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                         Oficio  
                         Folios                        5

**10480**

|                                     |                                                |                                                 |
|-------------------------------------|------------------------------------------------|-------------------------------------------------|
| Patente de Invención                | <input checked="" type="checkbox"/>            | Patente de Modelo de Utilidad                   |
| Vía Nacional                        |                                                |                                                 |
| Vía PCT (Fase Nacional)             | <input checked="" type="checkbox"/> Capítulo I | <input checked="" type="checkbox"/> Capítulo II |
| No. Solicitud Internacional         | PCT/SE2007/000086                              |                                                 |
| Fecha de Presentación Internacional | 31/Enero/2007                                  |                                                 |

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

1. Documentos estudiados

|                   |                |                 |
|-------------------|----------------|-----------------|
| Descripción:      | Folios 19 a 38 | 23/Julio/2008   |
| Reivindicaciones: | Folio 59       | 27/Octubre/2008 |
| Prioridad:        | US 60 764 551  | 02/Febrero/2006 |

2. Análisis de la Prioridad

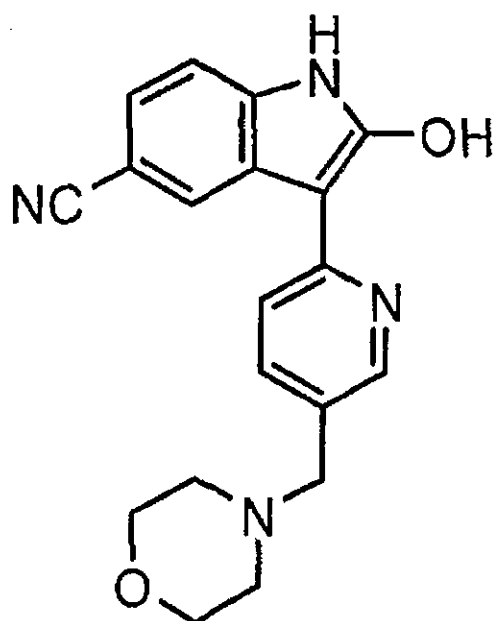
Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "NUEVA SAL DE CITRATO DE UN DERIVADO DE INDOL Y SU USO FARMACEUTICO"  
Expediente 08-76353            1er Art 45

El problema planteado en esta solicitud consiste en la necesidad de proporcionar compuestos que presenten un efecto selectivo sobre glucógeno sintasa quinasa-3 (GSK3)

Para resolver este problema técnico la solicitud en estudio proporciona una sal del compuesto de la fórmula (I), un proceso para prepararla y composiciones que la contienen.



(I)

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C 07 D 401/04; A 61 P 25/00

#### 4. De la Solicitud de Patente

##### Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 2 no es clara cuando menciona el término "sustancialmente" el cual no es claro ni limitativo por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere eliminar esta reivindicación del pliego reivindicatorio.

La reivindicación 4 no es clara ni concisa cuando reclama un proceso que comprende la reacción con ácido cítrico en un solvente. Esta denominación genérica no es válida pues no define un componente como tal, lo cual no permite distinguir la invención del estado de la técnica. Se recomienda restringir la solicitud al proceso sustentado en la descripción. Igual observación aplica para la reivindicación 5.

La reivindicación 8 no es clara ni concisa cuando reclama una formulación farmacéutica que comprende como principio activo una cantidad terapéuticamente eficaz de la sal opcionalmente en asociación con diluyentes, excipientes o portadores inertes. Esta manera de definir el segundo componente de la formulación no es aceptable, puesto que no se define ningún componente como tal. Se recuerda al solicitante que las composiciones se deben definir por características técnicas esenciales como son los ingredientes activos y auxiliares de formulación específicos. Se requiere al Solicitante hacer las aclaraciones necesarias.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: Febrero 02 de 2006, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| Item | Documento    | Título        | Fecha de Publicación |
|------|--------------|---------------|----------------------|
| D1   | WO03082853A1 | New Compounds | 09/Octubre/2003      |

6. Examen de Patentabilidad (Art 14 D486).

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en una sal, que es el citrato de 2-hidroxi-3-[5-(morfolin-4-ilmetil)piridin-2-il]1H-indol-5-carbonitrilo

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

| SOLICITUD                                                                          | D1                                                                                                             |
|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Citrato de 2-hidroxi-3-[5-(morfolin-4-ilmetil)piridin-2-il]1H-indol-5-carbonitrilo | Clorhidrato de 2-hidroxi-3-[5-(morfolin-4-ilmetil)piridin-2-il]1H-indol-5-carbonitrilo (página 8 líneas 16,17) |

El documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulga la sal clorhidrato de 2-hidroxi-3-[5-(morfolin-4-ilmetil)piridin-2-il]1H-indol-5-carbonitrilo

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D1 consiste en que la invención corresponde al citrato del compuesto y D1 corresponde al compuesto base (Ver página 8 línea 27) y al clorhidrato del compuesto (Ver página 8 línea 16,17)

El efecto que logra el utilizar el citrato en lugar del clorhidrato es aumentar la

estabilidad química del compuesto debido a la higroscopicidad presentada por los clorhidratos.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar el compuesto conocido en D1 para aumentar la estabilidad química.

