens to detect drug-excipient incompatibilities recently have been developed using elevated temperature and added

water to accelerate potential interactions in ternary and more complex powder blends.4° Such methods have been shown to be
capable ofrapidly detecting chemical incompatibilities and giv-ing good correlations with results using powder blends of drug and excipients at elevated temperatures and humidity. Processing incompatibilities can be more difficult to trouble-shoot than chemical incompatibilities. For example, tablet per-formance has been shown to vary for ketorolac tromethamine, depending upon the kind ofstarch that was used. Cornstarch

showed a decreased disintegration time and dissolution rate as a function of blending time whereas pregelatinized starch
showed no such dependency. The difference between these two excipients was attributed to the formation of drug/cornstarch agglomerates with magnesium stearate.46 Blending studies have shown the potential benefits of using sodium lauryl sul-fate to offset these types of effects.47

Finally, manufacturing for a global market has forced a reevaluation of excipients that are used in formulations so that
manufacturing can be carried out with internationally accept-able components. The European Economic Community has fo-

cused recently the pharmaceutical industry on eliminating ex- cipients that have the potential for transmissible spongiform
encephalopathies, replacing ingredients like stearic acid, mag-nesium stearate, polysorbate 80, and simethicone with vegeta-ble grade sources.

API Specifications: Meeting Product
and Regulatory Requirements

POLYMORPHIC FORMS AND HYDRATES DECI-SION TREESA major portion of this chapter has been de-voted to characterizing the solid state, A. The left side of Figure summarizes some ofthe potential solid states that can exist for the un-ionized form ofA; if a salt form was chosen for the API, the same states also would be possible. Previous sections have discussed the impact on API consistency and dissolution for the different solid states. The critical rela-tive humidity (CR11) and the transition point (Ta) for enantio-

Agure 38-14. Solid-stae forms, and specification
"setting.’49

cC

tropic polymorphic systems’ are especially important intrinsic, physical parameters that control solid-state consistency and
potential solid-state interconversion. Moisture and tempera-ture, as we have discussed, are the major environmental vari-ables that can promote these changes. Rapid methods, there-fore, are needed to characterize potential solid-state forms and their physical properties. The decision-tree on the right side of Figure 38-14 summarizes when specifications need to be set to maintain API consistency. Ifthe physical properties ofthe solid states differ, assessments need to determine the impact this will have on a formulated API. Specifications need to be set to ensure a consistent product.
PARTICLE-SIZE ACCEPTANCE CRITERIONOnce

the solid state,JA, has been characterized, the potential impact of particle size on absorption can be assessed. Figure 38-15 shows a decision-tree approach, suggested by the International Committee on Harmonization, for determining whether a par-ticle-size acceptance criterion is needed.50 Previous sections in this chapter have ’discussed nearly every asect of this tree. Although dissolution-limited absorption is a major concern, Figure 38-15 also includes dosage form issues such as content uniformity.
BIOPHARMACEUTICAL CLASSIFICATION OF API

Although it is possible to alter the solid state, A, such that dissolution and absorption can be enhanced, solubility and passive permeability are, in general, intrinsic properties ofthe NCE. Thus, even though the amorphous state, aA, in some situations can be stabilized to enhance dissolution, the equilib-rium solubility will be determined by the least soluble solid state. A classification has been proposed to segregate situations when in vitro and in vivo correlations (WIlT) are expected. Such designations may be used as a guide for determining when bioequivalent studies may need to be carried out. Table 38-4 shows the four major classes based on solubility and passive permeability.

ENGINEERING THE SOLID STATE

Speed is essential for any preformulation innovation ifit is to be effective in influencing discovery decision-making. In Figure 38-4, the early discovery stages, Steps 1 to 4 were introduced. The potential focal points of high-throughput physical screen-ing, predictions of physical properties, and artificial intelli-gence are shown in an expanded version ofthese early steps in Figure 38-16.

Solid State Family of Decision Tree

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I?- hA 4 N <,;A

IY

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JA=iA

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+INoActlonj Jsetspecs.I

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Solid?
Suspension?

Particle Stae N
No Action Needed

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Dsoluffo Stability Content Uniformity Solubility, Bloavallability ofProduct ofProduct ofProduct

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Library Expansion

’"’The development of mass-screening technologies has spawned a number of technologies that complement a com-pany’s in-house library. Besides the massive influx of com-pounds that can be obtained from combinatorial synthesis, computer-based analyses can be used to assess the diversity of the in-house chemical library and identify areas of weak-ness. Negotiations with other companies then might take place to fill in deficiencies. In addition, a number of commer-cial libraries, including natural products, are also available for mass screening. Figure 38-17 shows these aspects of library expansion.
Modern mechanism-based screens, based on recombinant proteins, have vastly increased the number and specificity ofin vitro screens. However, because the goal ofmass-screening is to

Table 38-4. In Vitro/In Vivo Correlation Expectations

for Immediate-Release Products Based on Biopharmaceutics Class for Passive Absorption
CLASS SOLUBILITY PERMEABILITY IVIV CORRELATION EXPECTATION

I High High IVIV correlation if dissolution

.

