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Referencia : Expediente No. 11.143.307
Asunto : Solicitud de patente para: FORMULACIONES LÍQUIDAS
DE SALES DE 1-[2-(-(2,4-DIMETILFENILSULFANIL)FENIL]-PIPERAZINA
Solicitante : H. LUNDBECK A/S
Fecha de solicitud : 24 de Octubre de 2011

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. 4699 notificado por fijación en lista el 12 de Marzo de 2013.

2. Mediante oficio No. 4699 se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio se refieren a excepciones de patentabilidad, a la claridad del pliego reivindicatorio, y al nivel inventivo de las reivindicaciones 1 a 17 en vista de los documentos D1: WO2007/144005, D2: WO2008/113358 y D3: WO2007/144006.

3. Respuesta a las objeciones

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"

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3.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 2 reivindicaciones.

3.2 Excepción a la Patentabilidad

El Examinador menciona que las reivindicaciones 6 y 7 están relacionadas con un método de tratamiento, el cual no es patentable de acuerdo con el Art 20 literal d.

Con el fin de superar esta objeción, las reivindicaciones 6 y 7 han sido eliminadas del presente capítulo reivindicatorio.

3.3 Claridad y concisión en las reivindicaciones

El examinador menciona que "de acuerdo con lo revelado en el capítulo reivindicatorio, la formulación reclamada no está definida por sus componentes que la hagan distinta de lo ya conocido, es decir, si bien menciona el principio activo no especifica el vehículo o excipientes que van en la composición.

Las reivindicaciones 14 a 16 no definen claramente las formas cristalinas a las que se refieren. Favor aclarar.

La reivindicación 17 que se refiere a un recipiente, está definido por su contenido y no por sus características técnicas. Favor aclarar".

Con el fin de superar estas objeciones, en primer lugar, nos permitimos aclarar que el capítulo reivindicatorio se han limitado a las composiciones líquidas que comprenden la sal de 1-[2-(2, 4-dimetilfenilsulfanil)fenil]piperazina seleccionada de la sal de adición del

ácido DL-láctico y la hidroxipropil-beta-ciclodextrina en una concentración superior a 2,5 mg/mL y a un recipiente de dicha composición.

Se aclara que con el fin de superar las anteriores objeciones, las reivindicaciones 14 a 16 y 17 han sido eliminadas del capítulo reivindicatorio.

Debido a las correcciones anteriores, la formulación farmacéutica líquida en las actuales reivindicaciones, se encuentran claramente definidas, estando las deficiencias del artículo 30 Decisión 486 de la Comunidad Andina, superadas.

3.4 Análisis de nivel inventivo

El Examinador refiere que los documentos D1, D2 y D3 se consideran el estado del arte cercano a la invención definida en las reivindicaciones 1 a 16 y que no son patentables por falta de altura inventiva.

Con respecto a esta objeción nos permitimos aclarar:

Según el examinador, D1 revela sales de 1-[2-(2, 4-dimetilfenilsulfanil)fenil] - piperazina y D2 y D3 revelan las sales lactato de 4-[2-(4-metilfenilsulfanil)fenil]piperidina altamente solubles. Además, según el examinador, el experto en la materia habría combinado las enseñanzas de D1 y D2-D3, basado en lo que la persona experta esperaría como es que las sales de lactato de 1-[2-(2, 4-dimetilfenilsulfanil)fenil]piperazina fueran también altamente solubles. Aunque la divulgación de D1 y D2-D3 tienen puntos en común, disentimos respetuosamente del examinador en cuanto a las expectativas de la solubilidad de las sales de lactato de 1-[2-(2, 4-dimetilfenilsulfanil)fenil]piperazina y que la persona experta en la materia se hubiere basado en estos documentos para caracterizar la solubilidad de las sales de las formulaciones líquidas de la presente invención

El examinador además señala que existe similitud química entre los compuestos 4-[2-(4-metilfenilsulfanil)fenil]piperidina y 1-[2-(2, 4-dimetilfenilsulfanil)fenil]piperazina.

Disentimos respetuosamente del Examinador. La persona experta la materia esperaría que las propiedades de solubilidad se rijan principalmente por el elemento básico de las dos moléculas, es decir, las entidades de la piperidina y la piperazina. Estos grupos no son químicamente similares. La molécula de piperidina contiene un átomo de nitrógeno, mientras que la molécula de piperazina contiene dos átomos de nitrógeno. Por otra parte, las características de ácido/base como es medido por las constantes de disociación son diferentes tanto para la piperidina y piperazina. El examinador claramente no ha sustentado cómo el experto en la materia esperaría que dos compuestos que contienen una molécula de piperazina y otra de piperidina, respectivamente, puedan comportarse de manera similar en sus patrones de solubilidad.

Por otra parte, si por el bien de la discusión se acepta que los dos compuestos son químicamente similares, el examinador no ha sustentado que similitud química puede traducirse en similitud de solubilidad. Hemos incluido una copia de *Adv Drug Deliv. Rev.* 59, 603-616, 2007 que examina los factores que influyen en la solubilidad de un ingrediente activo. Es útil estudiar la sección 2.6 que analiza las relaciones de solubilidad de la estructura. Discute además la previsibilidad de la solubilidad de diversas sales del mismo compuesto. El último párrafo dice "varias otras investigaciones también intentaron establecer relaciones entre formas de sal y su solubilidad acuosa. Sin embargo, no podría obtenerse ninguna relación predictiva general. ". Es decir, "con compuesto" solubilidad de diversas sales es impredecible. La predicción de la solubilidad "entre compuestos" de diferentes sales incluso es más imprevisible. Basándonos en esto, muy respetuosamente afirmamos que no es posible predecir la solubilidad de la sal de un compuesto basado en la solubilidad de la misma sal de un compuesto diferente.

Por último, si uno mira los datos de solubilidad de sales 1-[2-(2, 4-dimetilfenilsulfanil) fenil]piperazina y 4-[2-(4-metilfenilsulfanil)fenil]piperidina de acuerdo a lo establecido en D1 y D2, no se encuentra soporte para la posición del examinador. Al contrario, estos datos demuestran que la solubilidad de las sales de 1-[2-(2, 4-dimetilfenilsulfanil) fenil] piperazina no se puede predecir en base a datos de la solubilidad de las sales de 4-[2-(4-metilfenilsulfanil)fenil]piperidina.

La siguiente tabla resume los datos de solubilidad en D1, D2 y la aplicación de la presente. Además, los datos marcados con un * se presenta como parte de nuestra respuesta.

Ácido (Base: ácido)	4-[2-(4-metilfenil-sulfanil) fenil]-piperidina Solubilidad (mg/mL)	1-[2-(2, 4-dimetil-fenilsulfanil)fenil]-piperazina Solubilidad (mg/mL)
Ácido palmítico, ácido hexadecanoico 1:1	0.4	
Ácido DL-láctico, ácido DL-2-hidroxi propiónico 1:1	> 150	8 o 26 dependiendo de la forma cristalina
Ácido adípico, ácido 1,6 hexanodioico 1:1	2.5	1.5 *
Ácido adípico, ácido 1,6 hexanodioico 2:1	1.0	
Ácido fumárico 1:1	0.2	0.4
Ácido glutárico ácido, 1,5-pentanedioico 1:1	13	
Ácido malónico 1:1 (α)	5.2	1
Ácido oxálico 1:1	1.1	
Ácido sebacoínico, ácido 1, 8-octanedioico 2:1	0.7	
Ácido succínico, ácido 1, 4-butanodioico, 2:1	2.0	1-2 *
Ácido L-málico, ácido L-2-hidroxi butanodioico 1:1, β	2.8	

Ácido (Base: ácido)	4-[2-(4-metilfenil-sulfanil) fenil]-piperidina Solubilidad (mg/mL)	1-[2-(2, 4-dimetil-fenilsulfanil)fenil]-piperazina Solubilidad (mg/mL)
Ácido D-tartárico, ácido D-2, 3-dihidroxi butanodioico 1:1	1.8	0.4
Ácido L-aspártico 1:1	39	2.9*
Ácido glutámico 1:1	> 35	0.1*
Ácido cítrico 2:1	0.5	
Ácido fosfórico 1:1	6.0	1
HCl	4.5	3
HBr	2.4	1.2
Mesilato		45
Meso tartrato		0.7
L-tartrato		0.4
D-tartrato		0.4
Sulfato		0.7

El experto en la materia por lo tanto habría notado que mientras las solubilidades para el ácido fumárico y las sales de ácido D-tartárico de 1-[2-(2, 4-dimetilfenillsulfanil) fenil] piperazina son idénticos (0,4 mg/mL) hay casi una diferencia de 10 veces en las solubilidades de las mismas sales del 4-[2-(4-metilfenilsulfanil)fenil] piperidina (0.2 <-> 1,8 mg/mL). Esto demuestra que la solubilidad de las sales de 1-[2-(2, 4-dimetilfenilsulfanil)fenil]piperazina no se puede predecir en base a los datos de la solubilidad de sales de 4-[2-(4-metilfenilsulfanil)fenil]piperidina.

Al realizar además la comparación de los datos de solubilidad para las sales del ácido L-aspártico y el ácido glutámico también la solubilidad de las dos sales de 4-[2-(4-

metilfenilsulfanil)fenil]piperidina quizás son idénticas o las sales de ácido glutámico pueden ser (aún más) más solubles que la sal de ácido L-aspartico (39 <-> 35 mg/mL). Muy por el contrario, la sal de ácido L-aspartico de 1-[2-(2, 4-dimetilfenilsulfanil)fenil]piperazina es 30 veces más soluble que la sal del ácido glutámico (2.9 <-> 0,1 mg/mL). Una vez más, esto sirve para demostrar que no es posible predecir la solubilidad de las sales de 1-[2-(2, 4-dimetilfenilsulfanil) fenil] –piperazina en base a los datos de la solubilidad de las sales de 4-[2-(4-metilfenilsulfanil)fenil] piperidina.