Sin embargo, ya es conocido en el estado de la técnica el uso de diversas sales en lugar del clorhidrato debido a la alta higroscopicidad del clorhidrato así como el uso de citrato como posible sal farmacéutica<sup>1 2</sup>

En consecuencia, el la persona del oficio normalmente versada en la materia, reemplazaría el clorhidrato divulgado en D1 por citrato para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones 2 y 3 no presentan características inventivas adicionales tampoco se consideran inventivas.

La reivindicación 4 consiste en:

Un proceso para la preparación del citrato de 2-hidroxi-3-[5-(morfolin-4-ilmetil)piridin-2-il]1H-indol-5-carbonitrilo de acuerdo con las reivindicaciones 1 a 3 que comprende hacer reaccionar 2-hidroxi-3-[5-(morfolin-4-ilmetil)piridin-2-il]1H-indol-5-carbonitrilo con ácido cítrico en un solvente.

El documento D1 constituye el estado de la técnica cercano al objeto de la reivindicación 4 porque da a conocer el proceso para la preparación del clorhidrato de 2-hidroxi-3-[5-(morfolin-4-ilmetil)piridin-2-il]1H-indol-5-carbonitrilo (Ver página 32 líneas 19 a 22)

Una persona del oficio normalmente versada en la materia fácilmente de acuerdo al proceso divulgado en D1 para obtener el clorhidrato junto con sus conocimientos en la materia llegaría a la consecución de la sal del compuesto para llegar al objeto de la reivindicación 4 ya que la reacción reclamada es una reacción conocida en el estado de la técnica que consiste en obtener una sal a partir de la base libre por reacción con un ácido en el solvente adecuado<sup>3</sup>. Motivo por lo cual no se considera inventiva.

Puesto que las reivindicaciones 5-8 no presentan características inventivas adicionales tampoco se pueden considerar inventivas.

En conclusión las reivindicaciones 1 – 8 cumplen el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

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1 Berge Stephen M; Bighley Lyle D; Monkhouse Donald C. "Pharmaceutical Salts" Journal of Pharmaceutical Sciences 66,1 (1977) Página 10. (Ver folio 70)

2 Ohannesian Lena; Streeter Antony J. Handbook of Pharmaceutical Analysis Tabla 4 (Ver folios 73 a 75)

3 Ohannesian Lena; Streeter Antony J. Handbook of Pharmaceutical Analysis( Ver folio 76)

Expediente 08-76353

1er Art 45

## 7. Conclusión

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

| Item | Documento    | Reivindicaciones afectadas | Requisito que afecta |
|------|--------------|----------------------------|----------------------|
| D1   | WO03082853A1 | 1 – 8                      | Nivel Inventivo      |

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

  
**JOSÉ LUIS SALAZAR LÓPEZ**  
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha  
17 5 JUN. 2012

Elaborado por: Rodolfo Cadena Amaya.   
Revisado por: Gloria Jacqueline Alfonso.

# Journal of Pharmaceutical Sciences

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## REVIEW ARTICLE

### Pharmaceutical Salts

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DONALD C. MONKHOUSE<sup>\*</sup>

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

#### CONTENTS

|                              |    |
|------------------------------|----|
| Potentially Useful Salts     | 2  |
| Physicochemical Studies      | 4  |
| Dissolution Rate             | 5  |
| Solubility                   | 7  |
| Organoleptic Properties      | 8  |
| Stability                    | 9  |
| Miscellaneous Properties     | 10 |
| Bioavailability              | 10 |
| Formulation Effects          | 11 |
| Absorption Alteration        | 11 |
| Pharmacokinetics             | 13 |
| General Pharmacy             | 14 |
| Pharmacological Effect       | 14 |
| Dialysis                     | 14 |
| Miscellaneous                | 14 |
| Toxicological Considerations | 15 |
| Toxicity of Salt Ion         | 15 |
| Toxicity of Salt Form        | 15 |
| Conclusions                  | 15 |
| References                   | 16 |

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

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

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

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

equivalent quotient between the electrolytes in the surrounding fluid and the ionic drugs, (b) the amount of ions is far less in the saliva than in the gastric juice (the temporary electrolyte contents can be estimated at 0.05 mEq in the saliva and at 10 mEq in the gastric juice), and (c) the exchange rates should allow the equilibria to be attained within a fairly short period. Insoluble drug resins formed between dextran gel<sup>2</sup> cation exchangers and several basic drugs were in many cases much more pleasant tasting than their parent compounds. Furthermore, release of the drug from the ion-exchange adsorbate was quite rapid and complete under conditions prevailing in the GI tract.

