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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Evento : 378
Actuación : 444

Referencia : Expediente No. 11.112.338
Asunto : Solicitud de patente para: **SALES DE ADICIÓN DE AMINAS QUE CONTIENEN GRUPOS HIDROXILO Y/O CARBOXÍLICOS CON DERIVADOS DE ÁCIDO AMINONICOTÍNICO COMO INHIBIDORES DE DHODH**
Solicitante : ALMIRALL, S.A.
Fecha de solicitud : 01 de Septiembre 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. **9955** notificado por fijación en lista el 11 de junio de 2013.

2. Mediante oficio No. **9955** 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 la claridad del pliego reivindicatorio, a la falta de unidad de invención, y al nivel inventivo de las reivindicaciones 1 a 16 en vista de los documentos D1: WO2008077639 y D2: "Journal of Pharmaceutical Science, (1977), Vol 66(1): pp 002-019 (1977)".

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 16 reivindicaciones.

Se han introducido las siguientes modificaciones al pliego reivindicatorio:

- Las reivindicaciones 1 y 15 han sido modificadas debido a que se ha eliminado la expresión “y sus solvatos farmacéuticamente aceptables”.
- Las reivindicaciones 17 a 19 se han eliminado.

Así, las reivindicaciones son ahora claras y precisas en el momento de señalar la naturaleza de la invención reivindicada y es evidente que las características técnicas esenciales de la invención están establecidas.

Por lo anterior, las objeciones formuladas por el Examinador en cuanto a la claridad y concisión del pliego reivindicatorio se ven superadas. En consecuencia, se solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

3.2 Argumentos a favor de la falta de Unidad de Invención

El artículo 25 de la Decisión 486, hace referencia a:

“Artículo 25.-La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo.”

En la acción oficial pendiente, el Examinador identifica dos grupos inventivos definidos de la siguiente manera:

Grupo 1: Reivindicaciones 1 a 16.

Grupo 2: Reivindicaciones 17 a 19.

Con respecto a la objeción elevada a la falta de unidad de invención realizada por el señor Examinador, amablemente señalamos que se han eliminado las reivindicaciones 17 a 19 como se mencionó anteriormente. De esta forma, el nuevo pliego reivindicatorio se encuentra conformado solamente por las reivindicaciones 1 a 16, las cuales fueron incluidas dentro del primer grupo inventivo identificado por el Examinador. En consecuencia, es claro que el nuevo pliego reivindicatorio comprende un único concepto inventivo y por lo tanto, la objeción formulada a este respecto se debe tener por superada.

3.3 Argumentos a favor de la falta de Nivel Inventivo

El artículo 18 de la Decisión 486 señala lo siguiente:

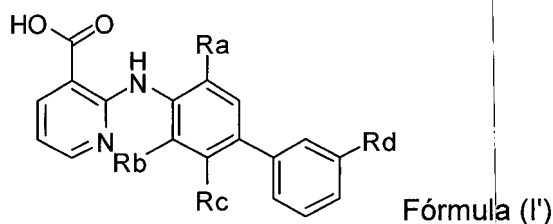
“Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”

Una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente, se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

A este respecto, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se objeta el nivel inventivo, con base en la siguiente información:

En primer lugar, deseamos señalar que la reivindicación 1 de la presente solicitud de patente se refiere a una sal de adición cristalina farmacéuticamente aceptable de (i) una amina que contiene uno o más grupos hidroxilo y/o carboxílicos con (ii) un derivado de ácido aminonicotínico de fórmula (I)



Tal y como se describe en la página dos de la memoria descriptiva, el documento WO 2008/077639 (D1) describe nuevos derivados de ácido aminonicotínico e isonicotínico como inhibidores potentes de DHODH.

Es evidente que la presente invención se basa en una selección de un subgrupo de compuestos concretos descritos en WO 2008/077639, así como en la selección unos contraiones concretos para obtener las sales de la presente invención.

Como se ha indicado anteriormente, los compuestos descritos en WO 2008/077639 son inhibidores DHODH. Por lo tanto, el problema técnico a resolver es proporcionar inhibidores DHODH que sean física y químicamente estable, con niveles aceptables de higroscopia y punto de fusión relativamente alto.

Así, las sales de la presente invención presentan un incremento significativo en la solubilidad frente al compuesto en forma de ácido tal y como se demuestra en los datos de solubilidad de la Tabla 1 (página 28 de la presente solicitud). Por lo tanto, el problema

a resolver por la presente invención es proporcionar derivados de ácido aminoricotínico con una solubilidad mejorada.

Por otro lado, el Examinador hace referencia al documento D2. Sin embargo, D2 no contiene ninguna enseñanza que permita a un experto en la materia concluir con seguridad que las sales de adición de una amina que contiene uno o más grupos hidroxilo y/o carboxílicos con un compuesto de fórmula (I) puedan presentar una solubilidad mayor que la base libre.

En consecuencia, una persona del oficio normalmente versada en la materia no consideraría que a partir de lo descrito en D2 se pueda generalizar que las sales de una amina que contiene uno o más grupos hidroxilo y/o carboxílicos (por ejemplo, trometamina, meglumina o L-arginina) de cualquier compuesto tendrían una mayor solubilidad que cualquier otra forma salina del mismo compuesto.

Por lo tanto, el documento O'Connor K M et al, International Journal of Pharmaceutics 226 (2001) 163–179 (presentado como documento adjunto a este memorial de respuesta), describe las propiedades físico-químicas de 6 tipos de sales diferentes del ácido diclofenaco. Las sales elegidas se describen en la Tabla 1 (página 165 del documento) y son: tert-butilamina (tBA), 2-amino-2-metilpropanol (AMP), 2-amino-2-metil-1,3-propanediol (AMPD), tris(hidroximetil)aminomethane (TRIS o trometamina), benzilamina (BA) y 2-(dimetilamino)etanol o deanol (DNL).

Como se puede apreciar en la Tabla 3 (página 172 del documento), la sal de trometamina del ácido diclofenaco es la que presenta la segunda más baja solubilidad de todas las sales ensayadas. En la Tabla 3 también se incluyen los datos de solubilidad de las sales del ácido diclofenaco con diethanolamina (DEA) y con hidroxietilpirrolidonio (HEP) obtenidos en estudios anteriores.

Por otro lado, en la página 176, primera columna se indica claramente que a partir de los datos de las Tablas 2 y 3 de las sales preparadas con las 4 aminas primarias ensayadas: tert-butilamina (tBA), 2-amino-2-metilpropanol (AMP), 2-amino-2-metil-1,3-propanediol (AMPD), y tris(hidroximetil)aminomethane (TRIS o trometamina) no existen

tendencias generales entre las propiedades del contraión, hidroficidad, punto de fusión y pKa, y la solubilidad de la sal correspondiente.

Por otro lado, también se indica que TRIS, el contraión más hidrofílico de esta serie, resultó en la sal con la solubilidad más baja.

Por otra parte, el documento David S E et al, Drug Development and Industrial Pharmacy, 2012; 38(1): 93–103 (presentado como otro documento adjunto a este memorial de respuesta), describe un estudio sobre la influencia del contraión en la solubilidad y propiedades físico-químicas de las sales de medicamentos con grupos carboxílicos.

Para ello se partieron de los compuestos flurbiprofeno, ibuprofeno, etodolac y gemfibrozil y se obtuvieron sus correspondientes sales con butilamina, hexilamina, octilamina, benzilamina, tert-butilamina, 2-amino-2-metil-propan-1-ol, 2-amino-2-methylpropan-1,3-diol y tris(hidroximetil)aminometano (tris o trometamina) (Tabla 1, página 94 del documento).

Para los cuatro medicamentos testados, flurbiprofeno, ibuprofeno, etodolac y gemfibrozil, las sales de trometamina se englobarían en la zona media de solubilidades (Tablas 2, 3, 4 y 5; páginas 96-97 del documento).

Por lo tanto, tal y como se manifiesta en los documentos O'Connor K M et al y David S E et al., no siempre la sal de trometamina de un compuesto específico tendrá una mayor solubilidad que otra forma salina del mismo compuesto.

Además, tal y como se indica en el Manual para el Examen de Solicitudes de Patentes de Invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina (Manual Andino de Patentes), Capítulo III, Apartado 10.7 (Información complementaria y ejemplos comparativos), *“Ante una objeción por falta de nivel inventivo, el solicitante puede aportar pruebas para apoyar ese nivel en forma de argumentos o documentos, ..., mediante ensayos especialmente comparativos para demostrar la presencia de un efecto técnico o ventaja de la invención, respecto del estado de la técnica más cercano.”*

Adicionalmente, en la memoria descriptiva de la presente solicitud se indica que se llevaron a cabo ensayos de cristalización de sales de algunos derivados de ácido amino nicotínico de fórmula (I) con una amplia gama de ácidos farmacéuticamente aceptables (comprendiendo entre otros los ácidos clorhídrico, metanosulfónico y sulfúrico) y bases (comprendiendo entre otras amoniaco, L-arginina, hidróxido de magnesio, meglumina, hidróxido de potasio, hidróxido de sodio y trometamina) en una gama de diferentes disolventes farmacéuticamente aceptables (incluyendo entre otros acetona, acetonitrilo, acetato de etilo, acetato de isobutilo, cloroformo, nitrometano, carbonato de dimetilo, N,N-dimetilformamida, etanol, isopropanol y metanol).

Las sales preparadas a partir de amoniaco e hidróxido de magnesio produjeron o bien aceites o sólidos amorfos. Las sales preparadas a partir de hidróxido de potasio e hidróxido de sodio eran higroscópicas. Por otro lado, las sales preparadas a partir de ácido clorhídrico, ácido metanosulfónico y ácido sulfúrico tenían solubilidad similar o incluso inferior a la de la forma de ácido libre. Además de esta baja solubilidad, las sales de estos ácidos manifestaron muy mala humectabilidad en agua.

Sólo las sales de la invención no eran higroscópicas ni deliquescentes y tenían un punto de fusión relativamente alto, lo que ha permitido micronizarlas y que tengan estabilidad a largo plazo.

Así, amablemente señalamos que aunque se argumente que sólo es una cuestión de rutina para la persona del oficio normalmente versada en la materia el preparar una sal de un compuesto particular para obtener una mejor solubilidad, tal y como se ha descrito anteriormente.

De esta manera, se hace evidente que, a pesar de que la literatura describa sales de adición de compuestos concretos con bases concretas, no se puede generalizar que con estas bases se puedan obtener sales estables con otros compuestos (por ejemplo los derivados de ácido amino nicotínico). En efecto, sin experimentación alguna no es posible predecir con absoluta certeza las sales específicas que presentarían una mayor estabilidad y/o predecir la mayor solubilidad de la sal acá reivindicada.

Por lo tanto, 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.

En consecuencia de lo anterior, la invención de la presente invención tiene nivel inventivo en vista de los documentos D1 y D2 del estado de la técnica citados por el Examinador.

3.4 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. La presente invención fue concedida por la Oficina de Patentes de Europa, patente No. EP2406225 (B1).

3.5 Conclusión

Por todo lo anterior, el documento D1, el documento D2, o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la invención de la presente solicitud. Por lo tanto, consideramos que el Examinador está excluyendo el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

4. 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. 9955, 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.

5. Anexos

- Nuevo pliego reivindicatorio conformado por 16 reivindicaciones
- Artículo 1: O'Connor K M et al, International Journal of Pharmaceutics 226 (2001) 163-179
- Artículo 2: David S E et al, Drug Development and Industrial Pharmacy, 2012; 38(1): 93-103

Señor Director,


LUZ CLEMENCIA DE PAEZ

C.C. 35.456.344 de Usaquén

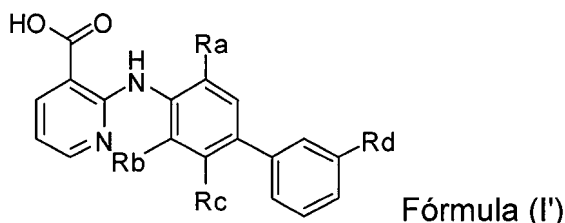
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REIVINDICACIONES

1. Una sal de adición cristalina farmacéuticamente aceptable de (i) una amina que contiene uno o más grupos hidroxilo y/o carboxílicos con (ii) un derivado de ácido aminonicotínico de fórmula (I)



en la que

R^a , R^b , R^c y R^d independientemente representan grupos seleccionados de átomos de hidrógeno, átomos de halógeno, grupos alquilo C_{1-4} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo, y grupos alcoxi C_{1-4} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo.

2. Una sal según la reivindicación 1, donde en el derivado de ácido amino nicotínico de fórmula (I) R^a representa un grupo seleccionado de átomos de halógeno y grupos alcoxi C_{1-4} , que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo.
3. Una sal según la reivindicación 1 o la reivindicación 2, donde en el derivado de ácido amino nicotínico de fórmula (I) R^b representa un grupo seleccionado de átomos de hidrógeno y átomos de halógeno.
4. Una sal según una cualquiera de las reivindicaciones precedentes, donde en el derivado de ácido amino nicotínico de fórmula (I) R^c representa un grupo seleccionado de átomos de hidrógeno y grupos alquilo C_{1-4} , que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo.

5. Una sal según una cualquiera de las reivindicaciones precedentes, donde en el derivado de ácido amino nicotínico de fórmula (I) R^d representa un grupo seleccionado de átomos de hidrógeno y grupos alcoxi C_{1-4} , que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo.
6. Una sal según la reivindicación 1, donde en el derivado de ácido amino nicotínico de fórmula (I) R^a representa un grupo seleccionado de átomos de halógeno y grupos alcoxi C_{1-4} , que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo; R^b representa un grupo seleccionado de átomos de hidrógeno y átomos de halógeno, R^c representa un grupo seleccionado de átomos de hidrógeno y grupos alquilo C_{1-4} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo; y R^d representa un grupo seleccionado de átomos de hidrógeno y grupos alcoxi C_{1-4} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxilo.
7. Una sal según una cualquiera de las reivindicaciones precedentes, donde la amina se selecciona del grupo que consiste en L-arginina, deanol, dietanolamina, dietiletanolamina, etanolamina, meglumina, 2-morfolina etanol, 1-(2-hidroxietil)-pirrolidina, trietanolamina y trometamina; preferiblemente la amina se selecciona del grupo que consiste en L-arginina, dietiletanolamina, meglumina, trietanolamina y trometamina.
8. Una sal según una cualquiera de las reivindicaciones precedentes, donde la amina contiene dos o más grupos hidroxilo y/o uno o más grupos carboxílicos.
9. Una sal según la reivindicación 1, donde la amina solamente contiene uno o más grupos hidroxilo; preferiblemente solamente contiene dos o más grupos hidroxilo.
10. Una sal según la reivindicación 9, donde la amina se selecciona del grupo que consiste en deanol, dietanolamina, dietiletanolamina, etanolamina, meglumina, 2-morfolina etanol, 1-(2-hidroxietil)-pirrolidina, trietanolamina y trometamina; preferiblemente la amina se selecciona del grupo que consiste en

dietiletanolamina, meglumina, trietanolamina y trometamina; más preferiblemente del grupo que consiste en meglumina y trometamina.