. rate is slower than gastric emptying rate. Otherwise
limited or no correlation.
II Low High IVIV correlation expected if
in vitro dissolution rate is
similar to in vivo
dissolution rate (unless
dose is very high).
Ill High Low Absorption (permeability) is
rate-determining and
limited or no IVIV
correlation with
dissolution rate.
IV Low Low Limited or no IVIV
correlation expected.

Source: Amidon GL, etal. Pharm Res 1995; 12:41 j.

Figure 38-15. Decision-tree for drug substance particle-size
distribution.50

flnd.compounds that have high in vitro activity, this exclusive focus tends to produce compounds with poor physical proper-ties. Such compounds, either because of their conformational restriction or their H-bonding with receptors, have much greater activity and selectivity than. previous generations of NCEs that were obtained from tissue screens and in vivo tests. These attributes have caused modern chemical libraries to

expand with compounds that have high melting points and low aqueous solubility. Chemists affectionately call such com-pounds brick dust. - Although brick dust compounds may provide a point of departure for an in vitro activity search, most of them are unacceptable for development because of their poor physical properties, especially poor aqueous solubility. It would be un-desirable for chemical library expansion to be dominated ex-clusively by such compounds because oftheir poor development potential. Selection of a good API, an active chemical with acceptable pharmaceutical properties, could be delayed. For this reason, there is an urgent need to integrate pharmaceuti-cal properties into the chemical library expansion and the mass-screening paradigm.
However, a greater mechanistic understanding is needed of those factors that promote desirable physical properties and good absorption. In lieu of this understanding, computed pa-rameters based on marketed drugs have been used to direct immediate library expansion based on the assumption that these drugs have physical and chemical properties that are desirable. 1 The potential future role pharmaceutics can play in influencing the rational direction oflibrary expansions based on a more fundamental, more molecular-based understanding of physical properties will now be discussed.

AQUEOUS INSOLUBILITY: MOLECULAR MECHANISMS

Although aqueous solubility is a major factor that affects drug absorption, better methods of understanding the molecular mechanisms and predicting this parameter are needed. Aque-
ous insolubility occurs when the attraction between molecules queous is greater than the ability ofwater to solvate the molecule and

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I

(1) Library Expansion

Aqueous Insolubility and Molecular Mechanisms /- Drug Delivery and Molecular Mechanisms

(2) Series Selection

II Physical Property Screens

I IpH-Solubility Profiles
(3) Analog Expansion
Absorption Engineering
Solid-State Engineering
Stability Engineering

(4) Analog Selection

Figure 38-16. Proactive pharmaceutical API decision- making: potential opportunities for high-through- Salt Selection put physical innovations. ____________
dislodge it from its solid phase. Generally speaking, most phar-

maceutical solids are manufactured in the form of crystals as opposed to amorphous solids because crystals are more stable.
Crystals are arrays ofmolecules that pack in a regular pattern

and thus have long-range order, ie, packing patterns that ex- tend in space over large numbers of molecules. Single-crystal

X-ray diffraction can be used to visualize the conformation of molecules in the crystal, the interactions between molecules, and exactly how repeating units of molecules are arranged in

three-dimensional space. When the forces that form crystals e sufficiently strong, either because the forces are sufficiently

ong in themselves or because there are a large number of orces on a given molecule, insolubility results. These forces are termed intermolecularforces (between molecules) as opposed to

intramolecular forces (within a molecule).

In the past, most of the predictive methods for solubility have been either thermodynamically or statistically based. In-
sight into the molecular basis ofinsolubility is now possible. By..

using single crystal X-ray diffraction, correlatiozi between mo- lecular packing motifs and solubility can be carried out. The major intermolecular factors that have been identified to date are
1. Hydrophobicity
2. Conformational restriction

Figure 38-17. Expansion of mass-screenable chemicals.

3. H-bonding networks
4. Hydrate formation
5. Zwitterion formation

Hydrophobicity needs no explanation; this brieffocus will con-centrate on the cohesive aspects of the latter factors. Conformational RestrictionUsing biotechnology, very spe-cific biological targets can be synthesized from genes. For ex-ample, pure dopamine receptor subtypes, D1D5, have been used as mechanistic targets for schizophrenia; cycloxygen-ase1 and cycloxygenase2 similarly are now available for anti-inflammatory screening. Developing a drug specifically for cy-cloxygenase2 inhibition promises to minimize the side effects of nonsteroidal anti-inflammatory inhibitors like aspirin.
Such molecular specificity is now possible because screening-feedback enables chemists to rigidify drug molecules such that interactions with the target protein are restricted to only a few conformations. However, this rigidity has a physical impact. Ri-gidified molecules appear to pack better because they can be arranged in fewer ways than flexible molecules. Consequently,
such molecules have increased dispersion force interactions (very

short ranged). This increased intermolecular interaction leads to a conformationally based insolubility that has been observed es-
pecially in molecules that are planar or linear.

