

Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database

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The Orange Book database published by the U.S. Drug and Food Administration (FDA) was analyzed for the frequency of occurrence of different counterions used for the formation of pharmaceutical salts. The data obtained from the present analysis of the Orange Book are compared to reviews of the Cambridge Structural Database (CSD) and of the Martindale “The Extra Pharmacopoeia”. As well as showing overall distributions of counterion usage, results are broken down into 5-year increments to identify trends in counterion selection. Chloride ions continue to be the most frequently utilized anionic counterions for the formation of salts as active pharmaceutical ingredients (APIs), while sodium ions are most widely utilized for the formation of salts starting from acidic molecules. A strong trend toward a wider variety of counterions over the past decade is observed. This trend can be explained by a stronger need to improve physical chemical properties of research and development compounds.

Introduction

Salt formation is a well-known technique to modify and optimize the physical chemical properties of an ionizable research or development compound. Properties such as solubility, dissolution rate, hygroscopicity, stability, impurity profiles, and crystal habit can be influenced by using a variety of pharmaceutically acceptable counterions.^{1–8} Even polymorphism issues can be resolved in many cases by formation of salts. The crystal structure of a salt is usually completely different from the crystal structure of the conjugate base or acid and also differs from one salt to another. The modification of physical chemical properties, mainly solubility and dissolution rate, may also lead to changes in biological effects such as pharmacodynamics and pharmacokinetics, including bioavailability and toxicity profile.^{1,9,10}

Owing to dramatic changes in the techniques applied in pharmaceutical discovery programs over the past 20 years, the physical chemical properties of development candidates have changed substantially.¹¹ Drug design based on high-throughput screening has in general led to more lipophilic compounds exhibiting low aqueous solubility.

There are many well-known formulation techniques to increase aqueous solubility,^{12–14} e.g., micronization, nanosizing, or complexation with cyclodextrins. The use of solid solutions and solid dispersions is another way to improve bioavailability for development candidates with low solubility. Nevertheless, formation of salts is almost the only chemical technique available to change aqueous solubility and dissolution rate without changing the API molecule. Further options for modifying these properties comprise the choice of the polymorphic form including solvates and formation of cocrystals. Although cocrystals in particular are an innovative way of designing APIs, this method is beyond the scope of this publication. An overview of this topic can be found in ref 15. Salt selection remains an important step at the interface between pharmaceutical research and development. A large number of publications covering

physical chemical properties of pharmaceutical salts and methods for salt screening exist, e.g., refs 4, 16–19 and references included therein. On the other hand, publications giving an overview of approved salt forms are very few.^{1–3} All publications known to the authors dealing with occurrence of counterions for formation of pharmaceutical salts list the counterions and their distribution in the respective data set only at a given point in time. Neither the distribution trends over time nor the causes for these have been analyzed to date.

The present contribution examines the selection of counterions for the formation of salts by analyzing the Orange Book Database²⁰ published by the U.S. Drug and Food Administration (FDA). The Orange Book lists all drug products approved in the U.S. Drug products approved after 1981 are listed including their date of approval. This enables an analysis of the changes in frequency of usage of the different counterions with time. Trends in salt selection over the past 25 years can thus be identified and the outcome of the overall analysis of the Orange Book compared to results based on other sources.

Study Design

The data were compiled from the FDA Orange Book Database as of the end of 2006. At this date, 21 187 drug products were listed, including 1356 chemically “well-defined” APIs. “Well defined” for the purpose of our analysis means that the API molecules are small chemical entities with a defined molar mass, typically below 1000 Da and that their chemical structure is completely known. Dosage forms containing multiple APIs, peptide hormones, biological APIs like antibodies, enzymes, extracts, and proteins, metal complexes, polymeric salt forms, inorganic APIs, and markers were excluded from our analysis. The APIs were classified into three categories: Category I consists of salts formed from basic molecules containing at least one atom suitable for protonation. Category II comprises salts formed from acidic species. Finally, category III is represented by APIs that are used as nonsalt forms. This class also includes zwitterions. Counterions are reported according to their type of charge as cations and anions. The stoichiometry of the salts is not discussed separately: for