11. Una sal según la reivindicación 1, donde la amina solamente contiene uno o más grupos carboxílicos.

12. Una sal según la reivindicación 11, donde la amina es L-arginina.

13. Una sal según la reivindicación 1, donde la amina se selecciona del grupo que consiste en meglumina y trometamina y, en el derivado de ácido amino nicotínico de fórmula (I), R^a representa un grupo seleccionado de átomos de halógeno y grupos alcoxi C_{1-2} que pueden estar opcionalmente sustituidos con 1, 2 o 3 átomos de halógeno; R^b representa un grupo seleccionado de átomos de hidrógeno y átomos de halógeno, R^c representa un grupo seleccionado de átomos de hidrógeno y grupos alquilo C_{1-2} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxí; y R^d representa un grupo seleccionado de átomos de hidrógeno y grupos alcoxi C_{1-2} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxí.

14. Una sal según la reivindicación 1, donde la amina es L-arginina y, en el derivado de ácido amino nicotínico de fórmula (I), R^a representa un grupo seleccionado de átomos de halógeno y C_{1-2} grupos alcoxi que pueden estar opcionalmente sustituidos con 1, 2 o 3 átomos de halógeno; R^b representa un grupo seleccionado de átomos de hidrógeno y átomos de halógeno, R^c representa un grupo seleccionado de átomos de hidrógeno y grupos alquilo C_{1-2} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxí; y R^d representa un grupo seleccionado de átomos de hidrógeno y grupos alcoxi C_{1-2} que pueden estar opcionalmente sustituidos con 1, 2 o 3 sustituyentes seleccionados de átomos de halógeno y grupos hidroxí.

15. Una sal según la reivindicación 1 seleccionada del grupo que consiste en:
sal de meglumina de ácido 2-[[3'-etoxi-3-(trifluorometoxi)-1,1'-bifenil-4-il]amino]nicotínico,

sal de meglumina de ácido 2-[[[(3,5-difluoro-2-metil-1,1'-bifenil-4-il)amino]nicotínico,

sal de trometamina de ácido 2-[[[(3,5-difluoro-2-metil-1,1'-bifenil-4-il)amino]nicotínico,

sal de meglumina de ácido 2-[[[(3,5-difluoro-3'-metoxi-1,1'-bifenil-4-il)amino]nicotínico,

sal de trometamina de ácido 2-[[[(3,5-difluoro-3'-metoxi-1,1'-bifenil-4-il)amino]nicotínico,

sal de L-arginina de ácido 2-[(3,5-difluoro-3'-metoxi-1,1'-bifenil-4-il)amino]nicotínico.

16. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de una sal como se ha definido en una cualquiera de las reivindicaciones precedentes y un vehículo farmacéuticamente aceptable.

RESEARCH ARTICLE

Impact of the counterion on the solubility and physicochemical properties of salts of carboxylic acid drugs

S.E. David^{1,3}, P. Timmins², and B.R. Conway^{3,4}

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Abstract

Aim: Salt formation is a widely used approach to improve the physicochemical and solid state properties of an active pharmaceutical ingredient. In order to better understand the relationships between the active drug, the selected counterion and the resultant salt form, crystalline salts were formed using four different carboxylic acid drugs and a closely related series of amine counterions. Thirty-six related crystalline salts were prepared, characterized and the relationship between solubility and dissolution behaviour and other properties of the salt and the counterion studied.

Methods: Salts of four model acid drugs, gemfibrozil, flurbiprofen, ibuprofen and etodolac were prepared using the counterions butylamine, hexylamine, octylamine, benzylamine, cyclohexylamine, tert-butylamine, 2-amino-2-methylpropan-1-ol, 2-amino-2-methylpropan-1,3-diol and tris(hydroxymethyl)aminomethane. Salt formation was confirmed, the salts were characterized and their corresponding solubilities determined and rationalized with respect to the counterions' properties.

Results and conclusion: The properties of the salt highly dependent on the nature of the counterion and, although there is considerable variation, some general conclusion can be drawn. For the alkyl amines series, increasing chain length leads to a reduction in solubility across all the acidic drugs studied and a reduction in melting point, thus contradicting simplistic relationships between solubility and melting point. Small, compact counterions consistently produce crystalline salts with high melting point accompanied with a modest improvement in solubility and the nature of hydrogen bonding between the ions has a major impact on the solubility.

Keywords: Salt selection, counterion, solubility, gemfibrozil, flurbiprofen, ibuprofen, etodolac, tris(hydroxymethyl)aminomethane

Introduction

Solid state modification offers the opportunity to alter unfavourable properties of active pharmaceutical ingredients (APIs) that may impact on successful development. Salification for ionisable drugs is a commonly employed strategy^{1,2} as the formation of a salt from a weakly acidic or basic drug will have a major impact on its properties including solubility, dissolution rate, hygroscopicity, stability, impurity profile and particle characteristics³. Modern high throughput automated processes of drug discovery are producing more lipophilic and increasingly

insoluble drugs⁴ and there are a number of studies focusing on streamlining the process of selection of an appropriate counterion for salt formation, often driven by physicochemical requirements, with non-optimal salt forms being systematically eliminated until the choice is narrowed down to likely candidates^{5–7}. Early identification of potential salt forms within the preformulation process can avoid delays and expense later in the development process⁸, however, the relationship between different solid crystalline forms and their properties is generally poorly understood, thus their properties are

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difficult to predict⁹ and conclusions regarding relationships between physicochemical properties and solubility have been contradictory and variable.

The most desirable properties are usually high solubility and dissolution rate, stability and crystallinity with the absence of polymorphic forms, usually followed by consideration of the ease of manufacture, formulation and processability. For dosage forms wherein the drug forms a large percentage of the formulation, the latter characteristics become more important with drug-carrying capacity of directly compressible tablets often limited to 25%¹⁰.

Inorganic counterions are most often used to modify a drug's properties: sodium is the most common cationic counterion used (65.3%^{3,11}) but the trend toward a broader diversity of counterions might be anticipated as more challenging molecules are selected for development. The solid state properties of crystalline salts depend largely on the nature of the counterion and rational salt selection, to optimize such properties based on predictive relationships between counterion choice and desired properties, has been suggested but only limited work exists in this area^{1,12}. Chowan¹³, Anderson and Conradi¹⁴ and Forbes et al¹⁵, investigated the effect of choice of counterions on the solubility of different carboxylic acids while Cheong and Choi¹⁶ sought to improve the physicochemical properties of piroxicam using ethanolamine. Only a small number of studies involve comparative evaluations of salts of weakly acidic drugs, including diclofenac¹⁷⁻²⁰, flurbiprofen¹⁴ and tris(hydroxymethyl)aminomethane salts of four anti-inflammatory drugs²¹.

The aim of this work was to conduct a systematic investigation of the impact of the counterion on salts of acidic drugs with the view to understanding the role of the counterion. Four carboxylic acids were selected due to their limited solubility in the unionized state: flurbiprofen, etodolac, gemfibrozil and ibuprofen (Figure 1). A range of different organic counterions was used to form the salts and the impact of the counterion on physicochemical and technological properties was studied. Rather than selecting only commonly used counterions, this study employs a related series of counterions, thus the impact of small structural changes on the properties can be studied in a systematic manner. The counterions used as the salt formers were butylamine (butyl), hexylamine (hex),

octylamine (oct) benzylamine (benz), cyclohexylamine (cyclo), tert-butylamine (tertBA), 2-amino-2-methylpropan-1-ol (AMP1), 2-amino-2-methylpropan-1,3-diol (AMP2) and tris(hydroxymethyl)aminomethane (tris) (Table 1).

Materials and methods

Materials

Gemfibrozil was supplied by DiPharma (Italy) and flurbiprofen was supplied by Erregierre (Italy). Ibuprofen was supplied by Sigma-Aldrich (Poole, UK). Etodolac was supplied by Ulkar Kimya (Istanbul). Tert-butylamine, AMP1, AMP2, tromethamine, benzylamine, cyclohexylamine, octylamine, hexylamine and butylamine were supplied by Sigma-Aldrich. Acetonitrile and methanol were supplied by Fisher (Loughborough, UK). All materials were of pharmaceutical, analytical or HPLC grade as appropriate.

Methods

Salt preparation

Crystalline salts were prepared by mixing equimolar amounts of drug and counterion dissolved in acetonitrile and the resultant crystals recovered by filtration under vacuum or following cooling to -4°C until crystals

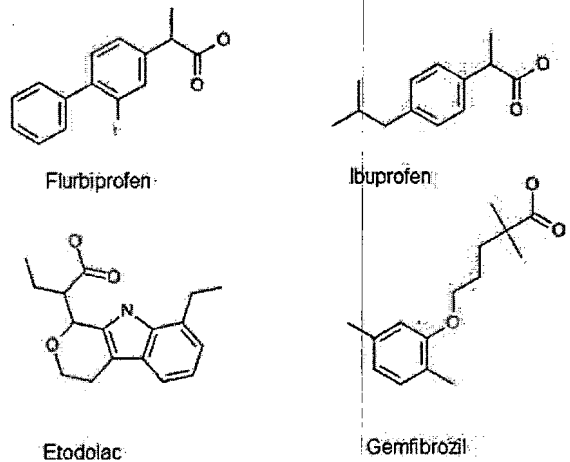


Figure 1. Chemical structures of the four carboxylic acid drugs.

Table 1. General molecular descriptors of amines used as counterions. *pK_a and logP values from the SPARC online calculator and ClogP version 4.0.

Drug	CLogP	pK _a	Counterion	CLogP*	pK _a *	Counterion	CLogP*	pK _a *
Etodolac	3.52	4.33,	Butylamine	0.92	10.33	Tert-butylamine	0.59	10.52
		4.65 ^a	Hexylamine	1.98	10.33	AMP1	-0.59	9.20
		4.35	Octylamine	3.04	10.33	AMP2	-0.59	7.94
Flurbiprofen	3.44	4.22 ^b	Benzylamine	1.09	9.36	Tris	-0.94	6.44
		4.72				Cyclohexylamine	1.37	10.52
		4.70 ^c						
Gemfibrozil	4.16	4.55						
		4.31 ^d						
Ibuprofen	3.68							

^aLee et al.⁴⁵; ^bAnderson and Conradi¹⁴; ^cGerbino⁴⁶; ^dSlater et al.⁴⁷.



appeared. For AMP1 and AMP2-containing salts, the amines were dissolved in a warmed solution of methanol which was added to a solution of the drug in acetonitrile, and the crystals collected by filtration. Products were dried overnight under vacuum and stored in sealed containers at room temperature until used.

Salt characterization

Nuclear magnetic resonance (NMR) and fourier-transform infra red spectroscopy (FTIR). Formation of 1:1 monovalent salts was confirmed using NMR and FTIR. Samples were dissolved in deuterated chloroform and chemical shifts and ¹H-NMR spectra were recorded on a Bruker AC 250 NMR (250 MHz) and a MAC Quadra 800 PC using WIN-NMR version 3.0 software was used to interpret the results. FTIR analysis of the drug or salt in KBr was carried out using a Unicam Mattson 3000 over 4000–400 cm⁻¹ with Galaxy software.

Thermal analysis. Differential scanning calorimetry (DSC) was performed using a Perkin Elmer PYRIS Diamond DSC. Each sample (3–5 mg) was accurately weighted and heated under nitrogen in vented pans at a scan rate of 10°C/min from 0°C to a temperature exceeding the melt or a maximum of 250°C. Thermogravimetric analysis (TGA) was performed on samples of between 5 and 10 mg using a Perkin Elmer Pyris 1 TGA over the temperature range 25–250°C in a nitrogen atmosphere.

Microscopy and powder X-ray diffraction. Crystal habit was assessed using a Nikon polarized light microscope over a range of magnification. Powder X-ray diffraction patterns of drug and salt samples and compacts were analyzed using a Rigaku Miniflex diffractometer (Rigaku, Sevenoaks, Kent, UK) with Cu K α radiation at 30 kV/15 mA. All samples were scanned from 2 to 60° 2 θ at a rate of 2° min⁻¹. Verification or standardisation tests for the instrument were conducted using mica and alumina reference standards.

True density measurements. The densities of the drug and salt powders were measured in triplicate using a Gemini Helium Pycnometer (Micromeritics, Dunstable, UK) and the pycnometer was calibrated before use.

Dynamic vapour sorption (DVS). Water vapour adsorption and desorption isotherms of the drugs and salts were measured in triplicate using a DVS-1 (Surface Measurement Systems, Alpertown, UK). Samples (~10 mg) were dried at 0% RH until a constant mass was obtained. Isotherms were constructed at 20°C over 0–100% humidity increased in increments of 10% after the equilibration of sample mass.

HPLC analytical method

High-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series HPLC system (Agilent Technologies, Wokingham, UK) with a G1312A

Binary Pump, G1313A ALS Auto-injector, G1316A COLCOM column section and a G1314A VWD variable wavelength detector. An ODS-2 Hypersil 150 cm $\times$ 4.6 mm 5 μ m column (ThermoScientific, Hemel Hempstead, UK) was used for all samples with a mobile phase of 65:35 acetonitrile:water (phosphoric acid 0.005% v/v), a flow rate of 1 ml/min and injection volume of 1 μ l. Gemfibrozil and its salts were analyzed at 276 nm; flurbiprofen and its salts were analyzed at 250 nm; ibuprofen and its salts were analyzed at 225 nm and etodolac and its salts were analyzed at 254 nm.