Los datos en la tabla anterior muestran además que la sal ácida de lactato es única en el sentido de que es la única que conoce sal con propiedades de solubilidad que hacen posible su uso en la fabricación de formulaciones líquidas altamente concentradas, como por ejemplo las gotas orales. Ninguna de las otras sales enumeradas en la tabla anterior tiene solubilidades que hacen posible dicha aplicación. Como se explica en la página 3, línea 25 – 29, se debe abstenerse de utilizar la sal mesilato por razones de toxicidad.

Estamos de acuerdo con cómo el examinador plantea el problema a resolver por la presente invención, es decir, la provisión de sales altamente solubles del 1-[2-(2, 4-dimetilfenilsulfanil)fenil]piperazina útiles por ejemplo para pacientes geriátricos. Según lo establecido anteriormente, la solución al problema, es decir, la sal de lactato no se podría predecir de estado de la técnica, y las reivindicaciones son así inventivas.

Conforme a lo anterior, se ha demostrado que el compuesto (1) tiene un efecto o actividad técnica no descrita en el estado de la técnica, es además inesperada, sin derivarse de manera obvia del documento D1 ni D2, siendo así mismo sus formulaciones líquidas teniendo por lo tanto nivel inventivo.

En cuanto al documento D2, éste no es considerado como cercano a las reivindicaciones 9 a 14, ya que no revela las características de las composiciones del compuesto (1) de la presente solicitud.

En consecuencia, un técnico con conocimientos medios en la materia no estaba en condiciones de plantearse el problema, tampoco de resolverlo en la forma en que se reivindica y tampoco de prever el resultado, por lo que la presente solicitud posee la altura inventiva para que se le conceda el privilegio solicitado.

4. Modificación de la solicitud en trámite

Con el objeto de subsanar las objeciones presentadas por su Despacho y de acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar nuevo capítulo reivindicatorio modificado.

Sin embargo, la solicitante desearía señalar que cualquier materia divulgada borrada o no contenida en la presente serie de reclamaciones no debe ser considerada como abandonada. Así mismo, la solicitante se reserva su derecho a incluir tal materia en futuras series de reivindicaciones.

5. Concesión de solicitudes equivalentes

Si bien entendemos y aceptamos que cada país es autónomo en la concesión o negación de los privilegios de patente, queremos resaltar el hecho que el análisis de los requisitos para el otorgamiento de esos derechos es prácticamente universal. Por lo mismo, también queremos llamar la atención de este Despacho en relación a que esta misma solicitud de patente ha sido concedida en Australia. Nos permitimos entonces presentar el documento AU201O238946B2 correspondiente al privilegio concedido en Australia.

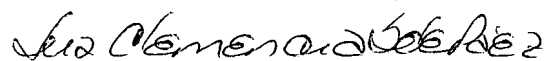
6. De acuerdo con los argumentos y modificaciones presentados con este escrito, la presente solicitud cumple a cabalidad con los requerimientos exigidos en la Decisión 486 y las objeciones formuladas por el Examinador se ven superadas.

Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 4699 toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

7. **ANEXOS**

- Nuevo pliego reivindicatorio conformado por 2 reivindicaciones
- Formulario de modificaciones en solicitud pendiente
- Portada y Reivindicaciones de la Patente Australiana AU2010238946B2
- Adv Drug Deliv. Rev. 59, 603-616, 2007

Señor Director,


LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-03003-0841-114-3
SML\SML\ID-244334\WPCL3003
No. M-2013-244334\SML

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DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. Identificación del Trámite	
☐ Error material	☒ Modificación a una Solicitud en trámite
☒ Patente de Invención	
☐ Patente de Modelo de Utilidad	
☐ Registro de Diseño Industrial	
☐ Esquema de Trazado de Circuitos Integrados	

2. Datos del solicitante		
Persona Natural	☐	Persona Jurídica ☒
H. LUNDBECK A/S		
Nombre o denominación / Nombre o razón social completa		
Nombre representante legal		
Tipo de empresa	Micro ☐	Pequeña ☐ Mediana ☐ Otra ☐
Documento de identificación:	☐ C.C.	☐ C.E. ☐ NIT ☐ Otro Número _____
Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
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3. Datos del apoderado:		
Apellidos y Nombre	Documento de identificación	Tarjeta profesional
De Páez Luz Clemencia	C.C. 35.456.344	T.P.A. 23.555
Dirección y domicilio		Ciudad
Carrera 4ª No. 72 –35		Bogotá
Dirección electrónica	No. Fax	Número telefónico
cavelier@cavelier.com	2 11 86 50	3 47 36 11
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4. Datos del trámite

Corrección:

Expediente No 11.143.307

Aparece

Debe ser

Modificación:



Modificación al capítulo reivindicatorio.

Presento nuevo capítulo reivindicatorio compuesto por 2 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y además se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.



Modificación al capítulo descriptivo.



Modificación al resumen.



Modificación a los dibujos.

5. Anexos



Poder, si fuere el caso.



Documento que contiene las modificaciones o correcciones.



Copia de la solicitud y sus anexos en formato magnético.

debo

6. Firma	
Nombre y apellidos LUZ CLEMENCIA DE PAEZ	Firma 
C.C. 35.456.344 DE Usaquén	Tarjeta Profesional 23.555

REIVINDICACIONES

1. Una formulación farmacéutica líquida que comprende una sal de 1-[2-(2, 4-dimetilfenilsulfanil) fenil] piperazina seleccionada entre sal de adición del ácido DL-láctico e hidroxil propil betaciclodextrina, en donde la concentración de dicha sal está por encima de 2,5 mg/mL.
2. Un kit que comprende: un recipiente, un gotero adosado al recipiente, en donde el recipiente comprende una formulación líquida de acuerdo con la reivindicación 1.

SML\SML\ID-244336\WPCL3003



Salt formation to improve drug solubility[☆]

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Abstract

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. In this article, physicochemical principles of salt solubility are presented, with special reference to the influence of pH–solubility profiles of acidic and basic drugs on salt formation and dissolution. Non-ideality of salt solubility due to self-association in solution is also discussed. Whether certain acidic or basic drugs would form salts and, if salts are formed, how easily they would dissociate back into their free acid or base forms depend on interrelationships of several factors, such as S_0 (intrinsic solubility), pH, pK_a , K_{sp} (solubility product) and pH_{max} (pH of maximum solubility). The interrelationships of these factors are elaborated and their influence on salt screening and the selection of optimal salt forms for development are discussed. Factors influencing salt dissolution under various pH conditions, and especially in reactive media and in presence of excess common ions, are discussed, with practical reference to the development of solid dosage forms.

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Keywords: Salt; solubility; pH–solubility profile; Common-ion effect; Self-association; Dissolution rate; Salt selection; Counterion; Microenvironmental pH

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[☆] This review is part of the *Advanced Drug Delivery Reviews* theme issue on “Drug solubility: How to measure it, how to improve it”.

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1. Introduction

Salts of acidic and basic drugs have, in general, higher solubilities than their corresponding acid or base forms. Salt formation to increase aqueous solubility is the most preferred approach for the development of liquid formulations for parenteral administration [1]. For solid dosage forms, Nelson [2,3] demonstrated as early as in 1950s that dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal (GI) pH conditions were much higher than those of their respective free acid forms. He attributed the higher dissolution rate of a salt to its higher solubility (relative to the free acid form) in the aqueous diffusion layer surrounding the solid. Pronounced differences were observed in rates and extents of absorption of novobiocin [4] and tolbutamide [5] as compared to their respective sodium salts. Monkhouse and coworkers [6,7] reviewed physicochemical and biopharmaceutical advantages of salts over their free acid or base forms. The interest in salt formation has grown greatly over the past half a century and, in recent years, it has become the most commonly applied technique of increasing solubility and dissolution rate in drug product development.

The primary reason for the increased interest in salt formation is that with the progress in medicinal chemistry and, especially due to the recent introduction of combinatorial chemistry and high-throughput screening in identifying new chemical entities (NCE) [8,9], the solubility of new drug molecules has decreased sharply [10]. While a value of less than 20 µg/mL for the solubility of a NCE was practically unheard of until the 1980s, the situation has changed so much that in the present day drug candidates with intrinsic solubilities (solubility of neutral or unionized form) of less than 1 µg/mL are very common [11]. Lipinski [12] reported that 31.2% of a group of 2246 compounds synthesized in academic laboratories between 1987 and 1994 had solubility equal to or less than 20 µg/mL. According to the recent experience of the present author, approximately one-third of new compounds synthesized in medicinal chemistry laboratories have an aqueous solubility less than 10 µg/mL, another one-third have a solubility from 10 to 100 µg/mL, and the solubility of the remaining third is >100 µg/mL. With such a predominance of poorly water-soluble compounds, careful attention must be paid to identification and selection of optimal salt forms for development. In certain cases, salt formation may not be feasible due to physical and chemical properties of NCEs. In other cases, even though salts can be synthesized, they may not serve the purpose of enhancing dissolution rate and bioavailability. It is important that the reasons behind such situations are understood.

Despite major advantages of the use of salts, only limited attention has been paid historically to the selection of optimal salt forms for pharmaceutical product development [6,13]. At

the beginning of drug development programs, salts were often selected based on ease of synthesis, ease of crystallization, cost of raw material, *etc.*, and no systematic studies to evaluate their physicochemical properties, such as physical and chemical stability, processability into dosage forms, solubility and dissolution rate at different pH conditions, *etc.*, were conducted. If a salt was later found to be suboptimal for the desired formulation or if problems developed, it was often difficult to change the salt form without delaying the drug development program, since it required repeating most of the biological, toxicological, formulation and stability tests that had already been performed [14]. For most practical purposes, identification and selection of salt forms of NCEs still remain a trial and error process.

One major objective of the present article is to review the basic principles of salt formation and how salts influence solubility and dissolution rate in a comprehensive manner, such that they can be easily applied to the development of drug substances as well as dosage forms. Efforts will be made to indicate the application of such principles in screening various salt candidates for a NCE, identification of optimal salt form, and ultimately formulation of dosage forms using the selected salt. Wherever possible, advantages and disadvantages of salt forms relative to their respective free acid or base forms will be presented.