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Table 1. Distribution of FDA Approved APIs among Categories I–III

| overall (%) | pre-1982 (%) | 1982–1986 (%) | 1987–1991 (%) | 1992–1996 (%) | 1997–2001 (%) | 2002–2006 (%) |
|--|--------------|---------------|---------------|---------------|---------------|---------------|
| Category I: API Salts Formed of Basic Entities | | | | | | |
| 38.6 | 38.4 | 42.0 | 40.2 | 38.0 | 40.3 | 32.7 |
| Category II: API Salts Formed of Acidic Entities | | | | | | |
| 12.8 | 13.6 | 10.1 | 11.1 | 13.3 | 11.1 | 14.6 |
| Category III: Nonsalt APIs | | | | | | |
| 48.6 | 48.0 | 47.9 | 48.7 | 48.7 | 48.6 | 52.7 |

example, the occurrence of bromides includes bromides and dibromides. Furthermore, the APIs were arranged by year of approval to analyze how trends in the choice of salt forms have changed in recent decades. Prior to 1981, no date of approval is given in the Orange Book. Therefore, the drug products approved before 1982 are summarized under “pre-1982”. The period from 1982 to 2006 has been divided into five intervals, each comprising 5 years. After completion of the analysis of all chemically well-defined APIs, a separate assessment of the subset of APIs of oral (844 APIs) and injectable (482 APIs) dosage forms was made. Our analysis shows how the route of administration influences the choice of a specific salt form. This observation can be assigned to the different requirements of the two routes of administration. For example, for the two basic compounds biperiden and pentazocine, the chloride salts are used for oral dosage forms, whereas the lactate salts are used for injectable dosage forms.

Results and Discussion

Distribution of API Salts Formed of Basic and Acidic Molecules and APIs in Nonsalt Forms. The 1356 chemically well-defined APIs listed in the Orange Book comprise 659 (48.6%) APIs in nonsalt forms, 523 (38.6%) salts formed from basic compounds, and 174 (12.8%) salts formed from acidic molecules. Thirty-eight different anions and 15 cations are used as counterions for the formation of salts. Thereof, 16 anions and 8 cations were only used once. During the past 25 years, 25 anions and 7 cations have been used to form salts. The ratios of APIs obtained by salt formation of molecules exhibiting basic properties, API salts obtained from acidic species, and APIs in nonsalt forms have remained virtually constant. This is shown in Table 1. During 2002–2006, there has been some decrease in the percentage of APIs obtained as salts of basic compounds. This leads to a small increase in both of the other categories. Figure 1 shows the corresponding distribution of APIs among the three categories used in oral and injectable dosage forms. Together, oral and injectable formulations represent the majority of FDA-approved formulations. However, the requirements placed on an API for oral and injectable dosage forms are quite different. For oral dosage forms, a key prerequisite of the API is a certain minimum solubility in the pH range of the gastrointestinal tract. An adequate dissolution rate and a sufficient permeability are also important. If these requirements are not fulfilled, bioavailability will be insufficient to achieve the desired therapeutic effect. In the case of solutions for injection, considerations such as pH of the solution, osmolarity, and solubility in a small volume are important for efficient and pain-free administration. In many cases, this can lead to situations where a considerably higher solubility is required for injectables than for oral formulations.

Distribution of Anionic Counterions Used To Form Pharmaceutical Salts. A summary of all anions used along with their distribution during different time periods is given in

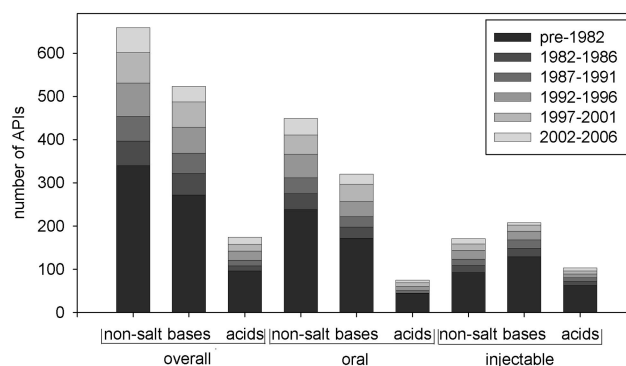
**Figure 1.** Classification and distribution of species in the Orange Book according to their type of charge and administration route.