Determination of saturated solubility and intrinsic dissolution rate

Excess solid was added to double distilled water in triplicate, the vials sealed and stirred for 48 h under ambient conditions. Extracted samples were filtered through a 0.45 μ m PTFE syringe filter, the pH measured and samples diluted as appropriate with mobile phase prior to HPLC analysis. The saturated solubilities of model drugs and prepared salts were also measured at pH 6 using phosphate buffer.

Compressed tablets of drug or salt powder were made using a Specac KBr press and 13 mm die using a pressure of seven tonnes on a powder of weight 0.01 moles $\pm$ 2 mg with a 5 min dwell time and a 24 h recovery time. This was shown to provide a compact whose X-ray diffraction pattern closely matched that of the raw powder (XRPD not shown). The tablets were attached to PTFE holders²² which exposed only one face of the compact. USP apparatus 2 (Hanson SR11 6-flask dissolution system) was used at 50 rpm for dissolution studies and phosphate buffers at pH 6.8 and 7.2 were used for flurbiprofen experiments and gemfibrozil experiments respectively in order to achieve the equivalent degree of ionisation in the solutions. According to the SPARC online calculator (Table 1) there is a 0.4 unit difference in pK_a values which is subsequently represented in the choice of pH values that were used to run the experiments.

Statistical analysis

SPSS (version 12.0.1) statistical package was used to perform an analysis of variance (ANOVA) on the solubility and intrinsic dissolution data. A one-way ANOVA test was performed using a Tukey *post hoc* at a significance level of 0.001 (*P* = 0.05).

Results and discussion

Salt characterization

In order to develop an understanding of how the counterion impacts the salt properties, we have used a number of structurally related series of amine counterions which will impact on the physicochemical properties of the resultant salts formed. The estimated pK_a and logP values from the SPARC online calculator and ClogP version 4.0 were calculated for all materials and are summarized together with literature values in Table 1.



The salts were formed by combining an amine (R-NH₃⁺) ion with the anion of an organic carboxylic acid (COO⁻). As the bases had sufficiently high pK_a values, the salts were generally easily formed and precipitated from organic solvents. NMR and FTIR were used to verify salt formation with the total proton count in ¹H-NMR studies confirmed that all the salts had the expected number of hydrogen atoms present, had formed in a 1:1 ratio (as expected from the valencies) and the ¹H-NMR traces had an acceptable signal to noise ratio. A signal at 1684 cm⁻¹ in the FTIR spectra for the parent drugs, attributed to a C=O stretching of the carboxylic acid group^{17,18,23,24}, was absent in the salts and was replaced by bands characteristic of carboxylic acid salts, at 1650–1550 cm⁻¹ and 1440–1335 cm⁻¹(ref. 25). An additional band was present between 3350–3150 cm⁻¹, and is attributable to NH₃⁺ stretching of solid amine salts²⁵.

Salt forms of an API may be useful for reasons of purity, thermal stability, manufacturability, and ease of production and the goal is a solid, crystalline, stable material with improved physicochemical and mechanical properties. Melting point relationships are complex when considering salts, which are a combination of covalent bonds, ionic bonds and intermolecular forces. Whereas the melting points of covalently bonded molecules can be related to aqueous solubility²⁶, once another molecule is added by ionic bonds, this alters the physicochemical

characteristics in an unpredictable way. Generally on addition of the amine counterion to the carboxylic acid drug, a crystalline product was formed with a sharp melting point(s), confirmed by DSC and each salt had a characteristic and unique XRPD pattern indicative of the crystalline nature of the particular salt form. There was a reduction in melting point and enthalpy of fusion as chain length increased for the alkylamine homologous series of salts of all drugs (gemfibrozil, etodolac, flurbiprofen and ibuprofen; Tables 2–5). Some of the salts with longer alkyl chain lengths, often associated with increasing mobility, have lower melting points than the parent probably due to an increased chain length creating disorder in the crystal lattice^{27–29}.

The melting points of all tertBA, AMP1, AMP2 and tris salts are higher than the parent drug (Tables 2–5) with the exception of Etodolac AMP2. A desolvation/melt peak was seen using DSC with a concomitant weight loss at 100°C upon TGA suggesting the salt may be a solvate. DVS of this salt resulted in a mass change of 0.05% w/w when the humidity was reduced to zero which corresponds to the monohydrate form of the salt (Figure 2). The extent of hydrogen bonding in crystal lattices of tertBA, AMP1, AMP2 and tris salts will vary with the number of hydroxyl groups in the counterions impacting their melting point. The AMP2 salts have lower melting points than the other salts in the series

Table 2. Measured physicochemical properties and solubilities of etodolac salts.

Etodolac	Mean density (g/cm ³) ±SD	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.24 ± 0.001	151–153	29.4	7.72 × 10 ⁻⁴	4.42
Butylamine	1.15 ± 0.001	148–155	25.2	0.0489	6.78
Hexylamine	1.10 ± 0.004	140–143	28.8	0.0151	6.79
Octylamine	1.08 ± 0.013	111–113	27.6	3.69 × 10 ⁻³	6.42
Benzylamine	1.20 ± 0.001	164–165	48.2	8.01 × 10 ⁻³	6.97
Cyclohexylamine	1.60 ± 0.001	199–203	28.8	0.0126	7.30
Tert-butylamine	1.15 ± 0.001	177–185	23.7	0.0435	7.34
AMP1	1.24 ± 0.002	165–167	33.2	0.199	8.68
AMP2	1.25 ± 0.001	116–122*	32.1	>0.510	n/a
Tris	1.24 ± 0.001	159–161	58.2	0.248	7.26

*based on combined desolvation/melt peak.

Table 3. Measured physicochemical properties and solubilities of flurbiprofen salts.

Flurbiprofen	Mean. density (g/cm ³)	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.29 ± 0.001	115–117	24.7	1.35 × 10 ⁻⁴	4.20
Butylamine	1.16 ± 0.002	139–141	23.6	0.0169	7.43
Hexylamine	1.12 ± 0.001	87–91	27.5	0.021	7.20
Octylamine	1.10 ± 0.002	103–104	33.8	6.93 × 10 ⁻³	7.30
Benzylamine	1.21 ± 0.001	136–138	38.9	8.12 × 10 ⁻³	6.44
Cyclohexylamine	1.20 ± 0.002	197–201	47.8	1.08 × 10 ⁻³	6.50
Tert-butylamine	1.17 ± 0.002	193–198	46.7	8.74 × 10 ⁻³	7.00
AMP1	1.24 ± 0.001	154–157	33.6	0.0268	7.56
AMP2	1.32 ± 0.033	123–126	36.4	0.0311	6.00
Tris	1.32 ± 0.002	150–152	39.4	0.0304	6.70



Table 4. Measured physicochemical properties and solubilities of gemfibrozil salts.

Gemfibrozil					
	Mean. density (g/cm ³)	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.09 ± 0.001	62-64	22.3	8.79 × 10 ⁻⁵	5.40
Butylamine	1.07 ± 0.002	75-77	25.5	0.111	8.70
Hexylamine	1.05 ± 0.002	70-72	22.7	0.0106	7.80
Octylamine	1.04 ± 0.001	37-40	28.7	2.32 × 10 ⁻³	7.50
Benzylamine	1.10 ± 0.001	91-93	20.9	7.45 × 10 ⁻³	8.60
Cyclohexylamine	1.09 ± 0.001	135-137	41.2	9.94 × 10 ⁻³	7.10
Tert-butylamine	1.04 ± 0.002	141-146	24.7	0.0243	7.60
AMP1	1.12 ± 0.003	119-122	52.0	0.0353	7.70
AMP2	1.18 ± 0.001	104-106	28.7	0.085	7.70
Tris	1.20 ± 0.001	119-121	68.0	0.0228	7.50

Table 5. Measured physicochemical properties and solubilities of ibuprofen salts.

Ibuprofen					
	Mean. Density (g/cm ³)	Mp (°C)	Enthalpy of fusion (kJ/mole)	Aqueous Solubility (mol/L)	pH of saturated aqueous solution
Drug	1.11 ± 0.001	76-79	24.2	3.45 × 10 ⁻⁴	3.67
Butylamine	1.07 ± 0.001	104-106	19.3	0.583	8.37
Hexylamine	0.98 ± 0.004	91-94	20.3	0.0200	7.73
Octylamine	0.75 ± 0.001	80-82	21.4	4.93 × 10 ⁻³	7.19
Benzylamine	1.08 ± 0.001	107-109	25.9	7.99 × 10 ⁻⁴	7.35
Cyclohexylamine	1.12 ± 0.001	197-201	49.0	3.37 × 10 ⁻³	6.43
Tert-butylamine	1.02 ± 0.001	185-190	35.9	0.018	6.53
AMP1	1.11 ± 0.001	130-134	51.1	0.458	8.21
AMP2	1.15 ± 0.001	112-116	23.3	>0.643	n/a
Tris	1.20 ± 0.001	160-164	60.8	0.0274	6.67

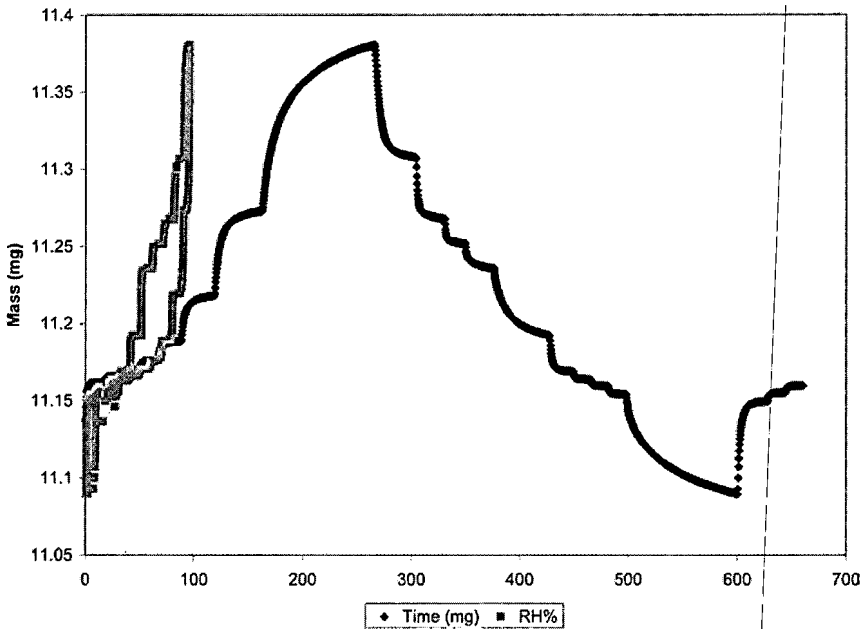


Figure 2. DVS data for etodolac AMP2 representing weight change over time and RH%.

(Tables 2-5) and generally have lower enthalpy values ($\Delta H_{\text{kJ}}/\text{moles}$) which, if a simple model were followed, would imply these would have the highest solubility within the groups³⁰.

The cyclohexylamine salts of all the drugs have high melting points, relative to the other salts, and have high enthalpies of fusion but the introduction of a benzylamine group may increase the risk of polymorph formation,



with both gemfibrozil benzylamine and ibuprofen benzylamine showing evidence of polymorphism. The ibuprofen benzylamine salt DSC analysis showed two peaks between 100°C and 120°C, (Figure 3). On reheating the sample under the same conditions a single peak was produced at 109°C, Figure 2. DVS results for ibuprofen benzylamine indicated that water was not present in the molecule but TGA revealed a decrease in mass (-1.5%) at a temperature exceeding the endothermic event on the DSC scan. No weight was lost at the temperature corresponding to the onset of the first endothermic event, therefore, two polymorphic forms of this salt may exist, one of which converts to the other on heating.

Upon heating, the TGA of gemfibrozil benzylamine reveals a loss of ~1% at a temperature exceeding the endothermic events on the DSC scan, indicating possible polymorph formation. The two forms of gemfibrozil benzylamine that are shown in Figure 4 resulted from the same preparation conditions and production of polymorphs is common when crystallising salt forms and has previously been described by O'Connor and Corrigan¹⁸ for benzylamine and AMP1 salts of diclofenac.

Drug salts should normally be selected to be non-hygroscopic, i.e. normally an upper limit of 0.5% at 90% RH³¹ although this figure has been reported to be as high as 2% at 25°C/60% RH^{32,33}. Without formation of a stable hydrate, water uptake of more than 5% at this condition will probably require major efforts in formulation development and compound handling. Despite the hygroscopic nature of some of the amine counterions used (e.g. tris) salt forms were generally stable to humidity as indicated by limited hysteresis in the change in mass versus humidity graphs (data

not shown). The largest change in mass was observed with gemfibrozil AMP1 and flurbiprofen AMP2 which showed a slight hysteresis on desorption and over 1% change in mass over the humidity range studied (2.00% and 1.30%, respectively).

True density

The true density plays a critical role in determination of powder porosity³⁴ and particle mechanical properties^{35,36}, indicating on a macro scale how the crystal lattice is arranged. Differences in the true density between polymorphic forms can be attributed to different packaging of molecules in the crystalline structure. For the straight-chain alkylamine series, the highest densities corresponded with the shortest chain length (Tables 2-5).

A variety of crystal habits resulted from the specified crystallisation conditions which will influence their pharmaceutical handling properties. Over 60% of the 40 crystalline materials studied were either needle-like crystals or agglomerated needle crystals, such as Gemfibrozil AMP1 crystals (Figure 5A) and would be predicted to have poor flow and poor compressional properties. Flurbiprofen hexylamine and octylamine salts formed plate-like crystals (Figure 5B) and gemfibrozil butylamine and tris salts formed prisms and tabular crystals (Figure 5C), which could improve compression and flow properties. Etodolac salts had different crystal morphologies, e.g. the benzylamine salt formed prisms while the tert-butylamine salt existed in plates. The ibuprofen tris and hexylamine salts formed lath-like crystals, whereas ibuprofen AMP1 salt existed as small tabular crystals.