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Chemical Library

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Other Compmi
chemical Ubcadcs

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H-Bonding NetworksPolar groups generally impart water solubility to a flexible molecule. Functional groups that have an H-bond donor and an acceptor group can help the molecule to form a hydration shell around itself and increase solubility. However, in more rigid molecules, these same groups can bind one molecule to another in the crystalline state through inter-molecular H-bonding. Single-crystal X-ray diffraction studies of crystals provide a detailed picture of how H-bonds form between such molecules. Insolubility due to H-bonding in con-formationally restricted molecules appears to increase as the number of H-bonds per molecule and between molecules in-creases. Predicting exactly how such molecules arrange in a crystal is difficult because there are two mutually opposing tendencies in crystal formation: (15 packing molecules as closely as possible, and (2) maximizing the number of H-bond-ing interactions. Crystals often achieve a balance between these opposing tendencies in unexpected ways. Conformational restriction also seems to increase the effi-ciency of H-bonding in crystals by increasing molecular rigid-ity. This may be because rigid molecules can form more uni-form, consistent H-bonds that are needed for long-ranged crystal order. Intramolecular H-bonding often adds to this rigidity.
The forces directing initial crystal formation would be ex-pected to be dominated by H-bonds due to their electrostatic nature. These are the longest-ranged intermolecular forces in a nonelectrolyte. Packing and dispersion interactions would then be expected to dominate the final crystal form. For some mol-ecules, the H-bonding ofwater can be very important in crystal formation. When the number of H-bonding acceptor groups is large compared to the number of donor groups, hydrates are 0ore probable. Water, due to its high-H-bonding capacity, often strongly binds molecules together in crystals by making up for molecular deficiencies. This can increase aqueous insolubility. It is generally observed that hemihydrates and monohydrates are more insoluble than the anhydrous forms.
Hydrate FormationHydrate formation in organic crystals increases the number of molecular options for qatisfying the. dual crystal maximization constraints of H-boning and dense packing. Water, because of its small size and di-donor and di-acceptor capacity for H-bonding, often acts as an interstitial H-bonding cement and spacer.52 Crystal surveys have found that water is a very weak donor, but the water oxygen is the strongest acceptor. On the other hand, water almost always donates two H-bonds but usually accepts one, not two, H-bonds. Because ofits unique characteristics and flexibility, predicting how water will interact with an H-bonding NCE is not possible. The earlier presumption oflinear and single acceptor H-bonds has been shown to be wrong. Nevertheless, although the exact structure ofwater interactions with NCEs cannot be predicted, generalizations can be drawn regarding the type of structure that is most likely to be hydrated. Water with its di-donor/mono-acceptor role tends to reduce proton deficiencies of the arent molecule. Molecules that have donor/acceptor ratios of ess that 0.5 are most likely to be hydrate candidates. Zwitterion FormationZwitterions are molecules that at a

given pH have both a positive and negative charge. Ifthey are conformationally restricted, they tend to be very insoluble. Evidently the localization of opposite charges at different re-gions in the same rigid molecule provide scaffolding that en-ables very efficient salt-bridge dimers to form. Sometimes a zwitterion not only forms dimers, but also has ample H-bonding groups to form H-bonding networks in addition to the dimers. Occasionally, zwitterion insolubility is caused by metabolism, for exampleby aromatic hydroxylation and subse-quent sulfation of a strong basic drug. Such metabolites have the potential to precipitate in the. kidneys as urine becomes concentrated in the renal tubules.

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DRUG DELIVERY: MOLECULAR MECHANISMS

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A9’
Membrane-Active SitesThe rich interaction of drugs with membrane receptors is modulated partially by their complex lipid matrix. For drugs that partition into membranes, lateral diffusion provides a rapid surface-dispersion mechanism for transporting drug to any integral membrane receptor. Func-tional groups on a molecule that help position it within the membrane help explain why some drugs act superficially or more deeply on integral membrane proteins.
Finally, intrinsic membrane curvature, with its concomitant asymmetric distribution of phospholipids, provides a rich po-tential for specific and allosteric interactions. Drugs, depending on their amphipathic nature, may insert themselves preferen-tially into the phosphatidyicholinerich outer leaflet or the phosphatidylseririe inner negative leaflet. Protein crystallo-graphic studies have confirmed the relationship between mem-brane localization and duration of action of a number of drugs. Membrane PermeabilityComputational approaches have been used to develop molecular models for passive membrane permeability. Exploration of a number of models, including homogeneous solubility-diffusion, defect, and free volume, have shown an inability to completely explain the permeability of simple molecules like water and ethanol. Recent progress has been made in this area by dividing the membrane into zones in which the mechanisms of-diffusion differ. The preferential im-pact of different zones on diffusion and the dynamic simulation of spontaneously occurring membrane conformational alter-ations can then be used to simulate and average diffusion trajectories to estimate permeation rates.

Series Selection

PHYSICAL PROPERTY SCREENS

Until computational methods for predicting physical properties reach an advanced state ofreliability, high-throughput screens for physical properties will play a major role in understanding how molecules can be designed for better absorption. New instrumentation makes this task more feasible than it was in the past. Rapid advances in analytical detection sensitivity, especially in powder X-ray diffraction and chromatography mass spectrometry, have helped reduce material consumption and analytical development time. Robots, and specialized au-tomated dispensers and spectrophotometers that have been developed for mass screens can be used creatively for develop-mental purposes. In short, the more rapidly and reliably phys-ical properties can be assessed, the more impact these mea-surements will have on the flow of new leads for development. However, the greatest advantage of automation is not physical evaluations on a grand scale, but rather the ability to custom-ize determinations to solve particular problems rapidly.