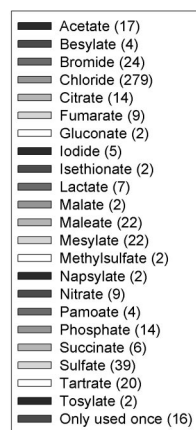
Table 2. Figure 2 displays the overall distribution of anions, whereas Figure 3 depicts the most recent period, 2002–2006. The anion encountered most frequently in FDA-approved pharmaceutical salts is the chloride ion. The fraction of chlorides increased from 52.9% (pre-1982) to 63.8% (1987–1991), remained almost constant at 63.3% over the next 5 years (1992–1996) and decreased significantly to 38.9% (2002–2006) over the past 10 years. The anion encountered with highest frequency after chloride is sulfate. However, it accounts for only 7.5% of APIs formed from basic molecules. Its peak incidence was 12.0% during the period 1982–1986. Further acidic counterions frequently encountered include bromides, with a total incidence of 4.6%, as well as maleates and mesylates, both with incidences of 4.2%.

There appears to be some tendency for “fashions” in anionic counterion selection, with certain counterions showing a noticeably higher occurrence during one period compared to their overall usage. For example, nitrates represented 8.0% of anionic counterions during the 1982–1986 period. The average usage of nitrates is only 1.7%. Further examples include acetate with a maximum incidence of 12.7% during 1987–1991 and an overall usage of 3.3%. Tartrates exhibited a higher incidence of 6.7% in 1992–1996 than the average of 3.8%. Fumarates showed most frequent utilization during 1997–2001, contributing 8.6% of FDA-approved salts formed of basic molecules during this period. They yielded an average fraction of 1.7%. For mesylates, the same is true with a peak occurrence of 13.8% during the same period and an average incidence of 4.2%. The number of anions used to form salts has varied during the past 25 years between 11 and 15 per 5-year period. In total, there are only two anions with an average incidence of more than 5% over the whole period. These are the chlorides and sulfates. Nevertheless, during the individual 5-year intervals, there are several anions reaching fractions of more than 5%. For example, in the pre-1982 period these are bromides and maleates. From 1982 to 1986, acetates and nitrates are encountered in more than 5% of the APIs of category I. From 1987 to 1991, acetate and from 1992 to 1996 tartrate are the only anions other than chloride that were used to form more than 5% of the FDA-approved salts of basic molecules. After 1996, a broader variety of anions has reached an incidence of more than 5% usage. During 1997–2001 five anions exhibit an occurrence of more than 5%: bromides, chlorides, citrates, fumarates, and mesylates. From 2002 to 2006, seven different anions including bromides, chlorides, maleates, mesylates, phosphates, sulfates, and tartrates had an incidence of 5% or more. These figures indicate a strong, recent trend toward increased diversity of anions applied for the formation of salts in category I. The trend can be explained as a consequence of the changes in research techniques