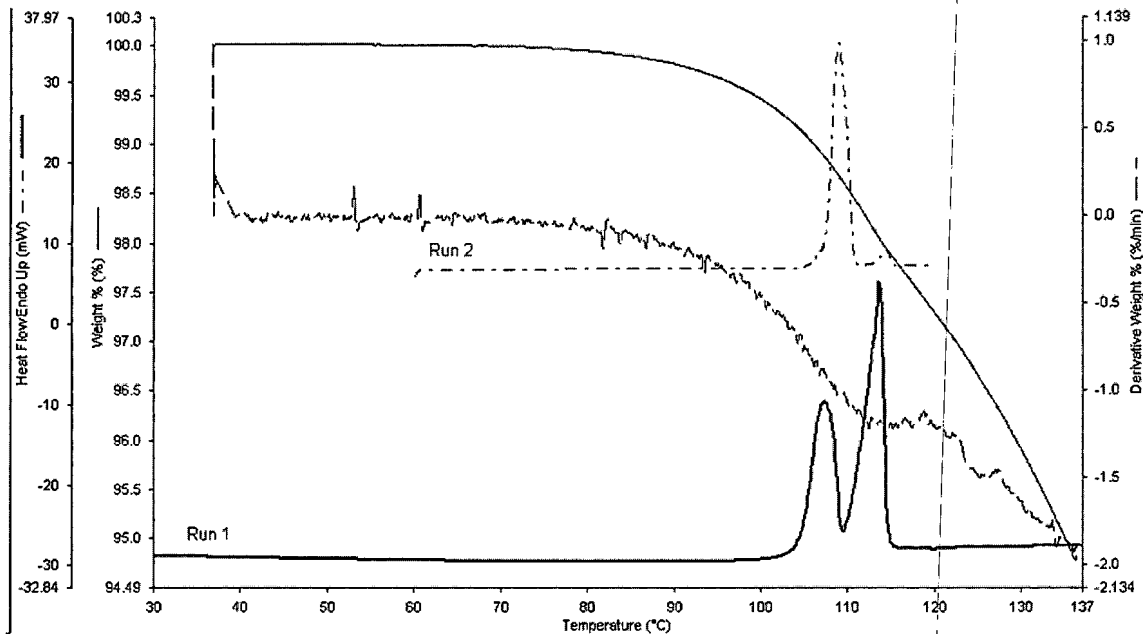


Figure 3. DSC and TGA profiles for ibuprofen benzylamine. Ibuprofen benzylamine upper scan is the second repeat of the run.



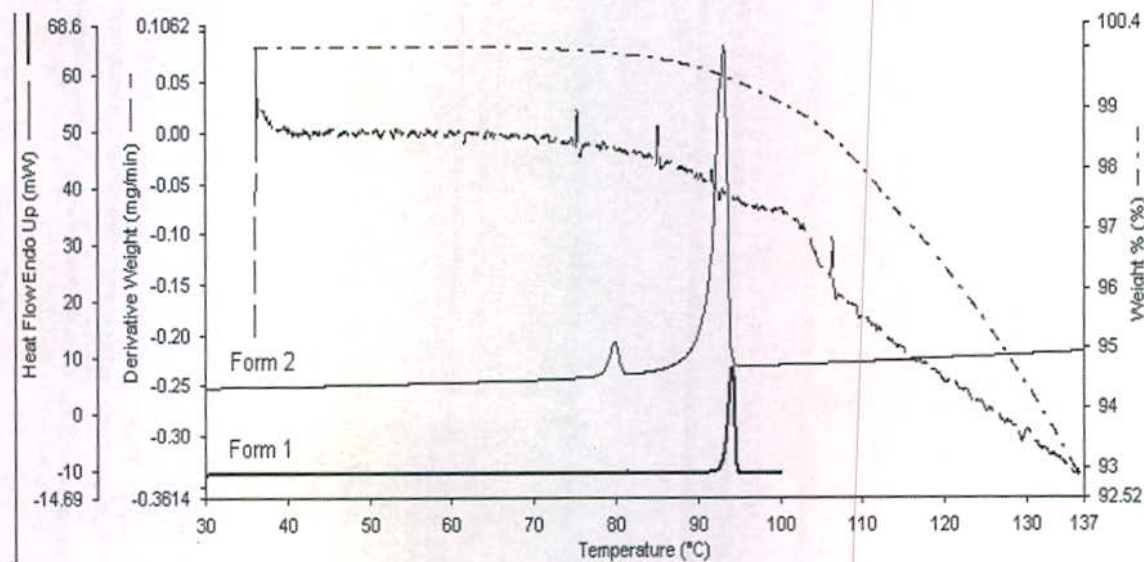


Figure 4. DSC and TGA profiles for the benzylamine salt of gemfibrozil showing the presence of proposed polymorphic form 2.

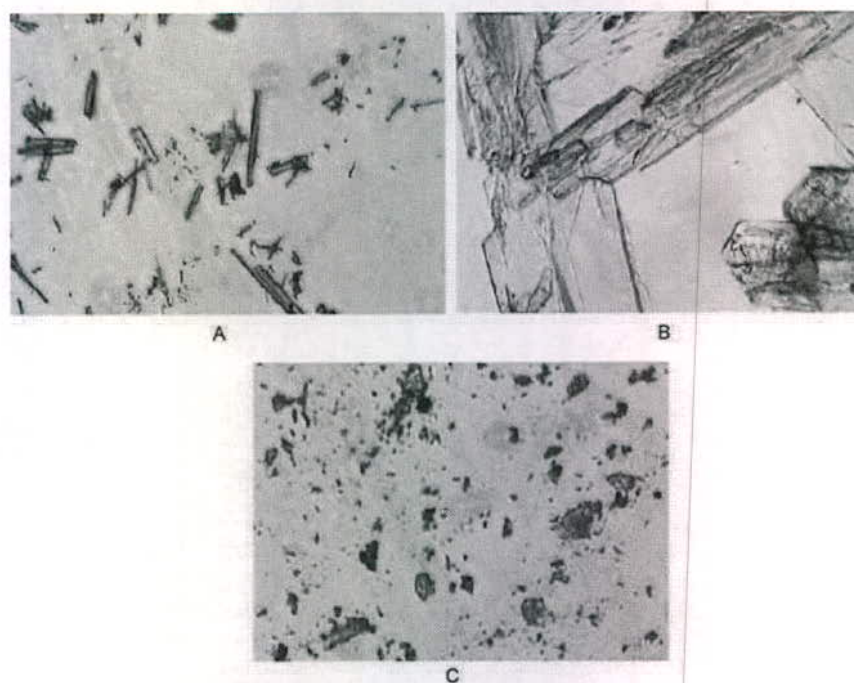


Figure 5. (A) Gemfibrozil AMP1 crystals x20. (B) Flurbiprofen octylamine crystals x10. (C) Gemfibrozil tris crystals x20.

Effect of the counterion on solubility and intrinsic dissolution rate

The molar solubilities of the salt forms vary over several orders of magnitude, over four orders of magnitude for ibuprofen salts. Solubility increases with chain length for salts of all drugs of the homologous alkylamine series, from highest to lowest (i.e. butylamine > hexylamine > octylamine). As the chain length increases the lipophilicity of the counterion increases and aqueous solubility

reduces. Combining these data with the melting point information from the DSC identifies a trend such that as melting point reduces, solubility is also reduced. This contradicts the attractive notion that as melting point reduces, solubility increases due to the reduced energy required to break the crystal lattice¹.

Over the range of amine salts studied here (etodolac ($n=10$), flurbiprofen ($n=11$), gemfibrozil ($n=10$) and ibuprofen ($n=10$)), no relationship was found between



salt melting point and solubility. This implies that melting point relationships are complex when considering salts, due to the complex nature of association with the counterion. Studies correlating solubility and melting point for salts of acidic drugs have produced mixed results including an inverse linear relationship between the logarithm of salt solubility and melting point^{30,37}, a direct relationship between the inverse of the melting point and the logarithm of the solubility³⁸ while Anderson and Conradi¹⁴ reported a non-linear relationship between the salt melting point and log K_{sp} (stoichiometric solubility) for a series of flurbiprofen salts. O'Connor and Corrigan¹⁸ observed a trend between salt melting point and the logarithm of the solubility and between the inverse of the melting point and the logarithm of the solubility for a selection of amine salts of diclofenac. Conversely, Gu and Strickley²¹ concluded that no simple solubility-melting point relationship could be established for tris(hydroxymethyl)aminomethane salts of four anti-inflammatory drugs.

Within the extended range of amine salts studied here for four different carboxylic acid drugs (etodolac ($n=9$), flurbiprofen ($n=9$), gemfibrozil ($n=9$) and ibuprofen ($n=9$)), no relationship was found between salt melting point and solubility, and simplistic relationships based on lipophilicity of the counterion have limited predictive reliability and a deeper understanding of the role of the counterion is required. Neither the cyclohexylamine nor benzylamine is as effective at improving solubility as the butylamine or the hydrophilic counterions (AMP1, AMP2 and tris). Benzylamine and cyclohexylamine are closely related structurally counterions and all their salt forms studied are more soluble than the acid (Tables 2-5), and cyclohexylamine as a counterion results in a greater enhancement of molar solubility (8-118-fold) in all cases.

Thus, cyclohexylamine salts have higher melting points, are slightly more lipophilic and are yet more soluble than corresponding benzylamine salts similar to the results of Parshad et al³⁹, who found that salt solubility increased as lipophilicity increased for salts of benzylamine derivatives with *p*-substituted benzoic acids.

The tert-butylamine counterion results in a over 50- to over 225-fold increase in solubility across the range of drugs (Tables 2-5). The presence of a single hydroxyl group (AMP1 salts) in the four carbon amine series increases the solubility compared to the parent drug from 200-fold to more than 1300-fold; a substantial enhancement compared to the tert-butylamine salts. For AMP2 salts, there is a large increase in solubility, over 1800-fold for ibuprofen AMP2, compared to the acidic drug, an increase factor similar to that of the butylamine counterion. For two salts within this study, etodolac AMP2 and ibuprofen AMP2, it was not possible to obtain a saturated aqueous solution. As the concentration was increased above 200 mg/ml, "foaming" was observed, and these materials were shown to demonstrate surfactant-like properties and CMC values were determined (7.65×10^{-2} M for etodolac AMP2 and 6.43×10^{-2} M for ibuprofen AMP2) (data not shown). For these samples a maximum measurable solubility was used to demonstrate the effect of the AMP2 counterion on solubility.

There is no further increase in solubility with additional hydroxyl groups (i.e. tris salts). Thus increasing hydrophilicity of the counterion is beneficial in solubility enhancement up to two hydroxyl groups. A similar result has been reported for diclofenac but solubility was maximal with the AMP1 salt¹⁸ and the diclofenac tris salt had the lowest solubility in the series⁴⁰. As the number of hydroxyl groups increases, the potential for hydrogen bonding increases. We have previously shown that the

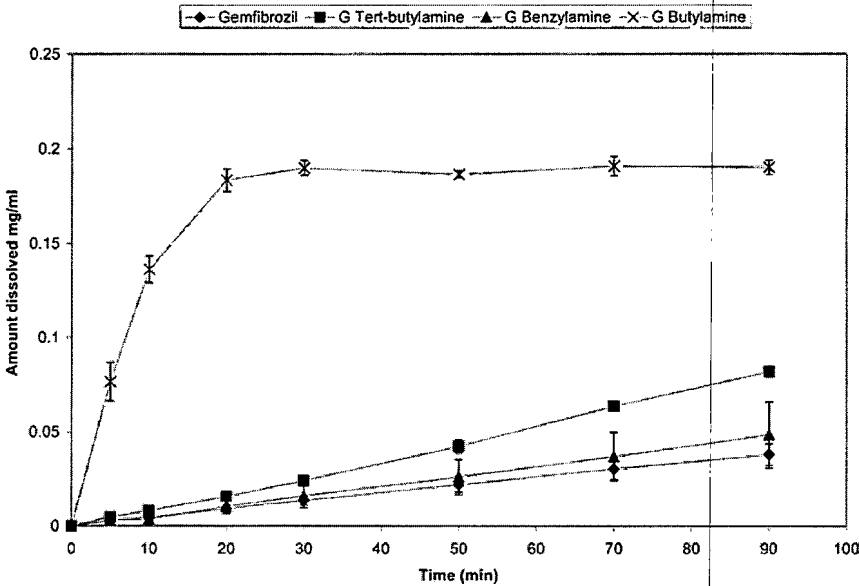


Figure 6. Intrinsic dissolution profiles for gemfibrozil and its salts in phosphate buffer pH 7.2.



Table 6. Solubility of selected salts in pH 6 buffer (n=3; mean ± SD).

Material	Solubility (mg/ml)	pH	Material	Solubility (mg/ml)	pH
Etodolac	2.11 ± 0.399	5.97	Flurbiprofen	0.480 ± 0.038	5.80
E butylamine	2.52 ± 0.357	6.15	F butylamine	0.735 ± 0.102	5.93
E hexylamine	1.32 ± 0.223	5.75	F hexylamine	0.955 ± 0.086	6.40
E AMP1	2.19 ± 0.156	6.12	F AMP1	0.569 ± 0.159	5.88
E AMP2	2.51 ± 0.346	6.22			
Gemfibrozil	0.038 ± 0.058	6.50	Ibuprofen	1.62 ± 0.284	6.10
G butylamine	0.263 ± 0.020	6.48	I butylamine	1.33 ± 0.130	5.89
G hexylamine	0.475 ± 0.020	6.62	I hexylamine	1.93 ± 0.041	6.35
G AMP1	0.232 ± 0.056	6.28	I AMP1	1.58 ± 0.110	6.05
			I AMP2	4.71 ± 0.034	6.55

F indicates salts of flurbiprofen and E, etodolac; G indicates salts of G, gemfibrozil and I, ibuprofen (n=3; G butylamine data represents first three data points only).

free acid and t-butylamine, AMP1, AMP2 salts of gemfibrozil have a common crystal packing motif comprising infinite H-bonded chains with cross-linking between pairs of adjacent chains. The sets of chains interact via van der Waals forces. The tris salt, with its increased capacity for hydrogen bonding, forms a different crystal structure comprising a two dimensional sheet-like network of H-bonds with complex intermolecular forces which are more difficult to break⁴¹. This accounts for the relatively lower solubility of the tris salt⁴².

O'Connor and Corrigan¹⁸ reported that there was a linear log-log relationship between [H⁺] and salt solubility for a range of diclofenac salts including benzylamine, tert-butylamine, AMP1, AMP2 and tris. In this study, there was a linear relationship between the logarithm of the concentration and the pH of the saturated solution, (R²=0.71 n=9), flurbiprofen (R²=0.45 n=9), gemfibrozil (R²=0.69 n=9) and ibuprofen (R²=0.71 n=9) was determined. When the pH of the vehicle is not controlled, the diffusion layer model proposes that the pH of the saturated solution represents the pH of the theoretical diffusion layer surrounding the salt as it dissolves.