pH-SOLUBILITY PROFILES

High-throughput determinations ofA° and A solubilities and values provide the basis for pH-solubility profiles. Series selection can then focus on the feasibility ofmodifying the pK for a given series as part of an optimization strategy to enhance absorption. Ideally, a pK that allows for ionization to enhance solubility while still providing some un-ionized form for absorp-tion is ideal. Consider Equation 40.

rapid eqiIibrnion k_

A’ (ionizing reservoir) A° I - GI membrane -

systemic circulation (sink) (40)

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1199% of the drug in the GI tract is in the ionized form A, and 1% in the un-ionized formA° (eg, 99%), A’ provides a reservoir ofdissolved drug while the systemic circulation provides a sink

for A°. These conditions should allow for good absorption as long as is not rate limiting. Modifying the pH solubility profile to approach this situation is one way to optimize absorp- tion. The impact of this type’ of optimization cannot be overes- timated, because pK,, values and intrinsic solubilities are mo- lecular parameters that neither salt selection nor formulation can alter. Further techniques to enhance absorption will be

discussed in the next section.

Analog Expansion

ABSORPTION ENGINEERING

Absorption-enhancement engineering of analogs can be ad-

dressed after the rate-limiting mechanism for poor absorption has been identified. Like the absorption-enhanced prop- erties must be designed into the NCE before it is passed on to

development. For this reason, it is important for preformula-

tion to integrate physical property design into the molecule as early as possible. Crystal EngineeringIf aqueous solubility and dissolution are the problem, crystal engineering might be possible. In this

case, it is important to identify the mechanism ofinsolubility as discussed above. Each mechanism will require a different ap- proach. Hydrophobic problems are usually the simplest and can often be handled using formulation approaches. The more difficult problems require a molecular understanding of the

intermolecularforces in the crystal. For H-bonding problems, it maybe possible to adjust the ruin,ofH-bond donor and acceptor groups to reduce the number and strength of H-bonds. It has been found that simple changes can alter H-bonding networks

and solubility in a dramatic way. The substitution, for example, of a t-butyl group for a phenyl group for one insoluble com- pound increased the intrinsic solubility 4-fold, and the solubil-

ity at pH 5 increased it 10,000-fold, despite the fact that

the resulting compound had the exact ionhation potential of the original compound. These enhancements were due to
changes in H-bonding network structure that released a water-solubilizing group for ionization. Other modifications would be directed at minimizing conformational restriction to reduce crystal-packing efficiency, such as by introducing an acyl chain in a compact heterocyclic system. Practical applications of these design suggestions can be difficult beause they often

reduce activity. However, as preformulation scientists work more closely with synthetic chemists, crystal-packing disrup-

tion strategies that are compatible with ease ofsynthesis and

in vitro activity will become commonplace. In addition, as com- puter predictions of crystal-packing structure and H- bonding networks from molecular structure become more prac- tical (see Engineering The Solid State, page 714), these types of

design considerations will be made as a matter of course as activity is being optimized.
Permeability EnhancementThis is another intrinsic pa-rameter of an API that, in general, is not enhanced in oral formulations. Recently, increased knowledge has helped to de-

sign drugs that will passively penetrate membrane barriers more easily. There has been a great emphasis in the past on the

partitioning of a solute out of the aqueous phase into a li-

pophilic membrane and not enough emphasis on the need for a drug molecule to desolvate from the aqueous phase. Molecules

have been designed successfully to enhance permeability by reducing the desolvating step. One way this has been accom- plished is by reducing a molecule’s solvation through the pro-

motion of intramolecular H-bonding in the molecule. In addi-tion, the ability of a membrane-bound drug to flip-flop from the outer leaflet of the bilayer membrane to the inner leaflet ap-

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pears to be important for efficient membrane permeability. Ultimately, such insiht may be possible from molecular mod4

eling studies of membranes.
Intrinsic Dissolution EngineeringCorrelating molecular

orientation with morphology in crystals has provided insight into molecular mechanisms of dissolution. In one study, it was shown that the relatively strong binding of a solvent at one subset ofsurface sites and repulsion at others provided a relay

type of dissolution that favored erosion from particular faces of the crystal. Such a mechanism also perpetuates the natural

corrugation of the surface at the molecular level and helps define the factors that may limit dissolution in the bulk phase.

In this regard, some progress has been made in predicting the intrinsic dissolution rate of an API from considerations of the surface pH of the API. Modifications of the classic Noyes Whitney relationship have to be made for weak acids, bases,

and their salts. The impact of dissolution in a reactive media was discussed under Preformulation Challenges, page 700. Pre-

dictions using such considerations are possible for NCEs whenredictions the pH of the medium, the solubility of the un-ionized form of the drug in water, and the pK, of the NCE are known.53

SOLID-STATE ENGINEERING

The computational ability to link molecular structure with crystal packing has advanced to the point that polymorphic predictions are becoming more reliable for small molecules. This has a number of implications.

Exploring the polymorphic possibilities of a given molecular struc-ture should allow evaluations to be made regarding which struc-tures have more elaborate polymorphic possibilities. In some in

stances, it may be desirable to avoid such structures; in others, these structures may provide the means for improving physical properties, assuming adequate conditions can be found to ensure physical and chemical stability.