Table 2. Distribution of Anions Used in APIs of Category I

| | overall (%) | pre-1982 (%) | 1982–1986 (%) | 1987–1991 (%) | 1992–1996 (%) | 1997–2001 (%) | 2002–2006 (%) |
|----------------------|-------------|--------------|---------------|---------------|---------------|---------------|---------------|
| acetate | 3.3 | 1.5 | 8.0 | 12.7 | | 3.5 | 2.8 |
| benzoate | 0.2 | | | | | 1.7 | |
| bessylate | 0.8 | 0.4 | 2.0 | | 3.3 | | |
| bromide | 4.6 | 5.2 | 4.0 | 2.1 | 1.7 | 5.2 | 8.3 |
| camphorsulfonate | 0.2 | 0.4 | | | | | |
| chloride | 53.4 | 52.9 | 52.0 | 63.8 | 63.3 | 46.6 | 38.9 |
| chlorotheophyllinate | 0.2 | 0.4 | | | | | |
| citrate | 2.7 | 2.6 | 2.0 | | 3.3 | 5.2 | 2.8 |
| ethandisulfonate | 0.2 | 0.4 | | | | | |
| fumarate | 1.7 | 0.4 | | 2.1 | 3.3 | 8.6 | |
| gluceptate | 0.2 | 0.4 | | | | | |
| gluconate | 0.4 | 0.7 | | | | | |
| glucuronate | 0.2 | | | | 1.7 | | |
| hippurate | 0.2 | 0.4 | | | | | |
| iodide | 1.0 | 1.5 | 2.0 | | | | |
| isethionate | 0.4 | 0.4 | 2.0 | | | | |
| lactate | 1.3 | 1.5 | 4.0 | 2.1 | | | |
| lactobionate | 0.2 | 0.4 | | | | | |
| laurylsulfate | 0.2 | 0.4 | | | | | |
| malate | 0.4 | 0.4 | | | | | 2.8 |
| maleate | 4.2 | 5.5 | 2.0 | | 3.3 | 3.5 | 5.6 |
| mesylate | 4.2 | 2.6 | 2.0 | 4.3 | 1.7 | 13.8 | 8.3 |
| methylsulfate | 0.4 | 0.7 | | | | | |
| naphthoate | 0.2 | | | | 1.7 | | |
| napsylate | 0.4 | 0.7 | | | | | |
| nitrate | 1.7 | 0.7 | 8.0 | 2.1 | 1.7 | | 2.8 |
| octadecanoate | 0.2 | 0.4 | | | | | |
| oleate | 0.2 | | | 2.1 | | | |
| oxalate | 0.2 | | | | | | 2.8 |
| pamoate | 0.8 | 1.1 | | | | 1.7 | |
| phosphate | 2.7 | 3.3 | | 2.1 | 1.7 | 1.7 | 5.6 |
| polygalacturonate | 0.2 | 0.4 | | | | | |
| succinate | 1.2 | 0.7 | | | 3.3 | 1.7 | 2.8 |
| sulfate | 7.5 | 9.6 | 12.0 | 4.3 | 1.7 | 3.5 | 5.6 |
| sulfosalicylate | 0.2 | 0.4 | | | | | |
| tartrate | 3.8 | 3.7 | | 2.1 | 6.7 | 3.5 | 8.3 |
| tosylate | 0.4 | 0.4 | | | | | 2.8 |
| trifluoroacetate | 0.2 | | | | 1.7 | | |
| number of salts | 523 | 272 | 50 | 47 | 60 | 58 | 36 |

employed by the pharmaceutical industry. The extensive use of combinatorial chemistry and high-throughput screening in drug discovery has led to higher lipophilicity and commensurate lower solubility and dissolution rate of new drug candidates over the past 20 years. This in turn has necessitated a more intensive search for appropriate salts as a tool to improve physical chemical properties, a search typically conducted at the end of lead optimization or during exploratory development.

**Figure 2.** Overall distribution of anions used in APIs of category I in the Orange Book.

Distribution of Cationic Counterions Used To Form Pharmaceutical Salts. All cationic counterions together with their respective incidences are listed in Table 3. Figure 4 shows the overall distribution of cations in salts formed from chemical entities exhibiting acidic properties. In Figure 5, the relative occurrence during the last period from 2002 to 2006 is depicted. Among the cations used to form API salts of acidic molecules, the sodium ion strongly dominates with an incidence of 75.3% over the entire period. From 1982 to 1991, the fraction of sodium salts was more than 90%. This decreased to 62.5% during the

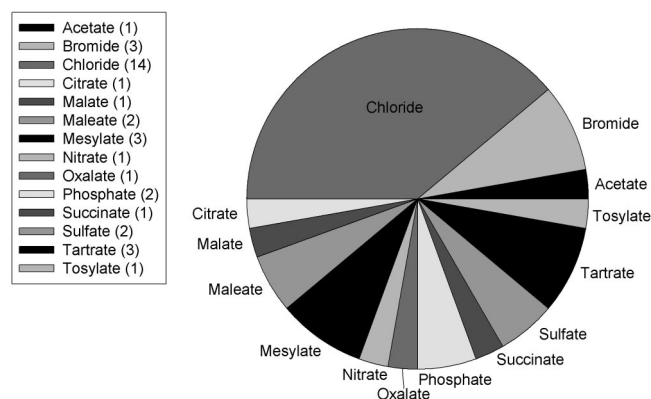
**Figure 3.** Distribution of anions used in APIs of category I from 2002 to 2006.