When using a buffer at a controlled pH, the diffusion layer is maintained at that fixed pH, thus inhibiting the dissolution of the drug-salt within the diffusion layer. The saturated solubility of selected salts was therefore also determined at pH6 and only a small increase in solubility was observed and in some cases, there was a reduction in solubility compared to the parent compound (Table 6). DSC studies showed that incubation with aqueous buffer did not lead to any phase changes in the material. The solubility of gemfibrozil at pH 6.5 was lower than that of the other acids, according to its very low intrinsic solubility (calculated here as 0.0038 mg/ml) and solubility has been found to remain below 0.03 mg/ml until pH 5.5⁴³. The etodolac salt series showed no increase in solubility for each salt and the hexylamine counterion reduced the solubility. Only the ibuprofen AMP2 salt showed a 2.9-fold increase in solubility, but this result could be due to the elevated buffer pH compared to parent (Table 6). From these data, it can be concluded that the increased solubilities observed when the pH of the saturated solution was not controlled are due to the counterion affecting

Table 7. IDR results for flurbiprofen, gemfibrozil and its cyclohexylamine, tert-butylamine and benzylamine salts.

Material	IDR (mg/min/cm ²)	Correlation coefficient r ²
Flurbiprofen	0.00062	0.9886
F cyclohexylamine	0.00013	0.9945
F tert-butylamine	0.00046	0.9998
F benzylamine	0.00057	0.9998
Gemfibrozil	0.00032	0.9991
G butylamine	0.00890	0.9200
G tert-butylamine	0.00089	0.9976
G benzylamine	0.00041	0.9985

the pH of the solution. This explains why the solubility is not elevated for all of the salts formed.

It was not possible to produce a full set of IDR results due to the poorly compressible nature of the parent drugs and some of the salt forms⁴⁴. The IDR profiles for both flurbiprofen and gemfibrozil and their salts are linear (Table 7) with the exception of gemfibrozil butylamine which dissolved too rapidly to accurately determine IDR (Figure 5). IDR rank order for the salts mirrors the order of solubility i.e. flurbiprofen benzylamine>tert-butylamine>cyclohexylamine. The salts of gemfibrozil show the largest enhancement in dissolution, significantly higher for gemfibrozil butylamine (p=0.05), compared to the other salts and gemfibrozil. Flurbiprofen has the highest IDR at pH 6.8 but it is only significantly different to the flurbiprofen cyclohexylamine salt (p=0.05), and is similar to the other salts tested. For the flurbiprofen series, the cyclohexylamine salt has a significantly different IDR than benzylamine (p=0.05), and the tert-butylamine salt has a similar IDR to the other salts (p=0.05). From the IDR experiments it can be concluded that dissolution characteristics can be related to saturated aqueous solubility data and that a rank dissolution order can be elucidated from solubility data.

Conclusion

Modification of the molecular properties of a drug to overcome a limiting factor, most often solubility, is common but the salt form will influence a range of other

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properties including dissolution rate, melting point, stability, hygroscopicity, crystal form and mechanical properties. Rational salt selection could therefore improve dissolution rates, solubility, bioavailability and may influence the mechanical properties of poorly soluble compounds. This paper employs a series of amine counterions with a selection of carboxylic acid drugs with the view to understanding the role of the counterion in salt formation.

Using a homologous series of amines, the significance of the counterion in controlling salt properties was investigated and increasing chain length leads to a reduction in melting point and a reduction in solubility across all the acidic drugs studied.

Addition of hydrophilic groups within the amine counterion increases solubility, reduces melting point and increases the likelihood of surface activity, up to a threshold of value of two OH groups in the counterion series studied. Despite the additional hydroxyl group in tris salts, solubility is not enhanced further as complex intermolecular hydrogen bonding can contribute to a strong crystal lattice.

Rational salt selection should begin with selecting small, compact counterions to improve solubility. Addition of a hydrophilic group improves the solubility characteristics however, the presence of additional H-bonding capacity can result in additional, possibly undesirable properties; for example polymorphism and hydrate formation. Benzylamine (unsaturated species) salts are prone to polymorphs so should not be used for salt formation. Cyclohexylamine and tert-butylamine counterions (small, rigid and compact) consistently produce a crystalline product with a high melting point and a modest improvement in solubility, which can improve the characteristics of an unstable drug. These counterions do not have a tendency for polymorphism or hygroscopicity so may be a useful salt formers. The nature of the hydrogen bonding between the anion and cation will change for each counterion and this will have an impact on the crystal structure and properties.

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Declaration of interest

The authors report no declarations of interest.

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Preparation and characterisation of a range of diclofenac salts

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Abstract

Physicochemical properties of diclofenac salts prepared using eight different counterions and including five novel salts, obtained with the bases 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methylpropanol, *tert*-butylamine, benzylamine and deanol, were compared. Four of the bases used to prepare these salts were related in their chemical structure, differing only in the number of hydroxy groups. Characterisation techniques included X-ray diffraction, differential scanning calorimetry, thermogravimetric analysis, thermomicroscopy, Karl Fischer titration, FT-IR spectroscopy and elemental analysis. In the case of salts prepared from 2-amino-2-methylpropanol and benzylamine, two polymorphic forms of each salt were identified. For the 2-amino-2-methyl-1,3-propanediol salt, a pseudopolymorphic form was identified. The aqueous solubilities of the salts studied ranged from 3.95 mM (tris(hydroxymethyl)aminomethane salt) to 446 mM (deanol salt), corresponding to a 113-fold difference in solubility. The solubility of diclofenac deanol was higher than the solubilities for diclofenac salts reported earlier. Correlation was found between the inverse of the salt melting point and the logarithm of salt solubility. A log–log relationship was observed between salt solubility and hydrogen ion concentration in the salt solution. Relationships between the properties of the salt-forming agents and those of the resulting diclofenac salts were explored. Reasonable correlation was found between the free base melting point and the salt melting point. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Salts; Diclofenac; Tris(hydroxymethyl)aminomethane; 2-Amino-2-methyl-1,3-propanediol; 2-Amino-2-methylpropanol; *tert*-Butylamine; Benzylamine

1. Introduction

Salt formation is a simple means of modifying

the properties of a drug having ionisable functional groups in order to overcome some undesirable feature of the parent drug (Anderson and Conradi, 1985). The physicochemical characteristics and resultant biological performance of a drug can be dramatically altered by conversion to a salt form (Berge et al., 1977; Bighley et al., 1996).

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Salt-forming agents are often chosen empirically. The preferred salt form is selected after considering the practical issues such as cost of raw materials, ease of crystallisation and percent yield and other basic considerations such as stability, hygroscopicity and flowability of the resulting salt form (Berge et al., 1977).

Ideally, it would be useful to be able to predict the salt properties from the properties of the counterion used. Several studies have described the dependence of salt properties on the nature of the counterion used (Chowhan, 1978; Gould, 1986; Pandit et al., 1989; Forbes et al., 1995). In addition, studies have been carried out to investigate quantitative relationships between counterion characteristics and properties of the resulting salt form (Anderson and Conradi, 1985; Gould, 1986; Rubino, 1989; Thomas and Rubino, 1996). Unfortunately, no reliable way of predicting the influence of a salt-forming agent on the behaviour of the parent compound has been reported. Only qualitative 'rules of thumb' are generally found. For example, increasing the hydrophilicity of the counterion has been proposed as a means of increasing the water solubility of the resultant salt, as reported for a series of erythromycin salts (Jones et al., 1969). However, these qualitative rules may not be very reliable (Anderson and Flora, 1996). Therefore, selection of an appropriate counterion to produce a salt with the desired combination of properties is still being carried out on an empirical basis.

Diclofenac, 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid (D), is a potent non-steroidal anti-inflammatory drug, therapeutically used in inflammatory and painful conditions of rheumatic and non-rheumatic origin. It is an acidic compound (pK_a 3.80 at 25 °C) with very low aqueous solubility (6×10^{-5} M at 25 °C) in the unionised form (Chiarini et al., 1984). Many studies have been carried out on the modification of the solubility and dissolution rate of diclofenac by the preparation of salts from a variety of inorganic and organic bases (Fini et al., 1991a,b, 1993a,b, 1994a, 1995a, 1996). However, no trends have been established between

counterion characteristics and the properties of the resultant salt forms.

In order to advance our understanding of diclofenac salts, a range of salts was prepared and examined. Six basic organic compounds were selected for salt formation. These are listed, with the abbreviations used and the chemical structures, in Table 1.

The study included four primary amines, each having four carbons and zero, one, two or three hydroxyl group(s), respectively; *tert*-butylamine (tBA), 2-amino-2-methylpropanol (AMP), 2-amino-2-methyl-1,3-propanediol (AMPD) and tris(hydroxymethyl)-aminomethane (TRIS). In addition, salts of the four-carbon, tertiary amine, deanol (DNL), and the aromatic primary amine, benzylamine (BA), were included in the study.

Tris(hydroxymethyl)aminomethane is used as an alkalisng agent in the treatment of metabolic acidosis (Martindale, 1999). It is a commonly used base in the preparation of salts (Roseman and Yalkowsky, 1973; Gu and Strickley, 1987; Wang and Chowhan, 1990; Gabr and Borg, 1999), including some commercially marketed salts (Berge et al., 1977). It has been used earlier to prepare a salt with diclofenac (Fini et al., 1996). The four-carbon primary amines selected (tBA, AMP, AMPD and TRIS) were used by Anderson and Conradi (1985) in a study involving the preparation of a series of salts of the non-steroidal anti-inflammatory drug, flurbiprofen. The study investigated possible relationships between the solubilities of the salts and their melting points and cation hydrophilicities. Deanol and benzylamine were used previously by Hirsch et al. (1978) to form salts with fenoprofen in an attempt to increase the stability of the drug.

Relevant physical properties of the six bases selected are outlined in Table 2. The salts formed using these counterions were characterised by differential scanning calorimetry (DSC), thermogravimetric analysis (TG), thermomicroscopy, X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and elemental analysis.

2. Materials and methods

2.1. Materials

Salts were prepared from diclofenac acid (AMSA) and the following bases: AMP (Sigma), AMPD (Sigma), DNL (Sigma), BA (Sigma), TRIS (Aldrich) and *t*BA (Aldrich). The solvents used for salt preparation were acetone (BDH), methanol (Riedel-de Haën) and ethyl acetate (Riedel-de Haën).

2.2. Preparation of diclofenac salts

Salts were prepared by dissolving diclofenac acid in an appropriate solvent and mixing in an equimolar amount of base dissolved in the solvent. Initial attempts to prepare each salt were carried out using acetone. If acetone was found to be inappropriate, preparation was carried out using methanol or ethyl acetate. The resulting product was recovered by filtration under vacuum in cases where a precipitate resulted. If no precip-

Table 1
Bases selected for the preparation of diclofenac salts

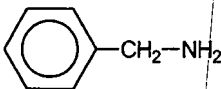
Name	Abbreviation	Chemical Structure	log P
<i>tert</i> -butylamine	<i>t</i> BA	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3 - \text{C} - \text{NH}_2 \\ \\ \text{CH}_3 \end{array} $	1.19
2-amino-2-methylpropanol	AMP	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3 - \text{C} - \text{NH}_2 \\ \\ \text{CH}_2\text{OH} \end{array} $	1.04
2-amino-2-methyl-1,3-propanediol	AMPD	$ \begin{array}{c} \text{CH}_2\text{OH} \\ \\ \text{CH}_3 - \text{C} - \text{NH}_2 \\ \\ \text{CH}_2\text{OH} \end{array} $	0.89
tris(hydroxymethyl)aminomethane	TRIS	$ \begin{array}{c} \text{CH}_2\text{OH} \\ \\ \text{HOCH}_2 - \text{C} - \text{NH}_2 \\ \\ \text{CH}_2\text{OH} \end{array} $	0.74
benzylamine	BA		1.69
2-(dimethylamino)ethanol or deanol	DNL	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3 - \text{N} \\ \\ \text{CH}_2\text{CH}_2\text{O} \end{array} $	0.92

Table 2
Properties of bases selected for the preparation of diclofenac salts

Base	Molecular weight	pK _a	Melting point (°C)	Boiling point (°C)	Solubility/miscibility ^a
tBA	73.14	10.69 ^b	−66.9 ^c	44 ^c	Miscible with alcohol
AMP	89.14	9.69 ^b	25.5 ^c	165.5 ^c	Miscible with water; soluble in alcohols
AMPD	105.14	8.80 ^b	109–111 ^a	151–152 ^a	250 g dissolved in 100 ml water at 20 °C; soluble in alcohols
TRIS	121.14	8.30 ^a	171.5 ^c	219–220 ^c	Solubility in water: 550 mg/ml at 25 °C; soluble in alcohol, acetone, methanol
BA	107.2	9.35 ^b	10 ^b	185 ^c	Miscible with water, alcohol, ether
DNL	89.14	9.26 ^b	−59°C ^c	134 ^c	Miscible with water, alcohol, ether
DEA	73.14	10.84 ^d	−49.8 ^c	55.5 ^c	Miscible with water, alcohol
HEP	115.18	9.72 ^e	< −60 ^f	79–81 ^g	–

^a From Merck Index (1996).

^b From Dean (1987).

^c From CRC Handbook of Chemistry and Physics (1995).

^d From Albert and Serjeant (1984).

^e From Fini et al. (1994a).

^f Information obtained by DSC: temperature reduced to −60 °C (2 °C/min), no thermal events observed.

^g Supplier's catalogue.

itate was formed, the product was recovered by removing excess solvent using a Büchi Rotavapor apparatus linked to a Büchi vacuum system. All products were allowed to dry by exposure to ambient conditions for 48 h. Salt formation was confirmed by powder X-ray diffraction, differential scanning calorimetry, infrared spectroscopy and elemental analysis.

2.3. Powder X-ray diffraction

Powder X-ray diffraction measurements were carried out on a Siemens D500 X-ray powder diffractometer. Powdered samples were mounted in conventional cavity mounts; compressed discs were mounted in a holder with a 13 mm diameter aperture. Samples were scanned in the 2θ range of 5–35° at a rate of 3°/min.

2.4. Differential scanning calorimetry

Differential scanning calorimetry was performed on powdered samples ($n = 3$) using a Mettler Toledo DSC 821^e, with Mettler Toledo STAR^e software version 5.1. Unless otherwise specified, each sample (5–10 mg) was run in sealed aluminium pans with three vent holes pierced in the

lid. Each run was carried out under nitrogen purge at a heating rate of 10 °C/min (unless otherwise specified). The onset temperature and enthalpy change for each thermal event was calculated.