One particular issue with the use of salts in drug development is that, while salts are usually prepared from organic solvents, they are destined to encounter aqueous environment (water, humidity) during dosage form development and, in case of an orally administered tablet or capsule, at the time of dissolution in GI fluid. Therefore, a perfectly good salt isolated from an organic solvent may not behave well in an aqueous environment due to low solubility, conversion to free acid or base forms, poor stability, *etc.*, thus limiting its use in dosage forms.

2. Principles of salt formation and salt solubility

The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts or not and, if salts are formed, what some of their physicochemical properties might be [15]. pH–solubility interrelationships also dictate what counterions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ions [15,16].

2.1. pH–solubility interrelationship of free base and its salt

Kramer and Flynn [17] demonstrated that the pH–solubility profile of a basic drug may be expressed by two independent

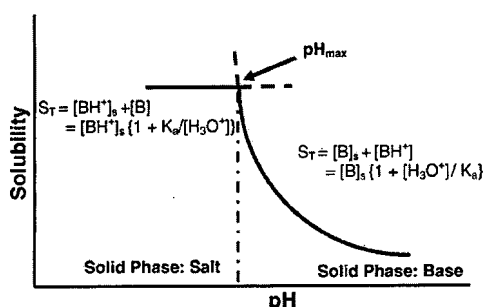


Fig. 1. Schematic representation of the pH-solubility profile of a basic drug indicating that the solubilities may be expressed by two independent curves and that the point where two curves meet is the pH_{max} (reproduced from Ref. [15] with permission).

curves, one where the free base is the saturation or equilibrium species and the other where the salt is the equilibrium species. Essentially, the following equilibrium exists when a basic compound or its salt is dissolved in water:



or

$$K_a = \frac{[B][H_3O^+]}{[BH^+]} \quad (2)$$

where BH^+ and B represent, respectively, protonated (salt) and free base forms of the compound. When the aqueous medium at a given pH is saturated with the free base, the total solubility (S_T) at that pH may be expressed as follows:

$$S_{T, \text{base}}(pH > pH_{max}) = [B]_s + [BH^+] = [B]_s \left(1 + \frac{[H_3O^+]}{K_a} \right) = [B]_s (1 + 10^{pK_a - pH}) \quad (3)$$

where the subscript “s” represents the saturation species. On the other hand, when the salt is the saturation species, the equilibrium solubility at a particular pH may be expressed by:

$$S_{T, \text{salt}}(pH < pH_{max}) = [BH^+]_s + [B] = [BH^+]_s \left(1 + \frac{K_a}{[H_3O^+]} \right) = [BH^+]_s (1 + 10^{pH - pK_a}) \quad (4)$$

The two independent curves mentioned above may be obtained by varying hydrogen ion concentrations (or pH) in Eqs. (3) and (4), and the point where the curves intersect is called pH_{max} , the pH of maximum solubility. This is shown schematically in Fig. 1, where the solubility profile at a pH higher than the pH_{max} is represented by Eq. (3), while Eq. (4) represents the solubility profile below pH_{max} . If the solid phase that is in equilibrium with a solution is analyzed, it would be the free base at $pH > pH_{max}$ and the salt at $pH < pH_{max}$. Only at pH_{max} , which theoretically represents

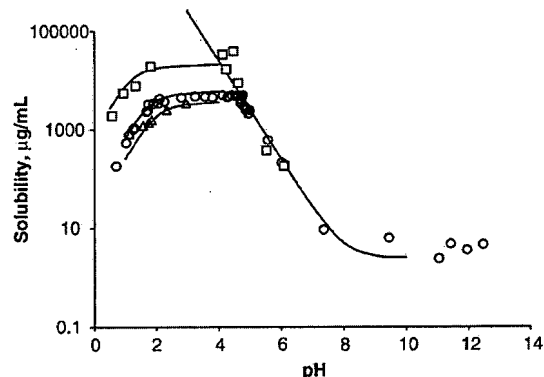


Fig. 2. pH-solubility profiles of haloperidol determined by using methanesulfonic (mesylic) ($\square$), hydrochloric ($\circ$) and phosphoric (Δ) acids (reproduced from Ref. [24] with permission).

only one point, can both the free base and salt coexist as solids. If the pH of a saturated solution with excess solid free base is lowered from above the pH_{max} to below the pH_{max} , the solid phase will convert to the salt, and it is important to note here that the pH will not drop below pH_{max} until enough acid is added to convert the entire excess free solid base into salt. The reverse is true for the conversion of a salt to the free base; no free base will precipitate out until the pH is raised above the pH_{max} .

There are numerous reports in the literature confirming interrelationships of solubilities of bases and their salt forms as per the schematics in Fig. 1 [17,18–23]. An example of typical pH-solubility profiles is given in Fig. 2, where solubilities of haloperidol and its methanesulfonate (mesylate), hydrochloride and phosphate salts as a function of pH are shown [24].

2.2. pH-solubility interrelationship of free acid and its salt

Fig. 3 shows a schematic diagram for the pH-solubility interrelationship of a free acid and its salt form. The free acid would be the equilibrium species at a pH below pH_{max} , and it would convert to a salt only if it is equilibrated with a solution at a pH above pH_{max} by adding a sufficient quantity of an alkali or

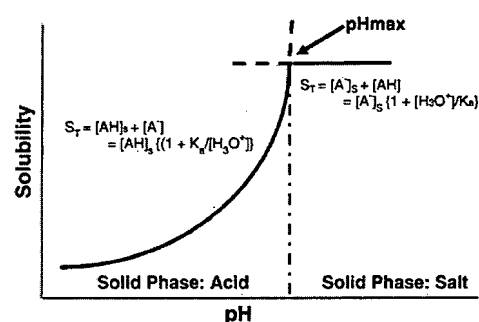


Fig. 3. Schematic representation of the pH-solubility profile of an acidic drug indicating that the solubility may be expressed by two independent curves and that the point where the two curves meet is the pH_{max} (reproduced from Ref. [15] with permission).

organic counterion. The relevant equations below and above $pH_{\max}$ are given below [25]:

$$S_{T, \text{acid}}(pH < pH_{\max}) = [AH]_s + [A^-] = [AH]_s \left(1 + \frac{K_a}{[H_3O^+]} \right) = [AH]_s (1 + 10^{pH - pK_a}) \quad (5)$$

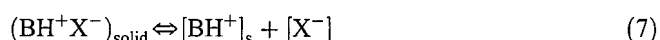
$$S_{T, \text{salt}}(pH > pH_{\max}) = [A^-]_s + [AH] = [A^-]_s \left(1 + \frac{[H_3O^+]}{K_a} \right) = [A^-]_s (1 + 10^{pK_a - pH}) \quad (6)$$

As indicated in Fig. 3, the solid phase in equilibrium with a saturated solution at $pH < pH_{\max}$ is the free acid and the solid phase at $pH > pH_{\max}$ is the salt; only at $pH_{\max}$, both forms coexist. Interconversion from the salt to the free acid form or *vice versa* may occur if the pH shifts from one side of the $pH_{\max}$ to the other. There are numerous reports in the literature indicating that Eqs. (5) and (6) are, in general, followed for solubilities of free acids and their salts, respectively [22,23,26–29]. In all cases, salts had higher solubilities than their corresponding free acids, although solubilities of different salt forms of a particular acid could vary.

2.3. Effect of counterion on salt solubility

Salt-forming agents used to prepare salts, such as acids to form salts of basic drugs and bases to form salts of acidic drugs, exert influences on salt solubility by exerting common-ion effects in solution. This may be seen in Fig. 2, where solubilities of methanesulfonate, hydrochloride and phosphate salts of haloperidol decreased gradually at pH below 2.5. This is due to the common-ion effect since the acids used to lower pH generated excess counterions.

The common-ion effect may be explained by the following equilibrium that exists below $pH_{\max}$ for the salt of a basic drug:



where $(BH^+X^-)_{\text{solid}}$ denotes undissolved solid salt that is in equilibrium with solution, $[BH^+]_s$ is the salt solubility, and $[X^-]$ is the counterion concentration. The apparent solubility product (K'_{sp}) can be derived from Eq. (7) as follows:

$$K'_{sp} = [BH^+]_s [X^-] \quad (8)$$

In the absence of excess counterion, $[BH^+]_s = [X^-]$, and therefore, solubility $= \sqrt{K'_{sp}}$. Under such a condition, the solubility of a salt remains unchanged as seen in the flat region of salt solubility in Fig. 2. On the other hand, if a significant amount of excess counterion is used either to lower pH or as a formulation adjuvant in dosage form (e.g., in adjusting ionic strength, tonicity, etc.), a major decrease in solubility may be observed, according to:

$$[BH^+]_s = K_{sp}/[X^-] \quad (9)$$

Streng et al. [30] studied the combined effect of the addition of NaCl and HCl on aqueous solubility of the HCl salt of a basic drug; the solubility in the relatively flat region of the pH–solubility profile (pH 3 to 6) decreased by a factor of 3 when 0.05 M NaCl was added to the solution, while at pH below 3 the solubility further decreased due to the effect of Cl^- ion associated with HCl added to adjust pH. Similarly, in developing a liquid formulation for the sodium salt of an acidic drug, Serajuddin et al. [31] observed a decrease in solubility from 7.8 mg/mL to 1.1 mg/mL with the addition of 0.1 M NaCl to adjust the ionic strength of solution. The common-ion effect also has a major influence on solubility and dissolution rates of salts in the GI tract, where the solubility of HCl salts are particularly sensitive to the presence of chloride ion [24].

The overall impact of counterions on salt solubility depends on the magnitude of K_{sp} value. According to Eq. (9), for an equal change in $[X^-]$, the common-ion effect will be less pronounced in a salt of higher K_{sp} (i.e. higher solubility) than in a salt with lower K_{sp} (i.e. lower solubility). For example, the aqueous solubility of tiaramide HCl at 37 °C remained practically constant around 200 mg/mL (~0.5 M) during the lowering of pH from 4.0 to 1.6 by the addition of HCl, since, as compared to the drug concentration, changes in the chloride ion concentration during the pH adjustment were negligible. Further, the solubility of tiaramide HCl decreased by just 25% to ~150 mg/mL at pH 1. In contrast, there are numerous reports in the literature indicating drastic common-ion effects on salts having relatively low aqueous solubilities [18,21]; three such examples demonstrating major impacts of maleate and chloride ions on solubilities of a maleate salt [32] and two hydrochloride salts [33,34], respectively, at low pH are shown in Fig. 4. Since, as mentioned earlier, most compounds currently synthesized in drug discovery laboratories have poor aqueous solubilities and, as a consequence, their salt forms are also found to have relatively low aqueous solubilities, an investigation of potential impacts of common ions is critically important in salt selection and during dosage form development.