Table 3. Distribution of Cations Used in APIs of Category I

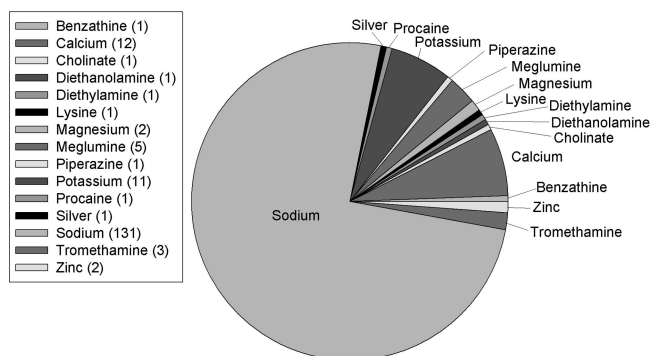
| | overall (%) | pre-1982 (%) | 1982–1986 (%) | 1987–1991 (%) | 1992–1996 (%) | 1997–2001 (%) | 2002–2006 (%) |
|-----------------|-------------|--------------|---------------|---------------|---------------|---------------|---------------|
| benzathine | 0.6 | 1.0 | | | | | |
| calcium | 6.9 | 7.3 | | | 9.5 | | 18.8 |
| choline | 0.6 | 1.0 | | | | | |
| diethanolamine | 0.6 | 1.0 | | | | | |
| diethylamine | 0.6 | 1.0 | | | | | |
| lysine | 0.6 | | | | | | 6.3 |
| magnesium | 1.2 | | | | | 6.3 | 6.3 |
| meglumine | 2.9 | 5.2 | | | | | |
| piperazine | 0.6 | 1.0 | | | | | |
| potassium | 6.3 | 6.3 | | | 14.3 | 6.3 | 6.3 |
| procaine | 0.6 | 1.0 | | | | | |
| silver | 0.6 | 1.0 | | | | | |
| sodium | 75.3 | 72.9 | 91.7 | 92.3 | 66.7 | 87.5 | 62.5 |
| tromethamine | 1.7 | | | 7.7 | 9.5 | | |
| zinc | 1.2 | 1.0 | 8.3 | | | | |
| number of salts | 174 | 96 | 12 | 13 | 21 | 16 | 16 |

2002–2006 period. The second most common cation is calcium with an average incidence of 6.9%. Its peak frequency of 18.8% was reached during 2002–2006. Another cation with frequent usage is potassium. On average, 6.3% of the FDA-approved drugs of category II are potassium salts. Potassium salts show their highest relative occurrence during 1992–1996, yielding 14.3% of API salts obtained from acidic entities. Benzathine, choline, diethanolamine, diethylamine, meglumine, piperazine, procaine, and silver have not been used over the past 25 years. They were only used once each during the time frame before end of 1981. Lysine and magnesium were both introduced as counterions during the past 10 years.

Only two basic counterions were utilized in each of the two 5-year periods 1982–1986 (sodium, zinc) and 1987–1991 (sodium, tromethamine). This number increased from three in the period 1992–1996 to five in the period 1997–2001 to six in the period 2002–2006. This analysis indicates that the trend toward a wider diversity of counterions observed for usage of anions is also occurring with cations.

Salts Used in Oral Formulations. Of the 1356 chemically well-defined APIs listed in the Orange Book, 844 are used for oral delivery. A total of 449 (53.2%) of them are nonsalt forms, 320 (37.9%) salts are formed from molecules exhibiting basic properties, and 75 (8.9%) are salts formed from entities with acidic behavior. A total of 30 different anions have been used, 17 of them during the past 25 years. Only eight cations have been employed for formation of salts from acidic moieties, five of which were employed over the past 25 years. The analysis shows that 15 anions and 3 cations were only used once.

Distribution of Anionic Counterions Used in Oral Formulations. Relative incidences of all anions used in FDA-approved oral formulations are presented in Table 4. The anion

**Figure 4.** Overall distribution of cations used in APIs of category II in the Orange Book.

applied most frequently in APIs utilized in oral formulations is chloride. Its fraction increased from 55.8% (pre-1982) through 65.4% (1982–1986) to 79.2% (1987–1991). After this period, there was a continuous decrease from 65.7% (1992–1996) through 45.0% (1997–2001) to 34.8% (2002–2006). Other important anions for oral delivery comprise sulfate with an incidence of 7.5%, maleate with 6.9%, and mesylate with 4.4% over the whole period. Mesylate salts exhibited a peak incidence of 15.0% during 1997–2001. Citrate salts were also frequently encountered during the same period, with 7.5% compared to an average fraction of 3.4% over the whole time period. The fifth anion according to frequency of usage ranking is bromide with an average value of 4.1% and a peak occurrence of 8.7% in 2002–2006.