2.5. Thermogravimetric analysis

Thermogravimetric (TG) analysis was carried out on powdered samples (5–10 mg) using a Mettler TG 50 linked to a Mettler MT5 balance. Data was processed using Mettler Toledo STAR^e software version 5.1.

2.6. Thermomicroscopy

Thermomicroscopy was carried out on a Reichert hot stage with and without crossed polarising filters. Samples were mounted in air or in silicone oil (to detect desolvation).

2.7. Karl Fischer titration

Karl Fischer titrations (KFT), for the determination of water content, were carried out on powdered samples using Metrohm 701 KF Titrino linked to a Metrohm 703 Ti stand. All analyses were performed in triplicate.

2.8. Elemental analysis

Elemental analysis (C, H, N) was carried out on powdered samples (~2 mg) using an Exetor Analytical CE440.

2.9. Fourier transform infrared spectroscopy

FT-IR spectra were obtained from 32 scans over the range of 4000–400 cm^{-1} (Nicolet 205). KBr discs were prepared by grinding 5–10 mg sample with 100 mg KBr.

2.10. UV assay for the determination of diclofenac concentration

Diclofenac was assayed by measurement of UV absorbance at $\lambda = 276 \text{ nm}$ (Adeyeye and Li, 1990) using a Hewlett–Packard 8452A diode array spectrophotometer.

2.11. Solubility studies

Equilibrium solubilities were determined using a modification of the sealed ampoule method of Mooney et al. (1981). Excess solid (approximately 2–3 times the estimated solubility) was placed in 5 ml deionised water in a 10 ml glass ampoule, which was then heat-sealed. Ampoules were placed in a shaker water bath (Precision Scientific) at 25 °C and agitated at 150 cycles/min. At 24, 48 and 72 h, samples were withdrawn from the ampoules, filtered through a 0.45 μm filter (Gelman Sciences), diluted appropriately and assayed for the drug content. The pH of the filtered solution was determined using an Orion Model 520A pH meter. Solubility determinations were carried out in triplicate. Where relevant, at the end of a solubility determination, the solid was recovered for powder XRD analysis, to ascertain any possible phase changes.

2.12. Intrinsic dissolution rate determination

Intrinsic dissolution rate (IDR) studies were performed using the USP 24 paddle method (United States Pharmacopeia, 2000). Discs were

prepared by compressing 200 mg of powder in a Perkin–Elmer hydraulic press, for 5 min under 8 ton of pressure, using a 13 mm punch and die set. Analysis of the compressed discs by XRD confirmed that the crystal form of the original powder was retained following the compression procedure. Paraffin wax was used to mount the discs in stainless steel disc holders, leaving one face exposed (surface area, 1.327 cm^2). The dissolution runs were carried out at 25 °C in 900 ml deionised water at 50 rpm (Sotax AT7 dissolution bath). Aliquots (5 ml) were withdrawn at 5, 10, 15, 20 and 25 min intervals, filtered through a 0.45 μm filter (Gelman Sciences), diluted if necessary and assayed for drug content. The withdrawn sample was replaced with 5 ml of deionised water. All dissolution runs were carried out in triplicate, in sink conditions. The initial linear portion of each dissolution profile (0–15 min) was used to derive the intrinsic dissolution rate.

3. Results and discussion

3.1. Characterisation of salt forms prepared

The XRD traces and DSC scans for the salt products are presented in Figs. 1 and 2, respectively. Using FT-IR, salt formation could be established by: (a) the absence of the carboxylic acid peak at 1684 cm^{-1} (Silverstein and Webster, 1998; Palomo et al., 1999); (b) the presence of bands characteristic of carboxylic acid salts, at 1650–1550 and 1440–1335 cm^{-1} (Socrates, 1994); and (c) absorption at 3350–3150 cm^{-1} , attributable to NH_3^+ stretching of solid amine salts (Socrates, 1994). The FT-IR spectra for each of the products were consistent with salt formation.

3.1.1. Diclofenac *tert*-butylamine (DtBA)

The DSC scan for DtBA, the salt formed between diclofenac acid and *t*BA from acetone, displayed an endothermic peak with an onset temperature of 153 °C, followed by a larger endothermic peak over the temperature range of

160–200 °C. The TG trace showed a marked increase in the rate of weight loss at a temperature corresponding to the onset of the second endotherm. Examination of the sample by thermomicroscopy revealed complete melting of the sample in the temperature range of 145–155 °C, corresponding to the first endotherm in the DSC scan. No further events were observed. The broad nature of the trace for the second endotherm and the sharp increase in the rate of weight loss suggested the occurrence of degradation at that temperature. Therefore, the two endotherms in the DSC scan (onset temperatures, 153 and ~160 °C) may result from melting of the salt, followed by degradation. The onset value of the first endotherm, 153 °C, was considered to be the melting point of DtBA.

3.1.2. Diclofenac 2-amino-2-methylpropanol (DAMP)

When the salt preparation procedure was carried out using AMP as the basic counterion, two different products were identified, DAMP-I and DAMP-II, prepared using 35 and 7.5% w/v of drug in acetone, respectively. The XRD patterns (Fig. 1) were found to differ in their peak position and relative intensities. The DSC trace for DAMP-I showed a melting peak with an onset value of 182 °C, followed by the broad volatilisation–decomposition peak characteristic of diclofenac salts (Fig. 2). The TG trace revealed an increase in the rate of weight loss from ~180 °C. The DSC scan for DAMP-II displayed subtle differences relative to that of DAMP-I. The peak temperature of the endotherm was close to that of

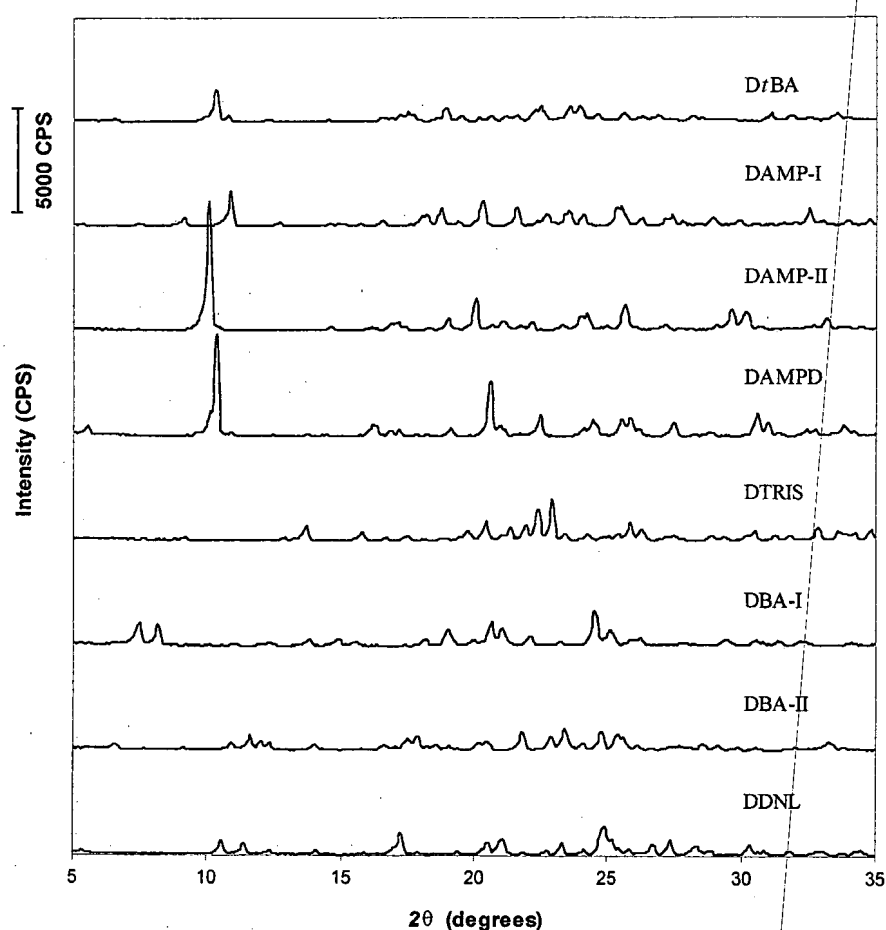


Fig. 1. XRD traces of the diclofenac salts prepared.

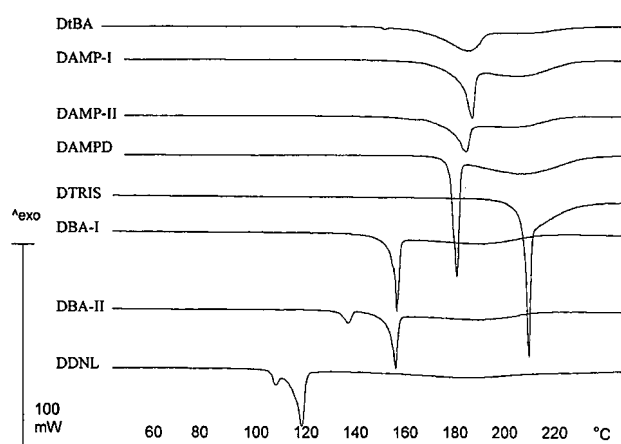


Fig. 2. DSC traces for the diclofenac salts prepared.

the endotherm in the DAMP-I DSC scan (188 °C). The onset value of 161 °C was considerably lower than that for DAMP-I. Further investigation of the thermal properties of DAMP-II was required to explain the presence of what appears to be two overlapping peaks. Altering the sample size or heating rate of DAMP-II resulted in no greater resolution of the two peaks. A sample of DAMP-II, when examined by thermomicroscopy, displayed melting from 130 °C, a temperature approximately corresponding to the onset of the endotherm in the DSC scan, followed by re-crystallisation and subsequent re-melting. Further investigation by DSC involved heating the sample to 170 °C, cooling the sample to 25 °C and re-heating the sample to 250 °C (a) after 10 min and (b) after 4 days. In each case, the DSC and XRD traces obtained were identical to those of DAMP-I. This suggests the existence of two forms of DAMP: DAMP-I, which melts at 182 °C; and DAMP-II, which converts on heating to DAMP-I.

3.1.3. Diclofenac

2-amino-2-methyl-1,3-propanediol (DAMPD)

The DSC scan for DAMPD, the salt formed from diclofenac acid and AMPD in methanol, displayed a sharp endotherm with an onset value of 180 °C (Fig. 2). Thermomicroscopic examination of the sample confirmed that this endotherm was attributable to the melting of the salt form. The broad endotherm from ~185 °C in the DSC

scan and the corresponding weight loss in the TG trace was consistent with decomposition and/or volatilisation of the molten drug.

Attempts to prepare a salt with diclofenac acid and AMPD using acetone or acetone with different quantities of methanol as the solvent resulted in products that differed from DAMPD, the 1:1 salt described above. Analysis by XRD, DSC, TG, thermomicroscopy, elemental analysis and KFT revealed the presence of water of crystallisation in varying proportions in the products. Re-crystallisation from water, by allowing slow evaporation of water from a saturated aqueous solution at room temperature, resulted in a new form of DAMPD. This form was characterised using XRD, DSC, TG, FT-IR, elemental analysis and KFT and identified as DAMPD monohydrate (DAMPD-MH). The XRD trace and DSC scan for the monohydrate are presented in Figs. 3 and 4, respectively.

3.1.4. Diclofenac

tris(hydroxymethyl)aminomethane (DTRIS)

The DSC scan for DTRIS, the salt formed from diclofenac acid and TRIS in methanol, revealed an endotherm with an onset value of 209 °C (Fig. 2). Thermomicroscopy confirmed that this endotherm was attributable to melting of the salt. This value differed from the melting point of 194–196 °C reported earlier for DTRIS (Fini et al., 1996). However, no XRD data was given in the latter study.

3.1.5. Diclofenac benzylamine (DBA)

Attempts to prepare a salt from diclofenac acid and benzylamine by precipitation from acetone were unsuccessful. Combination of solutions of diclofenac acid and benzylamine in methanol resulted in the formation of a product after the evaporation of the solvent. However, two products were identified when the procedure was carried out in ethyl acetate: DBA-I or DBA-II (the different products resulted from slight changes in preparation conditions). DBA-II was identical to the product prepared from methanol. The XRD patterns for the two forms (Fig. 1) were found to differ in their peak position and relative intensities. The DSC trace for DBA-I (Fig. 2) showed an

endothermic peak with an onset value of 157 °C, followed by the broad volatilisation–decomposition peak characteristic of diclofenac salts. Thermomicroscopy confirmed that the endotherm at 157 °C was due to melting of the salt. The TG trace revealed an increase in the rate of weight loss from a temperature corresponding to the onset of the endothermic event in the DSC scan. This may be attributed to the volatilisation of the sample as it melted. The DSC scan for DBA-II (Fig. 2) differed from that of DBA-I by the presence of a second endothermic peak with an onset value of 137 °C. The TG trace obtained was similar to that for DBA-I. Thermomicroscopy, displayed melting at a temperature corresponding to the onset of the first endotherm in the DSC scan, followed by re-crystallisation into acicular crystals. These crystals melted at ~160 °C, a temperature corresponding to the onset of the second endotherm in the DSC scan. Further investigation by DSC involved heating the sample to 143 °C (past the first endotherm), cooling to 25 °C and re-heating the sample to 250 °C (a) after 10 min and (b) after 2 days. In each case, the DSC and XRD traces obtained were identical to those of DBA-I. This suggests the existence of two forms of DBA: DBA-I, which melts at 157 °C; and

DBA-II, which converts on heating to DBA-I. This thermal behaviour is consistent with a Type 2 polymorphic transition (Giron, 1995).

3.1.6. Diclofenac deanol (DDNL)

The DSC scan for DDNL, the salt formed with diclofenac acid and DNL from acetone, showed two overlapping endotherms, the onset temperature of the first endotherm being 105 °C (Fig. 2). Thermomicroscopy revealed melting from ~105 °C, followed by crystallisation of crystals from the melt and subsequent re-melting. This crystallisation and melting of the newly formed crystals explained the presence of the second endotherm (peak temperature, 120 °C) in the DSC scan. An exothermic re-crystallisation peak may be masked because of the occurrence of the two melting endotherms close together. The TG trace showed an increase in the rate of weight loss from 110 °C, resulting in a step corresponding to a weight loss of ~6% w/w. Analysis by KFT excluded the possibility of water being present in the sample. The weight loss may be because of the volatilisation of deanol (b.p. 135 °C) from the melt. In conclusion, two forms of DDNL were shown to exist; one converted to the other on heating.