2.4. Effects of solubility, pK_a and K_{sp} on $pH_{\max}$

The concept of $pH_{\max}$ is an important one in the physical chemistry of salts. It is apparent from Figs. 1 and 3 that $pH_{\max}$ plays a major role in determining whether a salt would be formed or not, and, in case it is formed, whether it would remain 'as is' or would convert to the corresponding free acid or base form. As mentioned previously, it is only at the $pH_{\max}$ that both forms could coexist. Therefore, at the $pH_{\max}$, both Eqs. (3) and (4) can be valid for the solubility of a basic drug and, similarly, both Eqs. (5) and (6) can be valid for the solubility of an acidic drug. Bogardus and Blackwood [18] proposed that, for a basic drug, the saturation solubilities of free base and its salt form may be set equal at $pH_{\max}$, and solving the relevant equations for $pH_{\max}$, they derived the following relationship:

$$pH_{\max} = pK_a + \log \frac{[B]_s}{\sqrt{K_{sp}}} \quad (10)$$

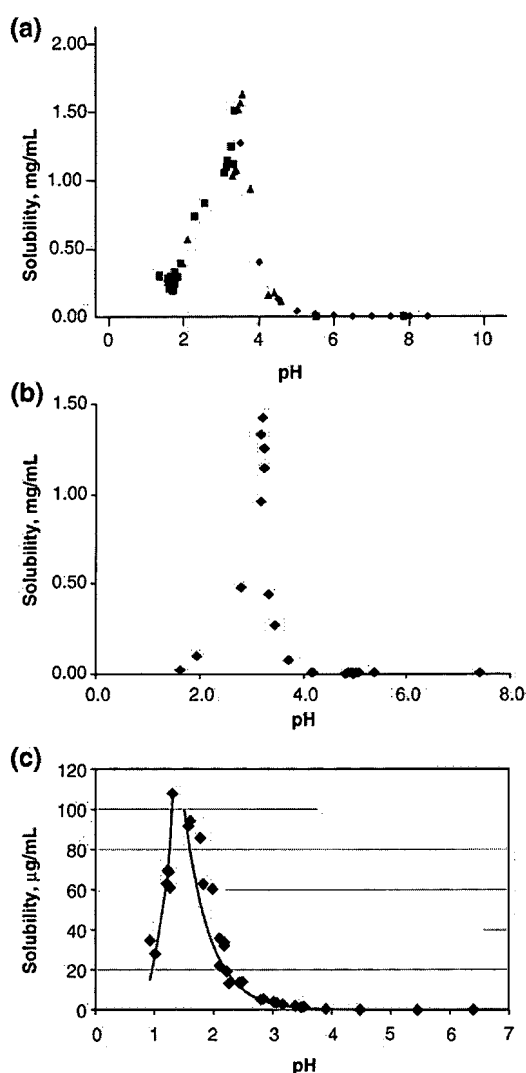


Fig. 4. Typical pH-solubility profiles of poorly water-soluble basic drugs: (a) the solubility profile of a compound with intrinsic solubility (S_0) of 2 $\mu\text{g/mL}$ and a pK_a of 6.3, for which a pH_{max} of ~ 3.4 and a common-ion effect below pH_{max} were observed when the pH was lowered using maleic acid (reproduced with permission from Ref. [32]); (b) solubility profile of a compound with S_0 of 3.4 $\mu\text{g/mL}$ and pK_a of 5.7, for which pH_{max} of 3.2 and common-ion effect below pH_{max} were observed when the pH was lowered using HCl; and (c) the solubility profile of a base having S_0 of < 0.0001 $\mu\text{g/mL}$ (below detection limit) and estimated pK_a in the range of 5.5 to 6.0, for which the pH was adjusted by HCl and the hydrochloride salt did not have acceptable properties for further development due to low pH_{max} (~ 1.5), low salt solubility (0.1 mg/mL at pH_{max}) and strong common-ion effect (reproduced with permission from Ref. [34]).

Pudipeddi et al. [16] depicted the influence of S_0 (or $[B]_s$), pK_a and K_{sp} on pH_{max} , according to Eq. (10), by using Fig. 5, where:

- an increase in pK_a by one unit increases the pH_{max} by one unit;
- an increase in intrinsic solubility, S_0 , of the base by one order of magnitude increases pH_{max} by one unit; and
- a decrease in salt solubility (K_{sp}) by one order of magnitude increases pH_{max} by one unit.

It is evident from Fig. 5 that a stronger basicity (higher pK_a), a higher intrinsic solubility and a lower salt solubility will favor salt formation for a basic drug by increasing pH_{max} . Analogous relationships may also be derived for the salt formation of an acidic drug where an increase in S_0 and decreases in pK_a and salt solubility will decrease pH_{max} and, therefore, favor salt formation.

2.5. Deviation of pH-solubility interrelationship from ideality

Organic compounds often undergo self-association in solution because of their amphiphilic nature [35,36]. Indeed, bile salts are great examples of how organic compounds exhibit surface activity and undergo self-association in aqueous solutions because of their amphiphilic properties [37]. It has been reported that salt forms of many drug molecules undergo similar aggregation in solution [38–41]. Because of self-aggregation, activities of saturated solutions of many salts and even non-salts are lower than their measured concentrations in solution, resulting in non-ideal pH-solubility behavior. An example of

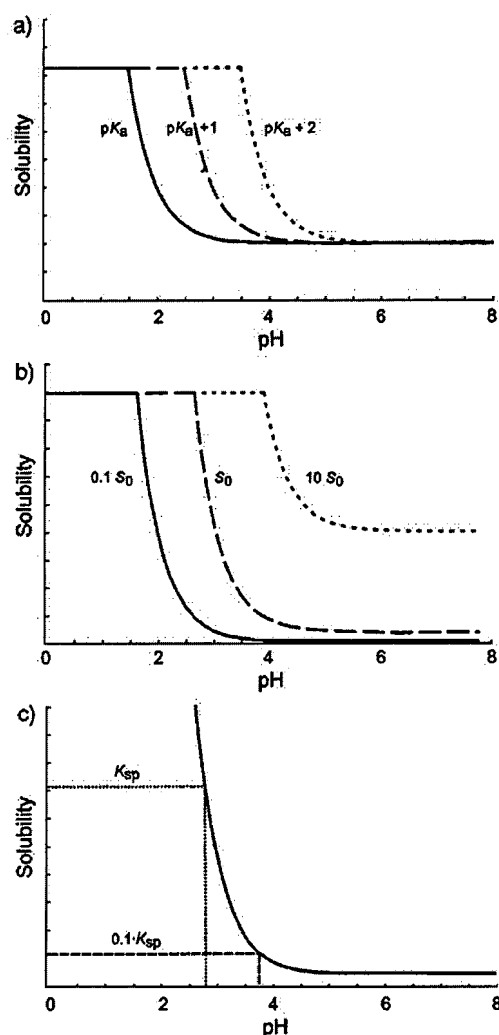


Fig. 5. Effects of (a) pK_a , (b) S_0 and (c) K_{sp} on pH_{max} (reproduced from Ref. [16] with permission).

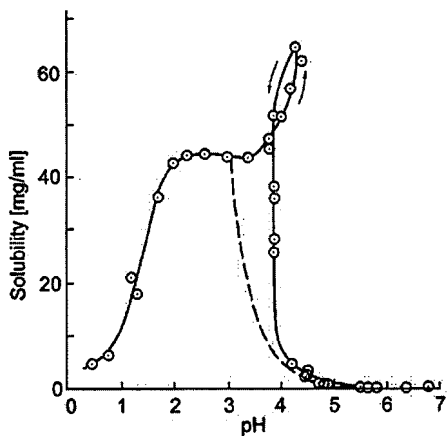


Fig. 6. pH–solubility profile of papaverine hydrochloride determined by using HCl or NaOH, as necessary, indicating supersaturation around pH_{max} and common-ion effect at low pH. The broken line shows the theoretical solubility profile determined based on S_0 and pK_a , and the positive deviation of experimental profile indicates self-association (reproduced from Ref. [19] with permission).

such non-ideality is shown in Fig. 6, in which the saturation solubility of papaverine hydrochloride at or below pH_{max} exhibits higher values than the theoretical profile. There are also numerous examples where metastable, supersaturated solutions are formed at or near pH_{max} [13,19–22]. Supersaturated solutions are formed more often when free base or free acid is used as the starting material in the phase solubility study due to ‘kinetic barriers’ in the transformation of free species to the salt form. Such kinetic barriers may also be present in the conversion of salts to free species, but they are relatively less pronounced. Serajuddin and Mufson [20] reported that the solubility of papaverine free base at 37 °C increased gradually when the pH was decreased by adding HCl to a suspension until the pH reached 4. Then, at an almost constant pH of 4 ± 0.1 , the solubility increased from <10 mg/mL to >120 mg/mL; the solubility kept on increasing with the addition of HCl as long as solid base was present to dissolve into solution. Although it was known that the aqueous solubility of papaverine hydrochloride was only 40 mg/mL, there was no sign of precipitation of the supersaturated solution to the salt form even at a concentration above 120 mg/mL, and it was only after nucleation of the supersaturated solution by adding a few crystals of papaverine HCl that the precipitation of the salt ensued and the solubility dropped to the level of the salt form. With a similar addition of HCl to a phenazopyridine aqueous suspension, the solubility of the free base at pH_{max} was observed to reach at least three times higher than that of phenazopyridine HCl before precipitation of the salt form ensued [21,22]. Such a supersaturation and the deviation from the ideal pH–solubility relationship were attributed to self-association of drug in solution.