During each of the periods from 1982 to 1986 and 1987–1991, salts containing five different anions were approved in oral formulations. Between 1992 and 1996, 10 different anions were used in API salts in newly approved drug products intended for oral use. During the two last periods of 1997–2001 and 2002–2006, 11 anions were applied per period. Thus, the overall trend toward a higher variety of acids and bases used for formation of salts is reflected in APIs for oral application.

Distribution of Cationic Counterions Used in Oral Formulations. All cations encountered as counterions for formation of API salts used in products for oral delivery are summarized in Table 5. Sodium represents the most common cation of this category. Its average frequency of occurrence during the whole time period analyzed is 65.3%. It strongly fluctuates during the different 5-year time periods with a relative

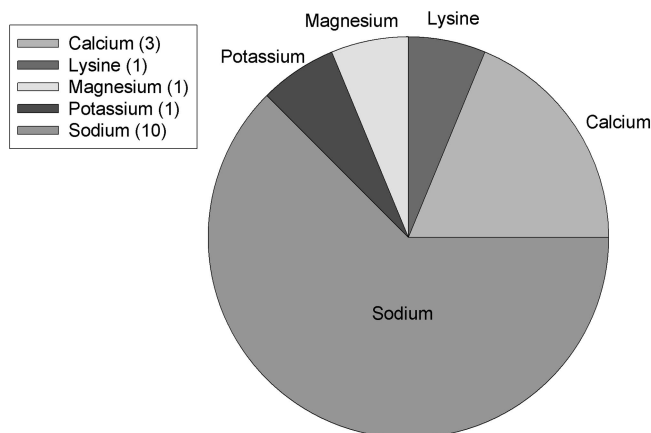
**Figure 5.** Distribution of cations used in APIs of category II from 2002 to 2006.

Table 4. Distribution of Anions for API Used in Oral Dosage Forms

| | overall (%) | pre-1982 (%) | 1982–1986 (%) | 1987–1991 (%) | 1992–1996 (%) | 1997–2001 (%) | 2001–2006 (%) |
|--------------------|-------------|--------------|---------------|---------------|---------------|---------------|---------------|
| acetate | 0.9 | 0.6 | 7.7 | | | | |
| benzoate | 0.3 | | | | | 2.5 | |
| beylolate | 0.6 | 0.6 | | | 2.9 | | |
| bromide | 4.1 | 5.2 | | | | 5.0 | 8.7 |
| chloride | 56.6 | 55.8 | 65.4 | 79.2 | 65.7 | 45.0 | 34.8 |
| chlorthophyllinate | 0.3 | 0.6 | | | | | |
| citrate | 3.4 | 4.1 | | | 2.9 | 7.5 | |
| ethandisulfonate | 0.3 | 0.6 | | | | | |
| fumarate | 1.6 | 0.6 | | 4.2 | 2.9 | 5.0 | |
| gluconate | 0.3 | 0.6 | | | | | |
| hippurate | 0.3 | 0.6 | | | | | |
| iodide | 0.3 | 0.6 | | | | | |
| lactate | 0.3 | 0.6 | | | | | |
| laurylsulfate | 0.3 | 0.6 | | | | | |
| malate | 0.3 | | | | | | 4.4 |
| maleate | 6.9 | 8.7 | 3.9 | | 5.7 | 5.0 | 8.7 |
| mesylate | 4.4 | 1.7 | | 8.3 | 2.9 | 15.0 | 8.7 |
| methylsulfate | 0.6 | 1.2 | | | | | |
| napsylate | 0.6 | 1.2 | | | | | |
| nitrate | 0.6 | | 3.9 | | 2.9 | | |
| octadecanoate | 0.3 | 0.6 | | | | | |
| oxalate | 0.3 | | | | | | 4.4 |
| pamoate | 0.9 | 1.7 | | | | | |
| phosphate | 2.5 | 2.9 | | | | 2.5 | 8.7 |
| polygalacturonate | 0.3 | 0.6 | | | | | |
| succinate | 1.9 | 1.2 | | | 5.7 | 2.5 | 4.4 |
| sulfate | 7.5 | 7.6 | 19.2 | 4.2 | 2.9 | 5.0 | 8.7 |
| tartrate | 2.8 | 1.7 | | 4.2 | 5.7 | 5.0 | 4.4 |
| tosylate | 0.3 | | | | | | 4.4 |
| number of salts | 320 | 172 | 26 | 24 | 35 | 40 | 23 |