As our molecular understanding ofthe dissolution process increases (see Intrinsic Dissolution Engineering, above), it will eventually be possible to predict molecular structures that can enhance dissolu-tion for a particular analog series and to predict the solvents that will be necessary to obtain the most advantageous crystal habit. Hydrate predictions are also within the realm of possibility as the molecular study of existing hydrates yields rules that can be used

by expert systems and molecular-modeling programs. Finally, an increased understanding of the molecular conditions necessary for the homogeneous and heterogeneous nucleation process of crystal- lization will aid in the practical synthesis of industrial APIs.
STABILITY ENGINEERING

The ability to predict the products of chemical reactions means that evaluations of potential NCEs that are being considered

at the analog-expansion stage can be considered on the basis of their presumptive chemical stability and degradation pathways before they are even synthesized. Although poor predictions have the potential to inhibit the synthesis ofpoten-

tially valuable compounds, with future advances in computer- generated molecular diversity such considerations may become less important as predictions become more accurate. The pre- formulation implications for such predictions are also evident. Anticipation ofpotential degradants and their characterization can be used to identify proactively unknown chromatography
peaks and predict pharmaceutical excipient incompatibilities.

Analog Selection

Physical properties that are oriented toward in vivo conditions are most useful at this stage. Solubility and dissolution deter-

minations in media and pus that mimic physiological pHs can be used as an early indicator of how well an in vitro/in vivo
correlation can be drawn. At this stage, a number of other

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studies from different divisions will be carried out. In vitro and in vivo metabolism studies, bioavailability studies in different animals, as well as possible selective toxicological studies can be used to determine the best analog. Degradant predictions of the different analogs at this stage may also help to differentiate and minimize problems that can occur later in development. In addition, high-throughput methods to determine the best salt form for a particular analog would mean that therapeutic test-ing could be carried out on the salt form that will be eventually used in development.

Conclusion: Application of Knowledge

"The actual product of the pharmaceutical industry is knowl-edge; pills and prescriptions ointments are no more than pack-aging for knowledge."M The introduction of methods to probe and exploit human and animal genomics has had a cascading impact on the industry. These new concepts had a number of qualities that ensured adaptation.5’ The systematic use of mechanism-based reagents was a tangibly better solution for finding new therapeutic entities than the more serendipitous methods of the past. Such high-throughput screens were com-patible with increasing use ofrobotics whose advantages could easily be understood by all in the pharmaceutical industry. Each company was able to hold trial runs to test the utility of such screens and in the end obtain observable results. To-day, the recombinant DNA innovations of the 1980s still pro-vide the driving force for other =ovations in the pharma-ceutical industry: miniaturization, customizing, and artificial intelligence.
Miniaturization began in earnest with the micronization of e transistor concept onto silicon&’chips. In the pharmaceuti-cal industry, mass screening, the demand for higher and higher throughput, and the need to conserve chemical libraries have accelerated analytical and synthetic nanotechnology. This lat-ter need is extremely important because chemical libraries are expendable resources that are not easily replaced. Old library entries were synthesized in gram quantities, aid.newer entries in milligrams. Conservation of this resource will require a combination of nanotechnology along with a host of regenera-tion technologies including combinatorial synthesis, high-throughput purification, and promotion of an increasingly di-verse molecular library for mass screening. In addition, chromatographic columns, HPLCs, and electrophoresis on the nanoscale hold promise for extremely high resolution with ex-tremely low material consumption. On this scale, area can efficiently be converted to a linear dimension. Thus a chip 10 x 10 mm can be converted easily to an electrophoretic path
of 9.5 cm. The potential for massive parallel processing is evident when one contemplates the possibilities of 100 nano-laboratories on a single chip.
Customization at low cost also will be possible with new technology. DNA probes located on biochips will permit the

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ofa treatment course depending on a person’s
ability to metabolize a given drug. Such innovations likely will cause a cascading demand on development to individualize dosage forms. Finally, the rapid and parallel demands placed
on preforniulation will force more decisions to be made us-ing artificial intelligence. High-throughput determinations of physical properties will result in high quality databases, which can in turn be systematically exploited by expert systems. Highly accurate predictions of solubility, permeability, and dissolution will be possible in the 21st century.
Although artificial intelligence is still in its infancy, the benefits ofits applications can be appreciated from a consider-ation ofthe differences between knowledge and information. A chemical reaction database, for example, stores information on particular reactions. However, it cannot apply this information to new molecules. Expert systems, on the other hand, so codify

knowledge that they can be applied to entirely new sitliations. Knowledge differs from information in that information is ran-dom and miscellaneous, and it tends to expand too rapidly and overwhelm us.’ Knowledge, on the other hand, requires that the structure of a subject be understood in a way that permits other things to be related to it in a meaningful way; it permits intuitive heuristic procedures to be developed to solve problems when no algorithms are available.57 Such applications of arti-ficial intelligence, however, are still in the early-stage knowl-edge revolution, in which knowledge is applied to produce results. In the postcapitalist society, knowledge will be applied toward systematic innovation: "It will be applied systemati-cally and purposefully to define what new knowledge is needed, whether it is feasible, and what has to be done to make knowl-edge more effective."
Knowledge and the productive application of knowledge are anticipated to be the sole factors that will drive the postcapi-talist society into the 21st century. In the pharmaceutical in-dustry, massive diffusion of innovations from discovery into development will pose an accelerating challenge for preformu-lation. To meet this challenge, preformulation, through a better understanding ofthe solid state, must seek to design improved characteristics into APIs at the earliest stages of discovery. This will be the edge that any company will need to facilitate the rapid movement of new therapeutics entries to market-place. The patient is waiting!