The aggregation of drug in solution does not occur only at the pH_{max} . Ledwidge and Corrigan [22] demonstrated that salts of both basic and acidic drugs may self-associate and exhibit surface activity at a wide range of pH. For hydrochloride salts, the addition of an excess of chloride ion during the pH adjustment showed a decrease in apparent K_{sp} values, which was attributed to a decrease in self-association and the consequent

increase in activity coefficients of salts in solution [18,21,22]. In other words, solubilities of HCl salts decreased not only due to common-ion effect, but also due to salting out effects that decreased self-association [42].

Bergstrom et al. [43] reported that experimentally determined solubility profiles of 25 amine drugs differed substantially from theoretical pH–solubility profiles generated by using the Henderson–Hasselbach (HH) equation. The HH equation used is essentially the same as Eq. (3) described earlier for the pH–solubility profile of a base. This equation would not describe the solubility of a salt form and, therefore, a deviation in solubility profile at $pH < pH_{max}$ was expected. Some of the deviations observed at $pH > pH_{max}$ could be due to self-association of dissolved species, especially at or near pH_{max} . The accuracy of a theoretical pH–solubility profile also depends on accuracies of intrinsic solubility and pK_a values used in Eq. (3). The work of Bergstrom et al. [43] highlights the importance of accurate S_0 and pK_a values; otherwise, the theoretical profiles generated may fail to appropriately predict the experimental behavior.

2.6. Structure–solubility relationships

As shown earlier in Fig. 2, aqueous solubilities of haloperidol salts differed depending on salt-forming agents used. There are numerous other reports in the literature presenting such results for both acidic and basic drugs [25,30,44–48]. For example, Streng et al. [30] reported that solubilities of terfenadine salts formed with phosphoric acid, hydrochloric acid, methanesulfonic acid and lactic acid showed up to 10-fold differences, ranging from 0.5 mg/mL to 5 mg/mL. It may be noted that acidities and structures of acids used to form the salts in this study differed greatly. On the other hand, Serajuddin [33] reported for a basic drug, avitriptan, that solubilities of salts could be similar if structurally similar acids are used (Table 1). Although avitriptan is a dibasic compound with pK_a values of 8.0 and 3.6 [15], it formed mono-salts with all acids tested, except for HCl, which was also able to form a dihydrochloride salt. The solubility differed significantly only for the hydrochloride salts. The results obtained by O’Connor and Corrigan [29] for diclofenac salts with a series of structurally similar amines, however, differed from the observation of Serajuddin [33] that similar counterions might provide similar solubilities; their values differed by a factor as much as >100 .

Anderson and Flora [13] indicated that no predictive structure–solubility relationships for pharmaceutical salts have yet been established. They, however, suggested that for

Table 1
Aqueous solubility of mono-salts of avitriptan containing various counterions

Acid used	pK_a of acid	Solubility (mg/mL at 25 °C)
HCl	–6.1	3.4 (9.0) ^a
Methanesulfonic acid	–1.2	16.3
Tartaric acid	3.0, 4.4	14.7
Lactic acid	3.9	15.2
Succinic acid	4.2, 5.6	16.1
Acetic acid	4.8	16.5

^a Value in parentheses is for the dihydrochloride salt.

understanding the effect of a series of salt-forming counterions on aqueous solubility, contributions of the counterions to crystal lattice energies and solvation energies should be considered. In dissolving a salt in water, the molar free energy of solution, ΔG_{soln} , may be represented by

$$\Delta G_{\text{soln}} = \Delta G_{\text{cation}} + \Delta G_{\text{anion}} - \Delta G_{\text{lattice}} \quad (11)$$

where ΔG_{cation} and ΔG_{anion} are molar free energies of hydration of the salt cationic and anionic species, respectively, and $\Delta G_{\text{lattice}}$ is the crystal lattice free energy. Thus, the overall effect of counterions on salt solubility will depend on whether hydration energies or lattice energies are most sensitive to changes in salt structure. By analyzing data for alkali and alkaline earth metal salts of several carboxylic acids, the authors suggested that a quantitative trend exists where the solubility increases with an increase in anion or cation charge and decreases with an increase in ionic radius. A general trend was also observed where solubility of various ammonium salts of an acidic drug, flurbiprofen, increased with a decrease in melting point, indicating that crystal lattice energy plays an important role in salt solubility.

Several other investigations also attempted to establish relationships between salt forms and their aqueous solubilities [28,29,44–46]. However, no general predictive relationships could be obtained. For example, it was reported that solubilities of diclofenac salts with several structurally related primary amines varied by a factor of as much as 100, and they did not show dependence on any one parameter, but on a combination of factors like salt crystal lattice and pH of saturated salt solution [29].

2.7. Effect of organic solvent on salt solubility

The pH–solubility principles described in this section are applicable to aqueous solutions. However, as reported by Wermuth and Stahl [49], pharmaceutical salts are usually synthesized either from organic solvents or from organic–water cosolvents. No systematic studies on the solubility of acidic and basic drugs in such solvents as a function of added counterions to form salts have been reported in the literature.

Organic solvents are used not only in the preparation of salts; they are also used in parenteral and other liquid dosage forms. Organic solvents may influence the solubility of a drug candidate by (a) increasing solubility of unionized species (S_0), (b) decreasing its protonation or ionization, and (c) decreasing solubility of the salt form [15]. Thus, as reported by Kramer and Flynn [17], an increase in S_0 in an organic cosolvent will increase pH_{max} for a basic drug, thus favoring salt formation. This is, of course, assuming that the $\text{p}K_a$ value of the compound would remain unchanged. However, the presence of organic solvents may adversely affect drug ionization by suppressing the dielectric constant [50]. For example, Albert and Serjeant [51] reported that the $\text{p}K_a$ of an acid increased by ~ 1 and that of a base decreased by ~ 0.5 in a 60:40 methanol–water mixture. As a consequence, any positive influence of organic solvents on salt formation may partly or fully be negated by the decreased ionization. The decreased salt solubility in the presence of organic solvents may influence drug

product development in two different ways: (a) it favors precipitation and crystallization of salts, when suitable organic solvents with low dielectric constants are used [52], and, on the other hand, (b) a lower solubility may not be desirable in the development of liquid formulations.

3. Principles of salt dissolution

The dissolution is the process by which a solid dissolves in a liquid, and the rate at which the dissolution takes place is referred to as the dissolution rate. There is, however, an important distinction between dissolution and solubility; the latter implies that the process of dissolution has been complete and the solution is saturated.

3.1. General solubility–dissolution rate relationships

Theories of salt dissolution have been reported in the literature [16,26]. The relationship between dissolution rate (J) and solubility (C_s) may be expressed by the Noyes–Whitney equation [53]:

$$J = KA(C_s - C) \quad (12)$$

where K is a constant, A is the surface area of the dissolving solid, and C is the concentration in the dissolution medium. Eq. (12) may be modified according to the Nernst–Brunner diffusion layer model [54], which implies that the outermost layer of the solid drug dissolves instantly into a thin film of solvent to form a saturated solution of concentration C_s , and the transfer of the dissolved drug to the bulk solution occurs by diffusion of drug molecules through this layer. If the diffusion layer thickness may be denoted by h and the diffusion coefficient of the solute in this layer by D , then K in Eq. (12) becomes equivalent to D/h , and the equation may then be rewritten as:

$$J = \frac{DA}{h}(C_s - C) \quad (13)$$

For a constant surface area A and under sink conditions ($C_s \gg C$), Eq. (13) becomes:

$$J = \frac{DAC_s}{h} \quad (14)$$

or

$$\frac{J}{AC_s} = \frac{D}{h} \quad (15)$$

where the left side of Eq. (15) may remain constant under a particular experimental condition, that is, when D and h remain constant.

Although according to Eq. (14), the dissolution rate is proportional to both solubility and surface area, the increase in C_s is the more effective way of improving the dissolution rate of a solid dosage form. For example, if the particle size of a drug substance is lowered by a factor of 5, say, from 25 μm to 5 μm ,

the surface area A increases by 5 times and, consequently, the dissolution rate J also increases by a factor of 5. There is also a practical limit how much particle size reduction one can achieve; for solid powders, the lowest particle size that can be achieved by conventional milling is about 2 to 3 μm . On the other hand, the salt formation may be able to increase C_s hundreds of times, and J would also increase by a similar factor.

3.2. Dissolution in reactive media

Eq. (13) functions well when the diffusion coefficient D does not change significantly and the drug does not undergo changes, such as degradation, complexation, change in ionization due to pH effect, etc. Bogardus and Blackwood [18] reported that dissolution rates of doxycycline hydrochloride at pH 4 and 7 were significantly higher than those of the free base, although solubilities of both forms at these pH conditions were the same. Similarly, dissolution rates of sodium salicylate were found to be higher than that of salicylic acid at all pH conditions studied (pH 1.1, 2.1 and 7.0) [26].

Such differences in dissolution rates were attributed to differences existing between the bulk pH and the diffusion layer pH. Li et al. [23] studied dissolution rates of mesylate salt, hydrochloride salt and the free base forms of haloperidol at pH 1, 2, 3, 5 and 7, and observed that the J/AC_s values of a salt did not remain constant as per Eq. (15) under all pH conditions. The dissolution profiles for the mesylate salt are shown in Fig. 7. Although the solubilities of the mesylate salt at pH 3 and 5 were about 1000 times higher than that at pH 7, the dissolution rates were very similar. This was because the pH at the surface of haloperidol mesylate solid ($\text{pH}_{h=0}$) was ~ 3 during the dissolution in a pH 7 medium (Fig. 8). Once the C_s value of the mesylate salt at pH 3 was used, instead of the solubility under the bulk pH condition of 7, the J/AC_s values under all pH conditions became similar. Unlike the mesylate salt, the surface pH values ($\text{pH}_{h=0}$) of the free base during dissolution at bulk pH of 1.1, 2.0, 3.0 and 5.0 were 1.1, 4.8, 5.9 and 7.0, respectively. Differences in C_s values under surface pH conditions are responsible for differences between dissolution rates of salts and bases, where the rates are, in general, higher for the salts.