Table 5. Distribution of Cations for API Used in Oral Dosage Forms

| | overall (%) | pre-1982 (%) | 1982–1986 (%) | 1987–1991 (%) | 1992–1996 (%) | 1997–2001 (%) | 2002–2006 (%) |
|-----------------|-------------|--------------|---------------|---------------|---------------|---------------|---------------|
| benzathine | 1.3 | 2.3 | | | | | |
| calcium | 12.0 | 11.4 | | | 11.1 | | 50.0 |
| choline | 1.3 | 2.3 | | | | | |
| magnesium | 2.7 | | | | | 11.1 | 16.7 |
| piperazine | 1.3 | 2.3 | | | | | |
| potassium | 13.3 | 13.6 | | | 33.3 | | 16.7 |
| sodium | 65.3 | 68.2 | 100.0 | 83.3 | 44.4 | 88.9 | 16.7 |
| tromethamine | 2.7 | | | 16.7 | 11.1 | | |
| number of salts | 75 | 44 | 1 | 6 | 9 | 9 | 6 |

fraction of at least 68.2% until 1991. This value decreased to 44.4% during 1992–1996. During the following period, 1997–2001, there was an increase to 88.9% followed by a huge drop to just 16.7% during 2002–2006. The strong fluctuations are caused by the small absolute numbers of approved drug products containing salts formed from acidic entities. There were a maximum of nine drugs approved in this category for oral usage during each of the 5-year periods. The second common cation is potassium with an average fraction of 13.3% over the whole period and a peak of 33.3% in 1992–1996. The third important cation for oral dosage forms, which accounted for a total frequency of 12.0% and a peak of 50.0% during the last period from 2002 to 2006, is calcium. Thus, calcium and potassium have changed positions in usage ranking for oral dosage forms in recent times.

A good example of how the counterion affects the physical chemical properties of an API in oral formulations is diclofenac and its salts. There are both sodium and potassium salts of diclofenac applied in drug products for oral delivery. The free acid is not used in FDA-approved drug products. Only the diclofenac sodium salt is utilized for extended and delayed release tablet dosage forms. In contrast, the diclofenac potassium salt is used for immediate release tablets. This suggests that

the different salt forms may influence dissolution rates. Fini et al.²¹ have discussed the difference in dissolution behavior between these salt forms.

Salts Used in Injectable Formulations. The 482 APIs used for injectable formulations consist of 171 (35.5%) nonsalt forms, 208 (43.2%) API salts of basic molecules, and 103 (21.4%) salts of acidic entities, whereas in APIs utilized in oral formulations about half of the APIs were used as nonsalt forms; in injectable formulations only about one-third were employed as noncharged forms. This shows that formation of salts is even more important for injectable dosage forms than for oral formulations. The more frequent usage of salt forms in injectable formulations can be explained by the need for even higher solubility compared to oral formulations. An oral dosage form needs to completely dissolve in 250 mL of aqueous media in the physiological relevant pH range of 1–8 to be classified as highly soluble with reference to the Biopharmaceutical Classification System.²² Typically, the preferred injectable dosage form comprises a volume of a few milliliters. If the solubility of the API is too low for this application, an infusion formulation becomes necessary. In many cases, there is a difference of at least one order of magnitude with respect to the solubility required for the formulation of an API as an injectable versus