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(57) Abstract: The present invention relates to novel amides and a process for preparing these amides.

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N-phenyl-2-pyrlmidine-amine derivatives

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The present invention provides novel amides, a process for preparing these amides and the use of these amides.

In particular, the present invention provides novel amides of formula I

R7}X(U

wherein
one of the radicals R1, A2, R3, R4 and R5 is
a) a radical selected from the group consisting of lower alkyl, amino; mono- or di-lower alkylamino; lower alkanoylarnino; lower alkoxy-carbonyl; and lower alkyl which is substituted by amino, mono- or di-lower alkylamino or lower alkanoylamino, or
b) an unsubstituted or substituted radical selected from the group consisting of benzylamino; benzoylamlno; pyrrolidlnyl; piperidyl; piperazinyl; piperazinyl-carbonyl; morpholinyl, thiomorpholinyl; and lower alkyl substituted by benzylamino, benzoylamino, halogene, pyrrolidinyl, piperidyl, piperazinyl, e.g. 4-methyl-piperazinyl-, thiomorpholinyl, or rnorpholinyl, the substituents of said substituted radical being selected from the group consisting of cyano; lower alkyl; hydroxy- or amino-substituted lower alkyl; trifluoromethyl; free, etherifled or esteritied hydroxy; lower alkoxy; lower alkanoyloxy; free, alkylated or acylated amino; mono- or di-lower alkylamino; lower alkanoylamlno; benzoylamino; free or esterifled carboxy lower alkoxycarbonyl and halogen, and
and the other four radicals are independently hydrogen, cyano; lower alkyl; hydroxy- or amino-substituted lower alkyl; trifluoromethyl; free, etherifled or esterified hydroxy, lower alkoxy; lower alkanoyloxy; free, alkylated or acylated amino; mono- or di-lower alkylamino; lower alkanoylamlno; benzoylamino; free or esterified carboxy; lower alkoxycarbonyl and halogen;

or

R1 and R2, A2 and A3, R3 and R4, or R4 and R5 together are a substituted or unsubstituted alkylene radical having 4 carbon atoms, the substituents preferably being selected from

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cyano, unsubstituted or hydroxy-, amino- or 4-methyl-piperazinyl-substituted lower alkyl, such as especially methyl, trifluoromethyl, free, etherifled or esterified hydroxy, free, alkylated or acylated amino and free or esterified carboxy;
and the other three radicals are independently hydrogen, cyano; lower alkyl; hydroxy- or amino-substituted lower alkyl; trifluoromethyl; free, etherified or esterified hydroxy; lower alkoxy; lower alkanoyloxy free, alkylated or acylated amino; mono- or di-lower aikyiamlno; lower alkanoylamino; benzoylamino; free or esterified carboxy; lower alkoxycarboriyl and halogen;
and one of the radicals R8, R7 and R8 is halogen, NH2, NO2, NHC(0)CF3, NHC(0)CH3, NHC(NH)NH2, and the other two radicals are Independently hydrogen, lower alkyl, lower fluorinated alkyl, benzyl or phenyl;

or a salt or crystal form thereof.

Compounds of formula I may be in the form of a salt preferably a pharmaceutically acceptable salt.

Such salts are formed, for example, as acid addition sails, preferably with organic or inorganic acids, from compounds of formula I or IV with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, proplonic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succlnlc acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxyrnaleic acid, methyimaleic acid, cyclohexanecarboxylic acid, adamantanecarboxyiic acid, benzoic acid, oxalic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, pheriylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonlc acid, ethane-1,2-disulfonic acid, benzenesulfonlc acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methyibenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsuifuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

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b) at least one pharmaceutically active compound of formula IV, and
c) between 000001% and 5% by weight of at least one compound of formula I, preferably between 0.00001% and 0.1%, most preferably between 0.0001% and 0.1%.

The present invention particUlarly relates to pharmaceutical compositions especially tablets comprising 4-(4-methylpiperazin-1 -ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yI)pyrimidin-2-ylamino)phenylj-benzamide or a pharmaceutically acceptable salt or crystal form thereof.

Preferably c) is a compound of formula I wherein, fl3 is (4-methyl-piperazlnyl)-methyl, R1, R2, A4, A5 and F:6 are hydrogen, R5 is Br, Cl, NH2, NO2, NHC(0)CF3, NHC(0)CH3 or NHC(NH)NH2, and R7 is methyl, or a salt thereof.

One or more pharmaceutically acceptable excipients may be present in the composition, e.g. those conventionally used, e.g. (1.1) at least one binder, e.g. microcrystalline cellulose, hydroxypropylmethyl cellulose, (1.2) at least one disiritegrant, e.g. cross-linked polyvinylpyrrolidlnone, e.g. Crospovldonefi, (1.3) at least one glidant, e.g. colloidal silicon dioxide, (1.4) at least one lubricant, e.g. magnesium stearate and/or (1.5) basic coating.
In the tablet according to the present invention, microcrystalline cellulose is used as a binder.