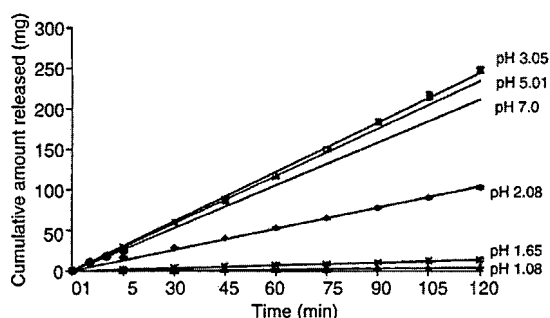


Fig. 7. Dissolution profiles of haloperidol mesylate salt at various pH-stat conditions from a constant surface area of 0.5 cm^2 at 200 rpm. The pH was adjusted either by HCl or NaOH (reproduced from Ref. [23] with permission).

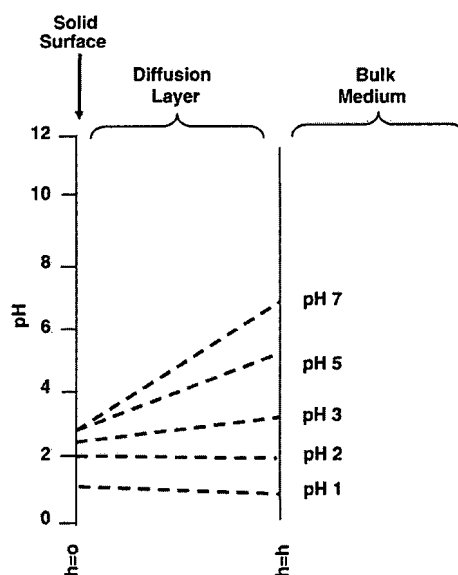


Fig. 8. Graphical representation of the buffering effect of haloperidol mesylate at the solid surface during dissolution at different bulk pH conditions. The pH values at $h=0$ were estimated from pH conditions of the media in equilibria with excess of solid. The dotted lines are schematic.

Serajuddin and coworkers [26,55] developed a practical method of estimating pH at the surface of a dissolving solid ($\text{pH}_{h=0}$) and thereby predicting the dissolution rate in a reactive medium. They observed that the pH of a saturated solution of a drug substance (salt, acid, base) in a particular aqueous medium is equivalent to the surface pH ($\text{pH}_{h=0}$) and that the solubility at this pH should be the one used in predicting dissolution rate.

For haloperidol mesylate, the pH 7 dissolution medium is considered to be a reactive medium, since the salt is expected to convert to the free base at this pH. Similarly, for salts of acidic drugs, an acidic dissolution medium would be considered reactive, since the salt would convert to the free acid form at such a pH. An investigation of the dissolution of pharmaceutical salts at pH conditions of gastric (pH 1–3) and intestinal (pH 5–8) fluids is important for the purpose of *in vitro*–*in vivo* correlation of solid dosage forms, since there is a potential for conversion of salts to their respective free acid or base forms [10]. Four situations may arise due to possible conversion of salts to relatively less soluble free acid/base forms under GI pH conditions:

1. The salt continues dissolving in the dissolution medium without any conversion to free form either because the drug concentration is below the saturation limit or a supersaturated solution has been formed. This was possibly the case during the dissolution of haloperidol mesylate at pH 7 (Fig. 7). There is, however, the potential that a precipitation of drug would occur if the dissolution is continued for a prolonged period of time or the dose is high.
2. The drug concentration reaches saturation limit (or forms a transient supersaturation) after initial dissolution in the medium and the excess salt dissolving from the solid surface converts to its free form and precipitates out in a finely divided state. This situation exists, for example, during the dissolution

of phenytoin sodium in an acidic medium. Phenytoin is an acidic compound with a pK_a value of 8.4 and a solubility of only 35 to 40 $\mu\text{g/mL}$ at 37 °C in the GI pH range of 1 to 7.4. Therefore, after oral intake of a dose of 100 to 300 mg, only about 10 mg of drug dissolves in the GI fluid (~250 mL) and the excess drug precipitates out in a finely divided state [56]. The precipitates, however, redissolve rapidly and maintain saturation in the GI fluid as the absorption continues [57]. This is a common situation during dissolution of salts of acidic drugs in gastric pH and salts of basic drug in intestinal pH, where the high surface areas of precipitates are responsible for relatively higher dissolution rates as compared to that of dosage forms containing free acid or base forms.

3. The free acid or base may precipitate out at the surface of dissolving salt as an insoluble layer. However, as it was demonstrated for phenazopyridine hydrochloride at pH 5 and 7, the precipitated drug forms a loose and porous layer and the dissolution continues, although at a somewhat slower rate due to the extra barrier to dissolution [21].
4. In this situation, the precipitated acid or base forms an impermeable layer at the surface of dissolving salt. Further dissolution is controlled by the solubility of the free form of the drug rather than the salt. Although the salt may exist below the surface layer, it is not available for dissolution. For this reason, it was concluded for a weakly basic drug that there was no advantage of using a salt form in an oral formulation, and the free base was selected for further development [58].

The above situations must carefully be considered in selecting salt forms for development since they might have major influence on both *in vitro* and *in vivo* performance of solid dosage forms.

Although salts, in general, are expected to have higher dissolution rates than free acid or base forms, there are situations where basic drugs may have higher dissolution rates under gastric pH conditions than that of salts. It has been reported that phenazopyridine free base had a much higher dissolution rate at pH 1 (0.1 M HCl) than that of the hydrochloride salt. This is because the surface pH values of the base and the salt during dissolution in 0.1 M HCl were 3.4 and 1.2, respectively, and the drug had a higher solubility at pH 3.4 than that at pH 1.2.

Pharmaceutical salts are sometimes used to slow dissolution rates. For certain pharmaceutical uses, such as inhalation products, parenteral depot systems, *etc.*, drug substances are converted to relatively less soluble forms by salt formation with long-chain fatty acids like stearic acid, palmitic acid, *etc.* Jashnani et al. [59] reported that albuterol stearate dissolved at pH 7.4 much more slowly than the free base and other salt forms, with potential application in extending the duration of drug in lungs following aerosol delivery. Relatively slow-dissolving salts were also studied for the development of slow-release oral dosage forms [60]. In identifying slow-dissolving salts, one needs to pay more attention to the pH–solubility profile of the salt-forming agent than that of the drug candidate. Smith and Anderson [61] reported that the pH_{max} of a long-chain fatty acid, lauric acid, was around pH 7 and the acid was very insoluble at a low pH. Depending on S_0 and pK_a , other long-chain fatty acids might have similar and even higher

pH_{max} . If a salt of a basic drug is prepared by using such an acid, the salt will dissociate to liberate insoluble free acid at the surface of the dissolving salt particle under physiological conditions, thereby retarding its dissolution rate.

3.3. Common-ion effect on dissolution of salts

It has been reported that dissolution rates of a hydrochloride salt decrease as the pH of an aqueous medium is lowered by adding HCl [21,23] or if NaCl is added to the medium [24]. Similarly, the dissolution rate of a sodium salt decreases in the presence of added NaCl in the medium [31]. Such decreases in dissolution rates are due to the common-ion effect. As mentioned earlier (Section 2.3), the solubility of a salt decreases if common ions, such as Cl^- and Na^+ , are present, and since the dissolution rate is proportional to the solubility in the diffusion layer at the surface of the solid, any impact of common ion on saturation solubility would also influence dissolution rate.

The chloride ion is also present in the intestinal fluid. Indeed, Dressman and Reppas [62] recommended that simulated intestinal fluids under fasted and fed conditions should, respectively, contain 0.1 and 0.2 M chloride ion. Since the common-ion effect on the dissolution of a HCl salt may occur throughout the GI tract, the question arises: Will the chloride ion still exert a common-ion effect if a non-HCl salt is selected for development? Li et al. [24] addressed this issue for mesylate and phosphate salts of haloperidol. They observed that a conversion from the non-HCl to the HCl salt form could still occur during dissolution if enough Cl^- is present in the dissolution medium. This was due to the conversion of mesylate and phosphate salts to the hydrochloride salt at the dissolving surface. The common-ion effect, however, depended on the kinetics of the conversion of non-HCl salts to the HCl salt form. Although intrinsic dissolution rates of haloperidol mesylate and phosphate decreased in the presence of Cl^- , they were still higher than that of the hydrochloride salt. The role of the non-HCl to HCl salt conversion kinetics was particularly evident during powder dissolution. Because of high surface area, powders of haloperidol mesylate dissolved completely in <5 min at pH 2 (0.01 M HCl containing 0.1 M NaCl) before its dissolution rate could be impeded by the conversion to the HCl salt form. In two other cases where besylate (benzenesulfonate) and bisulfate (hydrogen sulfate) salts were used, it has been the experience of the present author that the salts did not convert to the hydrochloride forms during the determination of solubility and dissolution rate in 0.1 M NaCl. Rather, the amorphous gels with high drug solubility and dissolution rates were formed; however, one had to take precaution that the gel formation did not retard disintegration of solid dosage forms. Thus, non-hydrochloride salt forms may have advantages over HCl salts in overcoming the common-ion effect. This was possibly the reason for 2.6 and 5 times higher bioavailability of mesylate salts of two poorly water-soluble bases in dogs than that of their corresponding HCl salt forms [63].

4. Solubility considerations in salt screening

The pH–solubility principles presented in this article (Section 2) may serve as a guide in selecting optimal salt forms for

development. They are also helpful in determining solubilities of salts accurately during the evaluation of physicochemical properties of salts.

4.1. Identification of chemical form

High-throughput screening methods are now routinely applied to prepare potential salt forms of new drug candidates [64–67]. Essentially, in such a method, drug solutions in different solvents are prepared in 96-well plates using minute quantities of drugs, solutions of salt-forming agents (counterions) are then added to the wells and the contents of the wells are observed for salt formation. In some cases the salt crystallization may be induced by changes in temperature, solvent evaporation, *etc.* Any solids formed in the wells are analyzed by Raman spectroscopy, powder X-ray diffraction, *etc.* Although techniques are available for automated solvent dispensing and ‘hit’ analysis, the whole salt-screening process is not such a simple one. The number of wells used in any salt screening could be in the hundreds, crystals observed in many of the wells might not be salts but rather just the free drug or salt-forming agents, so any positive hits must be verified by preparing relatively larger quantities of salts and by subjecting them to a variety of tests to assess their suitability for further development.