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

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

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

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

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

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

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

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

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

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

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

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

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

<sup>2</sup> Sephadex.

# Handbook of Pharmaceutical Analysis

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## B. Counterions

Salt formation involves proton transfer from an acid to a base. In theory, any compound that exhibits acidic or basic characteristics can form salts. The major consideration is the relative acidity and/or basicity of the chemical species involved. To form a salt, the  $pK_a$  of the acidic partner must be less than the  $pK_a$  of the conjugate acid of the basic partner. These  $pK_a$  values need to be about two units apart for total proton transfer to occur, otherwise an equilibrium mixture of all components (acid, base, and salt) is likely to result. Even so, equilibrium mixtures of this type can often be used to prepare salts if a driving force is present, such as the crystallization of the salt from solution.

Another consideration is the toxicity of the counterion. A large number of anions and cations are available for pharmaceutical compounds, and tabulations of those approved by the FDA have appeared in the literature (9,12). An expanded but not comprehensive list of acceptable ions is presented in Table 4. In general, ions related to normal metabolic chemicals or present in food or drink are usually regarded as suitable candidates for preparing salts.

Target salts are chosen by considering a number of factors. The structure and  $pK_a$  of the drug substance are important values to determine initially. Available literature on structurally related compounds can result in excellent leads for target salts. The chemical stability of the drug substance, especially as related to pH stability, will also play a role. The ease of large-scale preparation of the salt, as well as the cost of the counterion and processing, will need to be considered to determine if the salt is a feasible choice. The type of drug product and anticipated loading of the drug substance in the drug product can also influence the choice of salts. For high drug loadings, a large, bulky counterion, which adds substantial mass to the loading, may not be the best choice. Anions that irritate the gastrointestinal tract should be avoided for certain drugs, such as anti-inflammatories. The relative acid/base strength of the resulting salt and the tendency to disproportionate should be considered when using basic excipients in a formulation.

A common salt choice for basic drug substances is the hydrochloride, because of its availability. However, a number of issues also need to be considered when using this salt. Reports have shown that hydrochloride salts do not always increase the solubility of poorly soluble basic drugs (1,13,17,18), due to the common-ion effect. The presence of chloride ions in the gastric fluid can result in a lower solubility for the hydrochloride salt.

The hydrochloride salt is often a stronger acid than is needed for many drug substances, which can result in low pH values for the aqueous solutions. This can lead to limitations in parenteral formulations or processing. The highly polar nature of hydrochloride salts can also lead to excessive hygroscopicity of the resulting salt. Dihydrochlorides are also found to be hygroscopic and may lose

**Table 4** Summary of Acceptable Salts for Pharmaceutical Drug Substances (adapted from Ref. 9)

| Anions—organic                       | Anions—organic                                                  | Anions—organic                                      |
|--------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------|
| Acetate/diacetate                    | Fumarate                                                        | Napsylate                                           |
| Adipate <sup>a</sup>                 | Glucelate (glucoheptonate)                                      | Oxalate <sup>a</sup>                                |
| Alginate <sup>c</sup>                | Gluconate/digluconate                                           | Palmitate                                           |
| Aminosalicylate <sup>a</sup>         | Glucuronate                                                     | Pantoate (embonate)                                 |
| Anhydromethylenecitrate <sup>a</sup> | Glutamate                                                       | Pantothenate                                        |
| Arecoline <sup>a</sup>               | Glycerophosphate <sup>a</sup>                                   | Pectinate <sup>a</sup>                              |
| Arginine                             | Glycyllysylarginate ( <i>l</i> -glycylamidophenyl-<br>arsinate) | Phenylethylbarbiturate <sup>a</sup>                 |
| Ascorbate <sup>a</sup>               |                                                                 |                                                     |
| Aspartate                            | Hexylresorcinate                                                | Picrate <sup>a</sup>                                |
| Benzenesulfonate (besylate)          | Hydrabamine ( <i>N,N'</i> -di(dehydroabietyl)ethylenediamine)   | Polygalacturonate                                   |
| Benzoate                             | Hydroxynaphthoate                                               | Propionate                                          |
| Bicarbonate                          | Iselthionate (2-hydroxyethanesulfonate)                         | Saccharate                                          |
| Bitartrate                           | Lactate                                                         | Salicylate                                          |
| Butylbromide <sup>a</sup>            | Lactobionate                                                    | Stearate                                            |
| Butyrate                             | Lysine                                                          | Subacetate                                          |
| Calcium edetate                      | Malate                                                          | Succinate/dissuccinate                              |
| Camphorate                           | Maleate                                                         | Tannate                                             |
| Camsylate (camphorsulfonate)         | Mandelate                                                       | Tartrate                                            |
| Carbonate                            | Mesylate                                                        | Terephthalate                                       |
| Citrate                              | Methylbromide                                                   | Teoclate (8-chlorotheophyllinate)                   |
| Falate                               | Methylethylbis(salicylate) <sup>a</sup>                         | Thiocyanate <sup>a</sup>                            |
| Edisylate (1,2-ethanedisulfonate)    | Methylthiurate                                                  | Tosylate (toluenesulfonate)                         |
| Estolate (lauryl sulfate)            | Methylsulfate                                                   | Triiodide                                           |
| Esylate (ethanesulfonate)            | Mucate                                                          | Undecanoate <sup>a</sup>                            |
|                                      | Napadisylate (1,5-naphthalenedisulfonate) <sup>a</sup>          | Xinafoate (1-hydroxy-2-naphthalenecarbox-<br>ylate) |