Example A: Capsules with Imatinib (444-methvl-1-piperazin-1-ylmethyl)-N44-methvl-3414-(3-pvridinyfl-2-pvrimldinvllaminolphenyllbenzamide) methanesulfonate of formula IV. 1 - crystal form.
Capsules containing 119.5 mg of the compound named in the title (= SALT I) corresponding to 100 mg of lmatlnlb (free base) as active substance are prepared In the following composition. The composition containing also compounds of formula I wherein, A3 is (4-methyl-piperazinyl)-methyl, A1, R2, R4, R5 and A8 are hydrogen, R8 is Br, Cl, NH2, NO2, NHC(0)CF3, NHC(0)CH3, NHC(NH)NH2, and R7 is methyl.
Composition
SALT 119.5 mg
Compounds of formula I 0.0005mg
Cellulose MK GR 92 mg
Crospovidone XL 15 mg
Aerosll 200 2 mg

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(54) TItle: CRYSTAL MODIFICATION OF A N-PHENYL-2-PYRIMIDINEAMINE DERIVATIVE, PROCESSES FOR ITS MANU-
FACTURE AND ITS USE

(I)

(57) Abstract

The Invention relates to a new crystalline form of the methanesulfonic acid addition salt of 4-(4-niethylpiper-azin-1-yhnethyl)-N_(4_jnethyl_3-(4_pyridin_3_yl)pyrimidin-2-ylamino)phenyll-benzamide of formula (I), which may be used for example for tumour therapy.

WO 99/03854 PCT/EP98/04427

Crystal modification of a N-pheriyl-2-pyrimidineamine derivative, processes for its

manufacture and its use

The invention relates to a particular form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1 -ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]- benzamide, comprising certain crystals, processes for the preparation thereof, pharma-ceutical compositions containing this crystal form, and their use in diagnostic methods or preferably for the therapeutic treatment of warm-blooded animals, especially humans, or
their use for the preparation of pharmaceutical preparations for use in diagnostic methods
or preferably for the therapeutic treatment of warm-blooded animals, especially humans.

Background to the invention:
The preparation of 4-(4-methylpiperazin-1 -ylmethyl).N-4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide and the use thereof, especially as an anti-tumour agent, are
. described in Example 21 of EP-A-0 564 409, which was published on 6 October 1993, and in equivalent applications in numerous other countries. This compound is exemplified in
these publications only in free form (not as a salt).

It has now been surprisingly found that a crystal form may under certain conditions be found
In the methanesulfonate salt of this compound, which is described hereinafter as 13-crystal
form, and which has very advantageous properties.

Detailed description of the invention
The invention is described in more detail in the following with the help of drawings and other aids:

Description of the drawings
Fig. 1/3 shows the X-ray diffraction diagram of the a-crystal form of the methanesulfonic acid addition salt of a compound of formula I.
Fig. 2/3 shows the X-ray diffraction diagram of the 13-crystal form of the methanesulfonic acid addition salt of a compound of formula I.
Fig. 3/3 shows the crystals above of the ct-crystal form and below of the 13-crystal form of 4-(4-methylpiperazin-1 -ylmethyl)-N_[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)PheflYll-

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possible to obtain 4-(4-methylpiperazin-1 -ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidifl-2-ylamino)phenyljbenzamide methanesulfonate in a crystal form which is not needle-shaped. This form is described in the present text as a-crystal form.

The crystal form of 4-(4-methylplperazin-1 -ylmethyl)-N-j4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide methanesulfonate has the advantage that its flow properties are substantially more favourable than those of the cc-crystal form. This crystal form has the further advantage of being thermodynamically more stable at temperatures below 140°C. Finally, the n-crystal form is less hygroscopic than the cc-crystal farm and thus also stores better and is easier to process.

The invention relates to an acid addition salt of a compound of formula I comprising non-needle-shaped crystals, especially the 3-crystal form of the methanesulfonic acid addition

. salt of the compound of formula I.
The invention relates especially to a particular, essentially pure crystal form, preferably that which is referred to hereinafter as the p-crystal form, of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1 -ylmethyl)-N-[4-methyl-3-(4-pyrid-3-yl)pyrimidin-2-ylamino)pheriyl]benzamide methanesulfonate of formula I,

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Where the term methanesulfonic acid salt of a compound of formula I or of 4-(4-methyl-piperazin-1 -ylmethyl)-N-(4-methyl-3.(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide is used hereinbefore and hereinafter, this is especially taken to mean the methanesultonic acid salt of formula Il.

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(1 (54) Title: N-PHENYL-2-PYRIMIDINE-AMLNE DERIVATIVES
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(57) Abstract: The invention relates to N-phenyl-2-pyrirnidine-amine derivatives ot’formula (1) wherein the substituents are detined
_ as indicated in the description, to processes for the preparation thereof, to medicaments comprising those compounds, and the use thereof in the preparation of pharmaceutical compositions for the therapeutic treatment ofwarm-blooded animals, including humans.