Serajuddin and Pudipeddi [15] suggested that the salt-screening process may be simplified and many unnecessary attempts to prepare salts may be eliminated by applying the basic pH–solubility principles outlined earlier in the present article. They demonstrated that the presence of an ionizable moiety in an acidic drug and a protonatable moiety in a basic drug does not necessarily mean that a salt would be formed. As shown in Eq. (4), a salt would be formed only if the pH of an aqueous solution (or suspension) of a basic drug is adjusted below its pH_{max} , and, as per Eq. (6), the pH of an acidic drug must be adjusted above its pH_{max} to form a salt. From a pH–solubility relationship that may be generated either experimentally or theoretically and by having an idea of pH_{max} from a limited experiment data, one may be able to ascertain which counterions could provide pH values in appropriate salt-forming ranges [15]; the counterions that would not be able to shift the pH accordingly should be eliminated from consideration in order to minimize the number of experiments (or wells in the high-throughput method). Even if salts could be formed with weaker counterions by using organic solvents, they may not be suitable for development. In a salt-screening study for a very weakly basic compound [63], successful synthesis of seven salts, *e.g.*, hydrochloride, sulfate, mesylate, succinate, tartrate, acetate, and phosphate, were initially reported, out of which only two (hydrochloride and mesylate) were considered for further evaluation. If the pH–solubility profile and pH_{max} of the compound were determined, one could possibly find *a priori* that many of the counterions used would not form acceptable salts. This would save time and resources utilized in preparing and characterizing the undesirable salts. Similarly, using a multi-well technique, Bastin *et al.* [67] observed the formation of HCl, mesylate, citrate, tartrate and sulfate salt for a basic compound with a pK_a of 5.3 and S_0 of 10 $\mu\text{g/mL}$. The sulfate salt was selected for further development, with the mesylate salt serving as the

back-up. Again, if one had considered the pH–solubility principles and determined the pH_{max} , it would have been evident that only the relatively stronger acids, such as sulfuric acid, methanesulfonic acid, hydrochloric acid, *etc.*, should have been used in the first place, and the weaker acids could have been eliminated from consideration *a priori*.

Shanker *et al.* [68] reported a method, which was later elaborated by Tong and Whitesell [69], for screening the potential for salt formation in aqueous media. In this method, small volumes of concentrated drug solutions are prepared by using different counterions and the solutions are then set aside for crystallization of salts. Once crystals are formed, drug concentrations are measured. For basic drugs, the chemical nature of counterions used and their concentrations should be such that the pH values of solutions remain below pH_{max} , since, according to Tong and Whitesell [69], it is only from solubility experiments below pH_{max} that the solubility of a salt can be estimated. Similarly, pH values for solutions of acidic drugs are adjusted above their pH_{max} . One must, however, be careful that supersaturated solutions may be formed at or near the pH_{max} , and a lack of crystallization does not always mean that a salt would not be formed.

The identification of a salt form for development becomes more complex when an acidic or basic drug has more than one ionizable or protonatable groups. Serajuddin and Pudipeddi [15] extended Eqs. (4) and (6) to cover situations where, respectively, a basic molecule may be protonated at multiple locations (polybasic) and an acidic molecule may undergo ionization at multiple sites (polyprotic). Several other authors derived equations to describe acid–base equilibria of polybasic and polyprotic compounds [70–72]. In a typical salt-screening study, attempts are made to prepare mono- and poly-salts of such compounds by adding stoichiometric quantities of counterions. However, two important questions that need to be addressed under such a situation are: Is the compound capable of forming both mono- and poly-salts? If the synthesis of both forms is feasible, which one is preferred for development? According to Serajuddin and Pudipeddi [15], these questions may be answered by utilizing the pH–solubility interrelationship of the compound. They studied feasibility of salt formation for a basic drug, avitriptan, having pK_a values of 8.0 and 3.6 and the S_0 of 0.006 mg/mL, and determined that the compound had two pH_{max} values, one at pH 5 and the other at pH ~ 2 . All salt-forming agents tested could lower pH of the saturated solution of avitriptan below 5, and only HCl could lower pH below 2. Such information during the salt screening can save attempts to prepare poly-salts by using relatively weaker counterions, and one can also predict that a di-salt may in cases be weak and highly acidic (*e.g.* the dihydrochloride salt of avitriptan).

Having multiple sites for protonation or ionization in a molecule may also prevent salt formation. In one salt-screening study [73], extensive efforts to prepare salts for a basic drug with pK_a values of approximately 8, 6 and 4 and the S_0 value of 0.002 mg/mL failed. Although it was assumed that the preparation of all mono-, di- and tri-salt forms of the compound could be possible, a pH–solubility profile showed that the compound did not have well-separated pH_{max} . As a result, the solubility kept on increasing with a decrease in pH, and K_{sp} values for nucleation of

any salt crystal were never reached. Also, any attempt to prepare a salt by crash precipitation led to amorphous forms only, with non-stoichiometric base-to-counterion ratios. During salt screening of compounds with multiple pK_a values that are relatively closer together, chances are that either poly-salts (satisfying all protonation or ionization) are formed or no salts are formed at all.

4.2. Determination of salt solubility

One of the important considerations, if not the most important one, in the selection of a salt form for development is its aqueous solubility. However, Anderson and Flora [13] indicated that many of the salt solubility values reported in the literature could be in error due to conversion of salts to their respective free acid or base forms in aqueous media used. It could be possible that the excess solids in equilibria with solutions were not salts; they were either free forms or mixtures of salts and free forms. This situation may be explained by using Figs. 1 and 3; if the pH shifts to the side of free acid or free base during the determination of salt solubility, the solubility would represent that of the free form only at the equilibrium pH. For the salt of a basic drug, the shift in pH occurs according to Eq. (1), which indicates that the dissolved salt reacts with water liberating free base and producing hydrogen ion. Thus, if the hydrogen ion concentration is not sufficient enough to maintain pH below pH_{max} , the pH of solution will shift to a pH higher than pH_{max} , where the free base will be the equilibrium species. The situation may be further illustrated with a simulated example of the salt of a basic drug having the pH_{max} of 2, below which the maximum salt solubility of 1 mg/mL is attained, and the free base solubility of 1 μ g/mL above pH 6. If one adds, say, 1 mg of the salt to 10 mL of water (pH ~ 6) to determine its saturation solubility, the solution may equilibrate somewhere around pH 5 and the solubility will be very low, which will represent the solubility of the free base at that pH. If additional amounts of the salt are added to the solution, the pH will decrease gradually since more and more hydrogen ions will be produced and, consequently, the solubility of the compound will increase. This will continue until a high excess of the salt is added, when the pH will drop below 2 and the solubility of salt will be reached. If, on the other, water is added drop by drop to a mass of the solid salt, instead of adding the salt to water, a suspension of salt having $pH < pH_{max}$ will be produced representing the solubility of the salt. Similar situations also exist for the salts of acidic drugs. Thus, the equilibrium pH and, therefore, the drug solubility may change depending on the amount of salt added and the extent of conversion of a salt to its free form. Such conversions of salts to their free forms could be one of the reasons for variable solubilities and pH values observed in aqueous media for different salt forms of acidic and basic drugs [28,45,67]. Wang et al. [74] reported that the solubility could also be affected by the conversion of a di-HCl salt to its mono-HCl form.

4.3. Recent trends in salt forms

Because of low aqueous solubilities of many basic drugs, pH-solubility profiles similar to those in Fig. 4 are very common,

where the pH_{max} values are relatively low. As a result, most of the common carboxylic acids [75] do not usually form acceptable salts, and strong acids are needed to form salts with such drugs. It was, therefore, of interest to investigate what is the recent trend in salt forms approved by the US Food and Drug Administration (FDA). Table 2 gives the distribution of 120 salts approved by the FDA during the 12-year period from 1995 to 2006, where the hydrochloride salt is the predominant salt form among the basic drugs and the sodium salt is the predominant form for acidic drugs. While 30 years back [6] the mesylate salt was practically nonexistent, it now comprises 10% of all salts of basic drugs approved during the past 12 years. It is also interesting to note that 77% of the salts of basic drugs in Table 2 are prepared with relatively stronger counterions (hydrochloride, hydrobromide/bromide, sulfate/bisulfate and nitrate). It is expected that this trend in the use of relatively stronger counterions will continue in the future and we will see a greater percentage of non-hydrochloride salts used. Similarly, 14 out of 19 salts of acidic drugs in Table 2 are prepared with strong alkalis such as NaOH and KOH, and this trend is also expected to continue in the future.

Table 2
Salt forms of new chemical entities (NCEs) approved by the FDA from 1995 to 2006^a

Salts of basic drugs	Total number
Hydrochloride	54
Methanesulfonate (mesylate)	10
Hydrobromide/bromide	8
Acetate	5
Fumarate	5
Sulfate/bisulfate	3
Succinate	3
Citrate	2
Phosphate	2
Maleate	2
Nitrate	2
Tartrate	2
Benzoate	1
Carbonate	1
Pamoate	1
Total of all salts of basic drugs	101
Salts of acidic drugs	Total number
Sodium	12
Calcium	4
Potassium	2
Tromethamine	1
Total of all salts of acidic drugs	19

^a Sources: D.A. Hussar, New drugs of 1995, J. Am. Pharm. Assoc. 36 (1996) 158–188; D.A. Hussar, New drugs of 1996, J. Am. Pharm. Assoc. 37 (1997) 192–234; D.A. Hussar, New drugs of 1997, J. Am. Pharm. Assoc. 38 (1998) 155–198; D.A. Hussar, New drugs of 1998, J. Am. Pharm. Assoc. 39 (1999) 151–206; D.A. Hussar, New drugs of 1999, J. Am. Pharm. Assoc. 40 (2000) 181–231; D.A. Hussar, New drugs of 2000, J. Am. Pharm. Assoc. 41 (2001) 229–272; D.A. Hussar, New drugs of 2001, J. Am. Pharm. Assoc. 42 (2002) 227–266; D.A. Hussar, New drugs of 2002, J. Am. Pharm. Assoc. 43 (2003) 207–248; D.A. Hussar, New drugs of 2003, J. Am. Pharm. Assoc. 44 (2004) 168–210; D.A. Hussar, New drugs of 2004, J. Am. Pharm. Assoc. 45 (2005) 185–217; New drugs and biologic product approval, 2005, AJHP News, February 15, 2006 (www.ashp.org); New drugs and biologic product approval, 2006, AJHP News, February 15, 2007 (www.ashp.org).