| Anions—inorganic              | Cations—organic                                                                          | Cations—inorganic   |
|-------------------------------|------------------------------------------------------------------------------------------|---------------------|
| Bisulfate <sup>a</sup>        | Benethamine ( <i>N</i> -benzylphenethylamine) <sup>y</sup>                               | Aluminum            |
| Bromide                       | Benzathine ( <i>N,N'</i> -dibenzylethylenediamine)                                       | Barium <sup>z</sup> |
| Chloride                      | Chlorprocaine                                                                            | Bismuth             |
| Hydrobromide/dihydrobromide   | Choline                                                                                  | Calcium             |
| Hydrochloride/dihydrochloride | Clemizole (1- <i>p</i> -chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole) <sup>y</sup> | Lithium             |
| Hydrofluoride <sup>a</sup>    | Dichloramine                                                                             | Magnesium           |
| Hydroiodide <sup>a</sup>      | Diethylamine <sup>a</sup>                                                                | Potassium           |
| Iodide                        | Ethylenediamine                                                                          | Sodium              |
| Nitrate/dinitrate             | Meglumine ( <i>N</i> -methylglucamine)                                                   | Zinc                |
| Persulfate <sup>a</sup>       | <i>N,N'</i> -dibenzylethylenediamine                                                     |                     |
| Phosphate/diphosphate         | Piperazine <sup>a</sup>                                                                  |                     |
| Sulfate/disulfate/hemisulfate | Procaine                                                                                 |                     |
|                               | Tromethamine (tris(hydroxymethyl)amino-methane)                                          |                     |

<sup>a</sup>Drugs containing these counterions approved in other countries.

hydrogen chloride gas upon heating or under reduced pressure (lyophilization). Although hydrochloride is commonly used for salt formation, other salts may be better alternatives in the long run.

### C. Salt Preparation

Salts can be produced on a small scale using a variety of methods. Selected methods are described below.

#### 1. Salt Formation from Free Acid/Base

In salt formation from free acid or base, the free acid/base of the drug substance is combined with the base/acid containing the desired counterion in specific molar ratios in a suitable solvent system. There must be adequate solubility of each reactant in the solvent system chosen. The product can be isolated in different ways, often simply by evaporation of the solvent.

#### 2. Salt Formation by Salt Exchange

For salt formation by salt exchange, the salt of the drug substance is combined with a salt containing the desired counterion in specific molar ratios in a suitable solvent system. As described above, there must be adequate solubility of each reactant in the solvent system. If the desired salt of the drug substance is less soluble than the starting materials, it will precipitate out and can be isolated by filtration. If no precipitate is obtained, other isolation methods can be employed. A method that was described for iodide salts (19) involved precipitation of the unwanted counterion first. In this case silver salts were used for the counterions (silver sulfate, silver *ortho*-phosphate, silver lactate) and a silver iodide precipitate was isolated first by filtration. The desired salt of the drug substance was then precipitated from the filtrate by addition of an antisolvent.

#### 3. Other Reported Methods

Variations of the traditional methods for salt preparation described above have been reported. To produce the hydrochloride and hydrobromide salts of the anes-

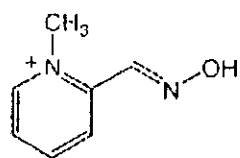


**Fig. 15** The structure of *N*-methyl pyridinium-2-aldoxime.