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N-phenyl-2-pyrlmidine-amine derivatives

The invention relates to N-phenyl-2-pyrimidine-amine derivatives, to processes for the preparation thereof, to medicaments comprising those compounds, and to the use thereof in the preparation of pharmaceutical compositions for the therapeutic treatment of warm-blooded animals, including humans.

The invention relates to N-phenyl-2-pyrimidine-amine derivatives of formula I

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A1 R8 --R5
(I),

2

R4

wherein
A1 is pyrazinyl; 1-methyl-i H-pyrrolyl; amino- or amino-lower alkyl-substituted phenyl, wherein the amino group in each case is free, alkylated or acylated; 1 H-indolyl or 1 H-imidazolyl bonded at a five-membered ring carbon atom; or unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen,
R2 and Ft3 are each Independently of the other hydrogen or lower alkyl,
one of the radicals A4, A5, R5, A7 and A8 is a radical of formula II

- N(R)-C(=X)-(Y)-R10 (II)

wherein
Ft9 Is hydrogen or lower alkyl,
X is oxo, thio, imino, N-lower alkyl-imino, hydroximino or 0-lower alkyl-hydroximino,
Y is oxygen or the group NH,
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such as a hydrohalic acid, for example lower alkanoylocy or especially halogen, such as iodine, bromine or especially fluorine or chlorine.

Aikylated amino is, for example, lower alkylamino, such as methylamino, or di-lower alkyl-amino, such as dimethylamino. Acylated amino is, for example, lower alkanoylamino or benzoylamino.

Esterified carboxy is, for example, lower alkoxycarbonyl, such as methoxycarbonyl.

Salt-forming groups in a compound of formula I are groups, or radicals having basic or acidic properties. Compounds having at least one basic group or at least one basic radical, for example a free amino group, a pyrazinyl radical or a pyridyl radical, may form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or a phosphoric acld, or with suitable organic carboxylic or sulfonic acids, for example aliphatic mono- or di-carboxylic acids, such as trifluoroacetic acid, acetic acid, proptonic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, rnalic acid, tartaric acid, citric acid or oxalic acid, or amino acids such as arginine or lysine, aromatic carboxylic acids, such as benzoic acid, 2-phenoxy-benzoic acid, 2-acetoxy-benzoic acid, salicylic acid, 4-aminosaticylic acid, aromaticaliphatic carboxylic acids, such as mandelic acid or cinnamic acid, heteroaromatic carboxylic acids, such as nicotinic acid or isonicotinic acid, aliphatic sulfonic acids, such as methane-, ethane- or 2-hydroxyethane-sulfonic acid, or aromatic sulfonic acids, for example benzene-, p-toluene- or naphthalene-2-sulfonic acid. When several basic groups are present mono- or poly-acid addition salts may be formed.

Compounds of formula I havng acidic groups, for example a free carboxy group In the radical A10, may form metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethyl-amine or td-(2-hydroxyethyl)-amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N’-dimethylpiperazine.

Compounds of formula I having both acidic and basic groups can form internal salts.

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ESCRITURA NIJMERO CUATRO NIL QUIN’S -
TREINTA Y NUEV (N0e4.539)’-------------
En la ciudad de Call, Capital del De.pa
tanento del Valle del Cauca, Repbllca de
Colombia, a 10/ VEINTITRES (23)das
delmçs de OCTUBRE del aio DOS NIL 1JNO --

(2,001), ante ’ml, JORE ENRIQUE CAICEDO ZANORANO, Notario
T E R C E P. 0 (3o,) del Crculo de Call, 

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Call,

jti.ficado con la cØdula de ciudadanIa nümero 14.949.561 de Call, dijo: Vt
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las leycs colornbianas, con domictlio sede principal’-.’en, Cali constituda
eescritura publica numero 2670 do Ia Notaria Segunda de Cali de fecha 12 do
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fltinio do 1957 reformada en distintas oportumdades segthi consta en el certificado expedido por la Camara de Comercio de Cali--- SEGUNDO: Qur n tal caracter,por este pdblico instrurnento, concede Poder Especial pero amplio y sur iente a JOSE LUIS REYES VILLAM1ZAR, mayor de edad, vecmo de Bogota, identifido con C C #79 152 473 c isaqudn, abogado en ejcrcicio portador de laT P 44655 del C S de Ia J, domicihado en Bogota, D.C., Republica de Colombia con direccion carrra 7 No 89.23 oficina205 do Ia misma ciudad, como su representante con poder especial, amplio y suficierite, parabbtener la protección de nuestra propiedad industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos represente ante cualØsquiera entidad o persona, ejerzan o no jurisdicción, especialmente
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que en todos Los asuntos arnba determinados,, tanto en los tØrminos seilalados por los articulos 42 com1ementanos de la Decisión 486 de Ia Comunidad Andina omo del artIculo70 del C P C pueda sustituir este mandato, transigir, conciliar, admitir los hecligs
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Se agregan comprobantea. Perechos $30.000.00 Decreto 1681 de S,eptiembre 16 de 1996. Reformado medlante ResoiuciSn No.5839
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En rep. de TECNOQUfl4ICAS S.A. ’r1"

El Notanlo Tercero de Call

Dr. JORGE ENRIQUE CAICEDO IA

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