5. Practical considerations of salt solubility in dosage form design

The topic of how salts can be used advantageously in the development of pharmaceutical dosage forms has been reviewed elsewhere [76] and is beyond the scope of the present article. Here, only a few points regarding how the solubility principles described in the present article may be applied to develop solution formulations and in resolving stability issues with solid dosage forms are discussed.

5.1. Liquid formulations

Determination of pH–solubility profiles of NCEs with different counterions provides information with respect to what counterion is best suited to optimize (often maximize) drug solubility in a liquid formulation. In selecting a salt form for development both as solid and liquid dosage forms, care should be taken to accommodate solubility needs of the liquid formulation. This is because a salt may have acceptable dissolution rate from a solid dosage form, but its solubility may not be adequate for the liquid formulation. Effects of counterions used to adjust tonicity or as buffering agents on drug solubility are also important considerations. Marra-Feil and Anderson [77] reported that the addition of multiple counterions so as not to exceed the solubility product (K_{sp}) of a salt may sometimes provide higher solubility than the use of any single counterion. The use of cosolvent may also be helpful when the pH adjustment alone does not provide solubility, since the solvent may modify the solubility profile by increasing the S_0 value. However, one should be careful that the overall solubility of the salt is not decreased due to the solvent effect. Many of the problems associated with liquid formulations are due to precipitation of free acid or base forms of drugs. If the pH of the solution is adjusted such that the solubility is no longer controlled by the salt form, special attention must be paid to buffering the system strong enough that there is no significant shift in pH. This is because the slopes of pH–solubility curves at $\text{pH} > \text{pH}_{\text{max}}$ for a basic drug and $\text{pH} < \text{pH}_{\text{max}}$ for an acidic drug could be very steep and a small change in pH may have an adverse effect on drug solubility [78].

5.2. Microenvironmental pH of salts in solid dosage forms

As mentioned earlier, high aqueous solubility in the diffusion layer at the dissolving surface is responsible for the high dissolution rate of a salt. The pH in this layer may be different from that in the microenvironment of a solid dosage form, and, if the microenvironmental pH of a formulation is significantly different from that of a salt, a conversion from the salt to free acid or base may occur in the products in accordance with pH–solubility and pH_{max} principles described earlier. The conversion of ifetroban sodium to its free acid form decreased dissolution rates of tablets during accelerated stability testing [79], and the conversion of the maleate salt of an experimental drug to free base resulted in volatilization of the relatively lower-melting base and the consequent decrease in drug assay [32]. Therefore, in developing dosage forms of a salt, the potential for any

conversion to the free form needs to be considered and excipients should be selected such that no such conversion occurs. If necessary, the microenvironmental pH should be adjusted [79].

6. Conclusions and outlook

Of approximately 300 NCEs approved by the FDA during the 12-year period from 1995 to 2006 for marketing, 120 were in salt forms. Although the salt formation was sometimes utilized to crystallize and purify drug substances, most were prepared to improve the solubility of drugs. Salts are often used to increase drug solubility in parenteral and other liquid formulations. Salt formation is also the most common approach of increasing solubility, dissolution rate and ultimately bioavailability of poorly water-soluble ionizable drugs in solid dosage forms. In applying the physicochemical principles of salt formation to enhance solubility and dissolution rate, care must be taken to consider and, if possible, avoid the conversion of salts to their respective free acid or base forms. These conversions may also take place during the determination of dissolution rates of salts in reactive media. Salts are also prone to common-ion effect that may lower solubility and dissolution rate, and they may undergo self-association to form supersaturated solutions. These factors, which can also occur *in vivo*, should be evaluated carefully during salt selection and dosage form development.

Looking forward to the future, salts formation will remain the primary approach to improve solubility and dissolution rate of poorly water-soluble acidic and basic drugs. However, as the potential drug candidates are becoming extremely water-insoluble, it might not be possible in many cases to form optimal salts. Careful analysis of the interrelationship of intrinsic solubility, pK_a and possible salt forms will be necessary to minimize unsuccessful attempts to prepare salts. Stronger anions and cations will be commonly utilized to enable salt formation. Even when a salt is formed, it might not be able to enhance bioavailability of drugs adequately. As mentioned earlier in this article, salts may precipitate out in the GI fluid after oral administration into their free acid and base forms. For newer drugs, the precipitates may not redissolve rapidly due to their very low aqueous solubilities. To overcome these limitations with salt formation and salt dissolution, it is expected that alternative formulation approaches, such as solubilization, complexation, solid dispersion, lipid-based drug delivery systems, *etc.*, to enhance bioavailability of poorly water-soluble will replace salt formation for many compounds. There is also an increased awareness of the effect of microenvironmental pH on the dissolution of salts from solid dosage forms. The pH-modifiers will be more commonly used in solid dosage forms to minimize conversion of salts to their respective free upon storage and also due to pH effects in the GI fluid.

The situation will become even more complex in the development of solutions for parenteral administration. For a compound with the intrinsic solubility 1 $\mu\text{g/mL}$, even a 1000-fold increase in solubility by salt formation will give a concentration only of 1 mg/mL , which might not be adequate for the purpose of dosage form development. In such a case, the salt formation may be combined with another solubilization strategy to obtain adequate drug solubility. For example, Kim et al. [80] reported the

increase in the solubility of ziprasodone mesylate by inclusion complexation with cyclodextrin sulfobutyl ether. The mesylate salt of ziprasodone has an aqueous solubility of 0.89 mg/mL (pH 2.7) and was used in solid dosage forms; it was only by cyclodextrin complexation that the target concentration in solution in the range of 20–40 mg/mL for intramuscular administration could be obtained. Similar strategy may also be applied in solid dosage forms by adding suitable adjuvants to enhance dissolution rates of salts.

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(54) Title: LIQUID FORMULATIONS OF SALTS OF 1-[2-(2,4-DIMETHYLPHENYLSULFANYL)PHENYL]PIPERAZINE

(57) Abstract: Liquid formulations of lactic acid addition salts of 1-[2-(2,4-dimethylphenylsulfanyl)- phenyl]piperazine are provided.

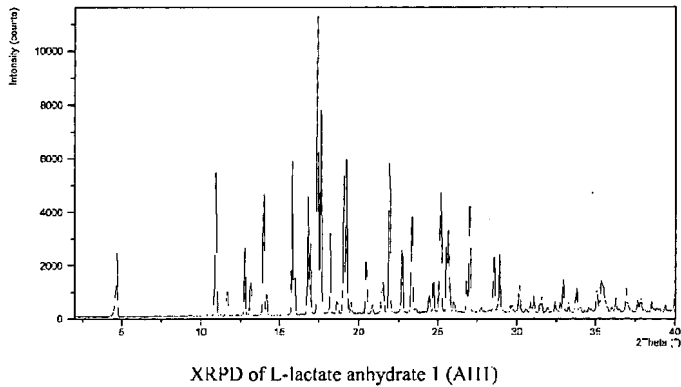


Fig. 1

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Claims

1. A liquid pharmaceutical formulation comprising a salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine selected from the DL-lactic acid addition salt, L-lactic acid addition salt and the D-lactic acid addition salt.
2. The liquid formulation according to claim 1, wherein said salt is the DL-lactic acid addition salt.
3. The liquid formulation according to claim 1, wherein said salt is the L-lactic acid addition salt.
4. The liquid formulation according to claim 1, wherein said salt is the D-Lactic acid addition salt.
5. The liquid formulation according to any of claims 1-4, wherein the concentration of said salt is above 2.5 mg/mL.
6. A method for the treatment of a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive impairment, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse, said method comprising the administration of a therapeutically effective amount of a liquid formulation according to any of claims 1-5 to a patient in need thereof.
7. The method according to claim 6, wherein a predetermined volume of said liquid formulation is measured out and the resulting volume added to a liquid, which liquid is administered orally to the patient.
8. The use of a salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine selected from the DL-lactic acid addition salt, L-lactic acid addition salt and the D-lactic acid

addition salt in the manufacture of a liquid formulation for the treatment of a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive impairment, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse, wherein said salt is in a liquid formulation.

9. The use according to claim 8 wherein said salt is the DL-lactic acid addition salt.

10. The use according to claim 9, wherein said salt is the β form of the DL-lactic acid addition salt.

11. The use according to claim 8, wherein said salt is the L-lactic acid addition salt.

12. The use according to claim 11, wherein said salt is the MH 2 form of the L-lactic acid addition salt.

13. The use according to claim 8, wherein said salt is the D-Lactic acid addition salt.

14. The use according to any of claims 8-13, wherein said liquid formulation comprises above 2.5 mg/mL of said salts.

15. A salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine selected from the DL-lactic acid addition salt, the L-lactic acid addition salt and the D-lactic acid addition salt for use in the treatment of a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive impairment, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse, wherein said salt is in a liquid pharmaceutical formulation.

16. The salt according to claim 15 wherein said salt is the DL-lactic acid addition salt.

17. The salt according to claim 15, wherein said salt is the L-lactic acid addition salt.

18. The salt according to claim 15 wherein the salt is the D-lactic acid addition salt.
19. The salt according to any of claims 15-18 wherein said liquid formulation comprises
5 above 2.5 mg/mL of said salt.
20. A compound which is the L-lactic acid addition salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine.
- 10 21. The compound according to claim 20 which is the MH 2 form of the L-lactic acid addition salt.
22. A compound which is the D-lactic acid addition salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine.
- 15 23. A compound which is the β form of the DL-lactic acid addition salt.
24. A container fitted with a drop aggregate, which container comprises a liquid formulation according to any of claims 1-5.