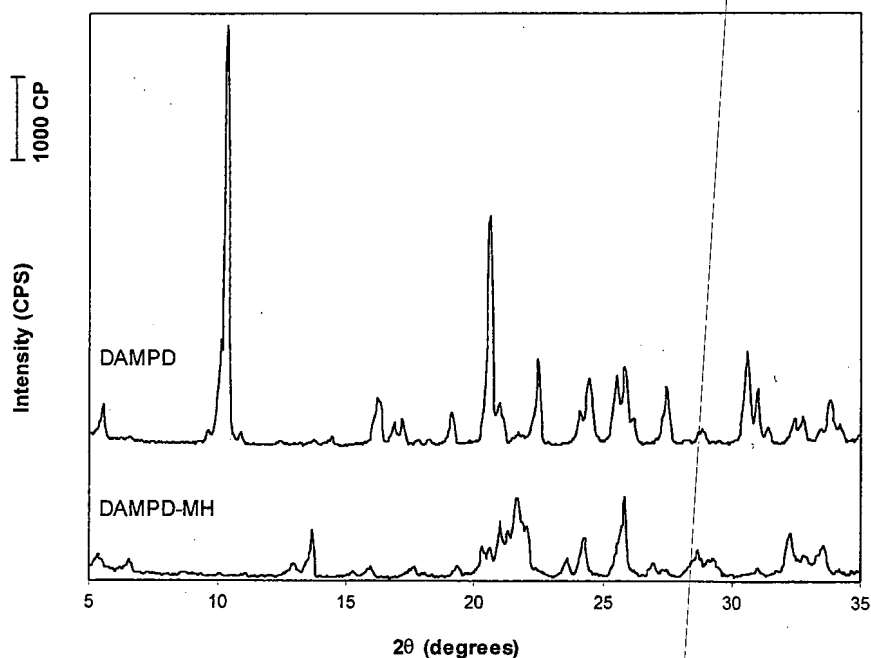


Fig. 3. XRD traces of DAMPD and DAMPD monohydrate (DAMPD-MH).

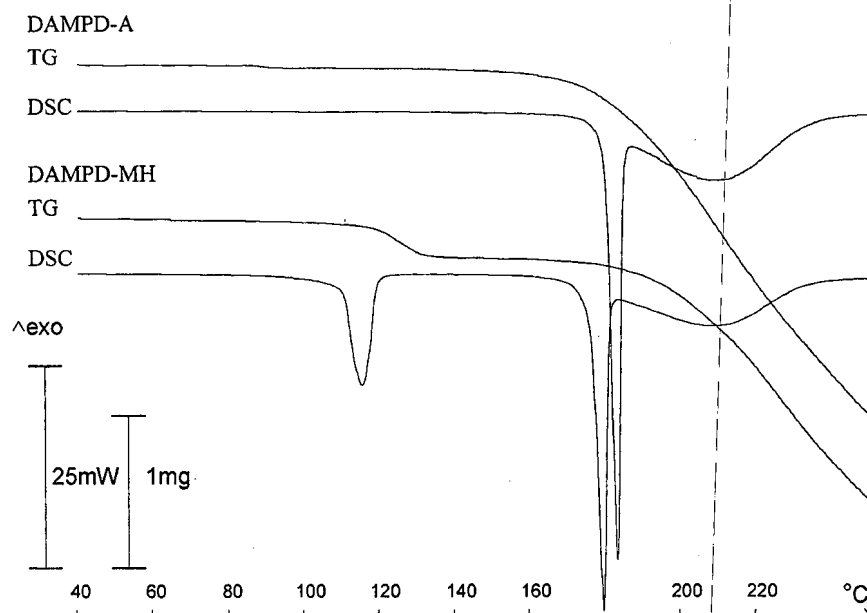


Fig. 4. DSC and TG scans for DAMPD and DAMPD monohydrate (DAMPD-MH).

3.2. Solubility and intrinsic dissolution rate studies of the diclofenac salts prepared

Of the two forms of DAMP, DAMP-I was selected for the investigation of solubility and dissolution rate because of: (a) its single melting endotherm in the DSC scan; and (b) its easiness in preparation relative to DAMP-II. For these same reasons, DBA-I was selected over DBA-II for the investigation of solubility and intrinsic dissolution rate.

Of the diclofenac salts studied, DBA was the only one for which a different XRD pattern, relative to a powder sample, was obtained following compression. An extra peak was observed at $2\theta = 9.45^\circ$ in the XRD trace for the disc. This extra peak suggested a change in the solid-state form of the salt due to the compression procedure. Despite the existence of an additional peak in the XRD trace, DSC analysis of disc re-ground after compression at 8 ton for 5 min did not reveal any change in the thermal behaviour of the salt. However, when the compression time was increased to 10 min, an additional endotherm was observed at $\sim 110^\circ\text{C}$ in the DSC scan of the re-ground disc. This endotherm was observed to

increase in magnitude with an increasing compression time, e.g. the ΔH values for the endotherms after 10 min and 12 h compression were 5.51 and 10.37 J/g, respectively. The changes in the solid-state properties of DBA-I following compression could not be accounted for by the conversion to DBA-II. The additional peak in the XRD trace following compression did not correspond to a peak characteristic of DBA-II. The extra endotherm in the DSC scan for the reground discs occurred at a temperature (onset 110°C) lower than that of the first endotherm in the DSC scan for DBA-II, which had an onset value of 137°C . Due to the effect of compression, the intrinsic dissolution rate study performed on discs prepared from DBA-I yielded a result ($4.57 \times 10^{-4} \pm 0.15 \times 10^{-4} \text{ mmol/min/cm}^2$) which did not relate to the salt in its original solid state.

The solubility and intrinsic dissolution rate values determined for the salts prepared are presented in Table 3. The solubility and intrinsic dissolution rate values for diclofenac diethylamine (DDEA) (O'Connor and Corrigan 2001) and diclofenac *N*-(2-hydroxyethyl)pyrrolidine (DHEP) (Ledwidge and Corrigan, 1998) reported earlier are also included in the table.

Using anhydrous DAMPD as the starting material, a solubility value of 6.77 ± 0.03 mM at 25 °C was obtained. The XRD trace of the solid in equilibrium with the saturated solution after 24 h (the first sampling time) was consistent with that of the monohydrate form of the salt. Therefore, the solubility of the salt is limited to that of its monohydrate form, which forms in a solution of the anhydrate. The intrinsic dissolution rate of the salt in water at 25 °C was determined as $4.51 \times 10^{-4} \pm 0.07 \times 10^{-4}$ mmol/min/cm². XRD analysis of a disc after 5 min dissolution generated a trace consistent with the monohydrate form of the salt, indicating that the conversion of the anhydrate to the monohydrate had occurred. The intrinsic dissolution rate determined therefore related to the DAMPD monohydrate. Almost instantaneous hydration of the solid on the surface of discs upon immersion in water has been reported earlier (Rubino 1989). The latter author reported no differences in the dissolution rates determined for the anhydrous, sesquihydrate and 4.6 hydrated forms of sodium sulfathiazole due to hydration of the anhydrate and sesquihydrate forms to the most hydrated form.

The measured solubility of DTRIS in water at 25 °C (3.89 mM) compared well with the value of 4.00 mM reported by Fini et al. (1996). The solubility of DDNL in water at 25 °C (446.65 mM) was found to be considerably higher than the solubilities determined for the other salts ex-

amined. This salt also showed a superior aqueous solubility to DHEP (273 mM, Ledwidge and Corrigan, 1998), the most soluble salt form of diclofenac available in pharmaceutical products.

Several studies have reported a direct relationship between solubilities and intrinsic dissolution rates for a large variety of substances (Parrott et al., 1955; Hamlin et al., 1965; Higuchi et al., 1965; Nelson and Shah, 1975; Shah and Nelson, 1975; Tsuji et al., 1978; Nicklasson et al., 1981, 1982; Sjökvist Saers and Craig, 1992; Forbes et al., 1995). This solubility–dissolution rate relationships can be used to estimate solubilities where limited amounts of material were available (Nicklasson and Nyqvist, 1983) and to aid salt selection (Forbes et al., 1995).

According to the Noyes–Whitney equation (Noyes and Whitney, 1897), under sink conditions the following relationship should apply

$$G = KC_s \tag{1}$$

where G is the intrinsic dissolution rate, C_s is the solubility and K is the dissolution rate constant. When the solubilities are plotted against the intrinsic dissolution rates on a log–log scale, a linear relationship with a slope of 1.0 is expected, in accordance with the following derivation of the Noyes–Whitney equation

$$\log G = \log K + \log C_s \tag{2}$$

Table 3
Melting points, solubility and intrinsic dissolution rates for diclofenac salts in water at 25 °C

Salt	Melting point (°C)	Solubility (mM)	PH of saturated solution	Intrinsic dissolution rate $\times 10^4$ (mmol/min/cm ²)
DtBA	152.37 $\pm$ 0.29	5.46 $\pm$ 0.05	7.45	3.86 $\pm$ 0.09
DAMP	183.21 $\pm$ 2.14	21.8 $\pm$ 0.3	7.62	13.8 $\pm$ 0.3
DAMPD	179.19 $\pm$ 0.70	6.77 $\pm$ 0.03	7.24	4.51 $\pm$ 0.07
DTRIS	208.92 $\pm$ 0.10	3.95 $\pm$ 0.04	7.13	2.45 $\pm$ 0.06
DBA	156.25 $\pm$ 0.58	4.16 $\pm$ 0.04	7.21	4.57 $\pm$ 0.15 ^a
DDNL	108.46 $\pm$ 0.35	447 $\pm$ 15	8.57	167 $\pm$ 3
DDEA	124.65 $\pm$ 0.35 ^b	35.0 $\pm$ 0.7 ^b	8.19 ^b	18.7 $\pm$ 0.4 ^b
DHEP	101.95 $\pm$ 0.07	273 ^c	8.21 ^d	36.2 ^d

^a This value does not relate to the original solid form of the salt.
^b From O'Connor and Corrigan (2001).
^c From Ledwidge and Corrigan (1998).
^d From Ledwidge et al. (1996).

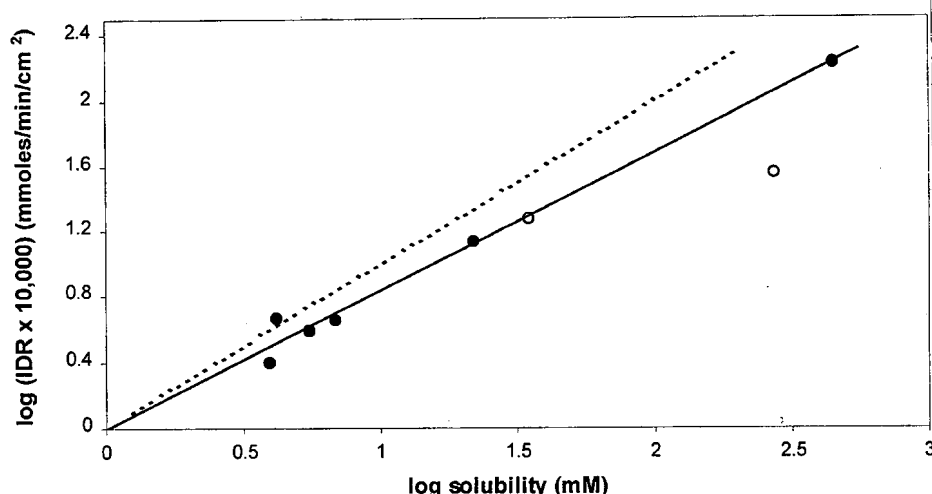


Fig. 5. Plot of log solubility (mM) vs. log (intrinsic dissolution rate $\times 10^4$) (mmoles/min/cm²) for the diclofenac salts studied (●) and DDEA and DHEP (○). The dashed line represents the theoretical relationship of slope unity.

The log–log plot of solubility against intrinsic dissolution rate for the diclofenac salts is presented in Fig. 5. Also included in the graph are the DDEA and DHEP data. The line of best fit ($R^2 = 0.985$, $n = 6$) was found to have a slope of 0.84 ± 0.05 . Deviation from the theoretical line with a slope of unity (indicated by the dashed line in Fig. 5) indicates lower dissolution rates than expected for salts with higher solubilities. This may be due to high viscosities of solutions of the higher solubility salts or micelle formation, resulting in a reduction in their diffusion coefficients. According to the Stokes–Einstein equation (Flynn et al., 1974), the diffusion coefficient is inversely related to the viscosity of the medium. The influence of the viscosity of a salt solution on diffusion through the aqueous boundary layer has been reported earlier (Nelson, 1957; Morozowich et al., 1962; Serajuddin and Jarowski, 1985a).

Previous studies have reported linear relationships between log solubility and log dissolution rate, with slopes of unity or close to unity: 1.02 ± 0.04 (Nicklasson et al., 1981), 1.00 ± 0.06 (Nicklasson et al., 1982) and 1.06 (Forbes et al., 1995). Nelson and Shah (1975) and Shah and Nelson (1975) reported slopes of 0.939 and 0.978, respectively, for a plot of $\log C_s$ versus $\log G$ for a series of alkyl esters of *p*-aminobenzoic acid. The authors proposed that a small change in diffusivity

over the ester series might have contributed to the reduced slope.

3.3. Relationships between salt melting point and solubility for the diclofenac salts studied

Thomas and Rubino (1996) reported an inverse linear relationship between the salt melting point and the logarithm of salt solubility for a series of secondary amine hydrochloride salts ($n = 8$). Ledwidge (1997) reported a similar relationship for a series of salts of an experimental basic drug CEL50 ($n = 7$). Gould (1986), on examination of data obtained from a range of salts of a basic anti-malarial drug (Agharkar et al., 1976), reported a direct relationship between the inverse of the melting point and the logarithm of the solubility ($n = 4$). Anderson and Conradi (1985) reported a non-linear relationship between the salt melting point and $\log K_{sp}$ for a series of flurbiprofen salts ($n = 6$). Conversely, Gu and Strickley (1987) concluded that no simple solubility–melting point relationship could be established for tris(hydroxymethyl)aminomethane salts of four anti-inflammatory salts.

The melting point values for the diclofenac salts studied, including DDEA and DHEP, are listed in Table 3. A trend was observed between the salt melting point and the logarithm of the solubility

($R^2 = 0.6651$, $n = 8$) and between the inverse of the melting point and the logarithm of the solubility ($R^2 = 0.7780$, $n = 8$).

3.4. Exploration of relationships between properties of the salt-forming agent and those of the resulting salt form

In accordance with the linear relationship between the conjugate acid and the salt melting points reported for a series of salts of UK47880 (Gould, 1986), examination of the data for the diclofenac salts revealed reasonable correlation ($R^2 = 0.7518$, $n = 7$) between the base and salt melting points (Fig. 6). However, no correlation was observed between the base melting point and salt solubility. This lack of correlation is in accordance with the results obtained by Ledwidge (1997) for a series of CEL50 salts.

No correlation was found between base pK_a and salt solubility for the diclofenac salts, in accordance with the reported poor correlation between counter-acid pK_a and salt solubility for a series of CEL50 salts (Ledwidge, 1997).

Examination of the data obtained for the diclofenac salts revealed a linear log–log relationship between $[H^+]$ and salt solubility ($R^2 = 0.8957$, $n = 8$). The pH of the saturated solution is plotted against the logarithm of salt concentration in Fig.

7. This trend is consistent with the linear relationship between the final solution hydrogen ion concentration, $[H^+]$, and salt solubility reported by Ledwidge (1997).

The solubility and saturated solution pH values obtained for each of the salts is plotted in relation to the theoretical pH–solubility curves in Fig. 8. The theoretical curves were derived from Eq. (3) (Chowhan, 1978), using values of 0.037 mM and 5.02 for intrinsic solubility and pK'_a , respectively (Ledwidge and Corrigan, 1998).

$$C_s = [HA]_s + [A^-] = [HA]_s \left(1 + \frac{K'_a}{[H_3O^+]} \right) \quad (3)$$

Whereas the data points for most of the salts are consistent with the expected pH–solubility relationship, the solubility values for DDNL and DHEP are considerably higher than expected given the pH of their saturated solutions. Similar deviations from theoretical pH–solubility profiles have been reported for the salts of acidic (Roseman and Yalkowsky, 1973; Chowhan, 1978; Serajuddin and Jarowski, 1985a) and basic (Serajuddin and Rosoff, 1984; Serajuddin and Jarowski, 1985b; Serajuddin and Mufson, 1985) compounds. As a result of these deviations, estimation of the apparent pK_a from the pH–solubility data would result in a lower (in the case of an acidic compound) or higher (for a basic compound) value

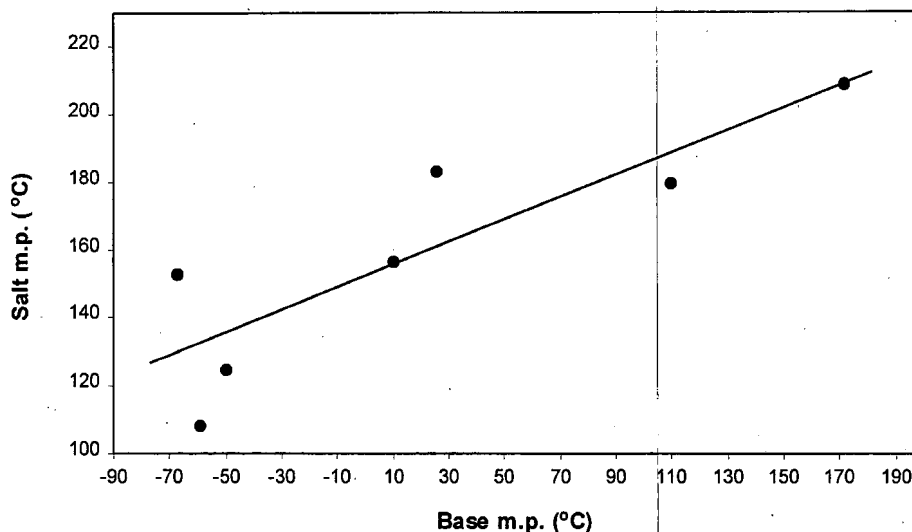


Fig. 6. Base melting point vs. salt melting point for the diclofenac salts studied.

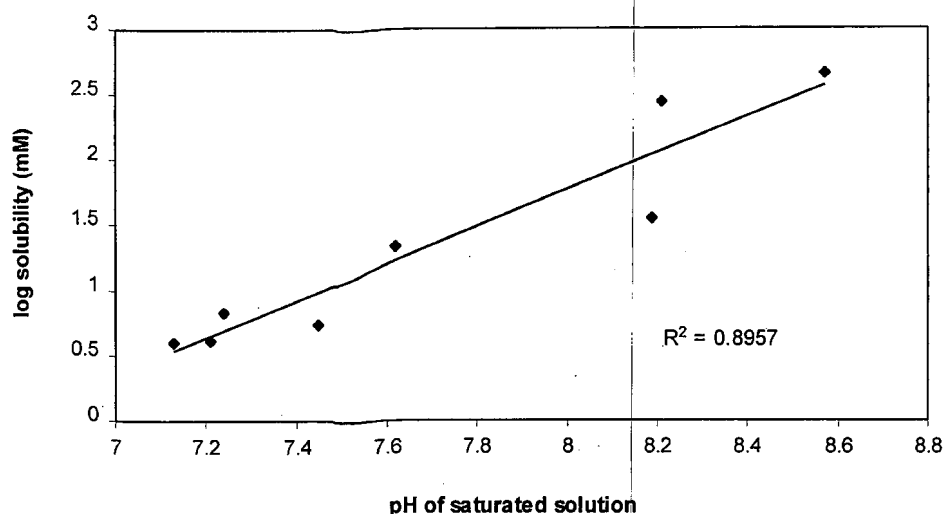


Fig. 7. pH of the saturated solution vs. solubility of the salt for the diclofenac salts studied.

than the potentiometrically determined value for the pK_a of the acid or base.

In line with the previous findings, deviation of the data points for DHEP and DDNL from the theoretical line (Fig. 8) indicated an apparent pK_a value lower than 5.02. Eq. (3) was used to fit a pH–solubility curve to the DDNL and DHEP data. The value for intrinsic solubility was fixed at 0.037 mM (Ledwidge and Corrigan, 1998); a value of 4.47 ± 0.04 was obtained for the pK'_a .

Roseman and Yalkowsky (1973) investigated the pH–solubility behaviour of the tromethamine salt of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and observed that at pH values above 5, there was a marked increase in solubility, significantly greater than what would be expected from the ionisation constant of the acid. This behaviour was attributed to the formation of micelles that solubilise the drug once critical concentration and pH values are reached.

In the current study and the previous studies (Roseman and Yalkowsky, 1973; Chowhan, 1978; Serajuddin and Jarowski, 1985a), the apparent reduction in the pK'_a value observed in the pH–solubility profiles can be attributed to the technique used in estimating the pK'_a and consideration of the equilibrium involved. The apparent dissociation constant, K'_a , is given by

$$K'_a = \frac{[H_3O^+][A^-]}{[HA]} \quad (4)$$

where $[X]$ denotes the concentration of species X. The association of the ionised molecules, $[A^-]$, into micelles resulted in the solubilisation of the protonated acid, HA, causing an increase in the effective concentration of HA. The method used in this study to estimate pK'_a involved the application of Eq. (3), which describes the pH–solubility relationship for a weak acid at pH values less than the pH_{max} . This equation assumes that the solubility of the free acid is limiting and that the increase in solubility with an increasing pH is due to the increasing $[A^-]$. Solubilisation of HA due to micelle formation resulted in an overestimation of the contribution of $[A^-]$ to the total solubility, C_s , and an exaggerated value for the ratio of ionised to unionised forms of the acid, $[A^-]/[HA]$, was obtained. From Eq. (4), it can be seen that the calculated K'_a value is therefore an overestimation, resulting in an observed pK'_a value lower than the true value.

The octanol–water partition coefficient ($\log P$) of each base, an indicator of base hydrophilicity, was estimated using fragment constants (Hansch and Leo, 1979) and is presented in Table 1. No correlation was found between the diclofenac salt solubility and counterion hydrophilicity. This is in

accordance with the results of the study by Anderson and Conradi (1985) on a series of flurbiprofen salts.

As can be observed from the data in Tables 2 and 3 for the salts prepared from the series of four-carbon primary amines, *t*BA, AMP, AMPD and TRIS, no general trends exist between counterion properties, hydrophilicity, melting point and pK_a , and salt solubility.

The rank order of diclofenac salt solubilities was found to be AMP > AMPD > *t*BA > TRIS. Anderson and Conradi (1985) prepared flurbiprofen salts using the same series of bases and reported a rank order of AMPD > TRIS $\cong$ AMP > *t*BA for their solubilities.

The most hydrophilic counterion within the series, TRIS, resulted in the salt of lowest solubility. This is contrary to the expected trend of an increase in water solubility with an increasing hydroxylation, or hydrophilicity, of the base.

However, the hypothesis that greater hydrophilicity of the counterion results in greater water solubility of the resulting salt neglects the possibility of stronger interactions in the crystal due to increased polarity of the counterion. DTRIS has the highest melting point (209 °C) within the series. Therefore, its low water solubility can be attributed to its strong crystal lattice. The strength of the crystal lattice can be attributed to the symmetry of the counterion (Gould, 1986; Anderson and Flora, 1996) and hydrogen bonding within the crystal. Fini et al. (1995a) studied the solubility of a range of diclofenac salts, including salts prepared using monoethanolamine, diethanolamine, triethanolamine and TRIS. They reported that the presence of hydroxyl groups in the ethanolamine cations did not result in an improvement in salt solubility. Furthermore, the increase in hydroxyl group number within the group was not reflected in an increase in solubil-

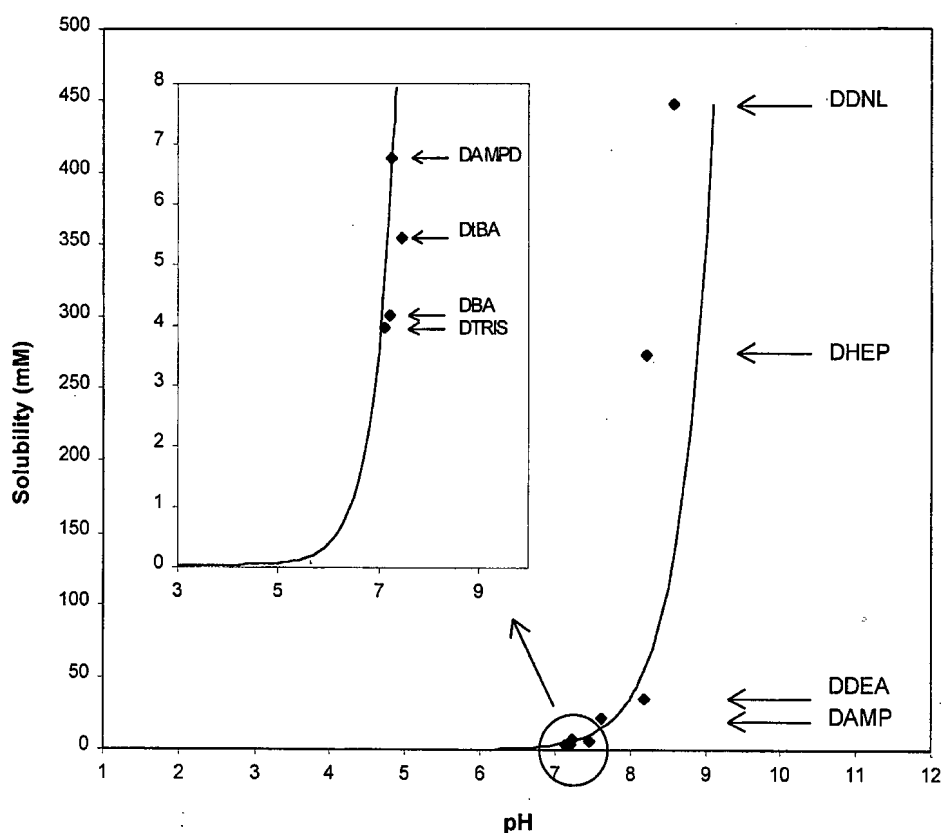


Fig. 8. pH of the saturated solution vs. solubility for each of the diclofenac salts. The lines represent the theoretical pH-solubility profiles.

ity. TRIS, with three hydroxyl groups, resulted in the salt of lowest solubility within the group. These observations were attributed to intermolecular hydrogen bond interactions existing in the solid state. Also, in the case of diclofenac salts, the influence of intramolecular hydrogen bonding needs to be considered (Fini et al., 1996). In a previous study, Dhanaraj and Vijayan (1987) examined the crystal structure of the meclofenamic acid–ethanolamine 1:1 salt in the solid state and reported that the hydroxyl group of the cation interacted via a hydrogen bond with the carboxylate group of the anion. Since meclofenamic acid closely resembles diclofenac acid in molecular structure, it was not surprising that this type of hydrogen bond was found to exist in salts of diclofenac containing cations carrying the hydroxyethyl moiety (Castellari and Sabatino, 1994). Therefore, the overall hydrophilicity of the salts was masked by internal interactions and their affinity for polar solvents was reduced.

The salt displaying the highest water solubility within the series (21.76 mM) is that of AMP, the base with one hydroxyl group. The melting point determined for DAMP (183 °C) is the second highest of the four salts. Therefore, the high aqueous solubility of the salt cannot be attributed to either the hydrophilicity of the base or weak crystal lattice forces in the salt.

The pK_a of TRIS (8.30) is the lowest in the series and the pH of a saturated solution of DTRIS (7.13) is lower than the values obtained for the other salts in the series. The low solubility of DTRIS is therefore consistent with the linear relationship between the pH of the saturated solution and the logarithm of the solubility of the salt (Fig. 7). In accordance with this trend, the pH of a saturated solution of DAMP, the most soluble salt, is higher than the pH of the solutions of the other salts in the series, despite the pK_a of AMP being one unit lower than that of tBA.

In summary, the solubility of the salts of diclofenac and the four-carbon primary amines was not shown to be dependent on any one parameter, but on a combination of factors such as salt crystal lattice strength and the pH of the saturated salt solution.

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