Table 6. Distribution of Anions for API Used in Injectable Dosage Forms

| | overall (%) | pre-1982 (%) | 1982–1986 (%) | 1987–1991 (%) | 1992–1996 (%) | 1997–2001 (%) | 2002–2006 (%) |
|---------------------|-------------|--------------|---------------|---------------|---------------|---------------|---------------|
| acetate | 5.8 | 2.3 | 5.0 | 26.3 | | 14.3 | 16.7 |
| besylate | 1.4 | 0.8 | 5.0 | | 5.0 | | |
| bromide | 4.3 | 3.9 | 5.0 | 5.3 | 5.0 | 7.1 | |
| camphorsulfonate | 0.5 | 0.8 | | | | | |
| chloride | 53.4 | 54.3 | 60.0 | 42.1 | 55.0 | 50.0 | 50.0 |
| chlortheophyllinate | 0.5 | 0.8 | | | | | |
| citrate | 2.4 | 1.6 | 5.0 | | 5.0 | | 16.7 |
| ethandsulfonate | 0.5 | 0.8 | | | | | |
| fumarate | 0.5 | | | | 5.0 | | |
| gluceptate | 0.5 | 0.8 | | | | | |
| gluconate | 0.5 | 0.8 | | | | | |
| glucuronate | 0.5 | - | | | 5.0 | | |
| iodide | 1.0 | 1.6 | | | | | |
| isethionate | 1.0 | 0.8 | 5.0 | | | | |
| lactate | 2.9 | 3.1 | 5.0 | 5.3 | | | |
| lactobionate | 0.5 | 0.8 | | | | | |
| malate | 0.5 | 0.8 | | | | | |
| maleate | 1.4 | 2.3 | | | | | |
| mesylate | 3.9 | 3.1 | | | | 21.4 | 16.7 |
| nitrate | 0.5 | 0.8 | | | | | |
| oleate | 0.5 | | | 5.3 | | | |
| pamoate | 0.5 | | | | | 7.1 | |
| phosphate | 3.4 | 3.9 | | 5.3 | 5.0 | | |
| succinate | 0.5 | | | | 5.0 | | |
| sulfate | 8.2 | 10.9 | 10.0 | 5.3 | | | |
| tartrate | 3.9 | 4.7 | | 5.3 | 5.0 | | |
| tosylate | 0.5 | 0.8 | | | | | |
| trifluoroacetate | 0.5 | | | | 5.0 | | |
| number of salts | 208 | 129 | 20 | 19 | 20 | 14 | 6 |

Table 7. Distribution of Cations for API Used in Injectable Dosage Forms

| | overall (%) | pre-1982 (%) | 1982–1986 (%) | 1987–1991 (%) | 1992–1996 (%) | 1997–2001 (%) | 2002–2006 (%) |
|-----------------|-------------|--------------|---------------|---------------|---------------|---------------|---------------|
| benzathine | 1.0 | 1.6 | | | | | |
| calcium | 2.9 | 4.8 | | | | | |
| diethanolamin | 1.0 | 1.6 | | | | | |
| diethylamin | 1.0 | 1.6 | | | | | |
| lysine | 1.0 | | | | | | 14.3 |
| meglumine | 4.9 | 7.9 | | | | | |
| potassium | 1.0 | 1.6 | | | | | |
| procaine | 1.0 | 1.6 | | | | | |
| sodium | 85.4 | 79.4 | 100.0 | 88.9 | 100.0 | 100.0 | 85.7 |
| tromethamine | 1.0 | | | 11.1 | | | |
| number of salts | 103 | 63 | 9 | 9 | 8 | 7 | 7 |

an oral dosage form, with higher solubility generally required for APIs used in injectable dosage forms. The increased percentage of APIs employed as salt forms in injectable dosage forms shows that formation of salts is a practical way to achieve this objective. A total of 28 different anions and 10 different cations were used as counterions for formation of salts utilized in FDA-approved injectable formulations. Seventeen anions and only three cations were used over the past 25 years.

Distribution of Anionic Counterions Used in Injectable Formulations. A summary of the frequency of occurrence of all anions used for the formation of salts of basic molecules in injectable formulations is presented in Table 6. As for oral dosage forms, the most important anion is chloride with an average fraction of 53.4%. This incidence has remained quite stable, exhibiting a minimum of 42.1% and a maximum of 60.0%. During the last two periods (1997–2001 and 2002–2006) the fraction was 50.0% each. The second widely used anion is sulfate with a total fraction of 8.2%. However, after 1991 no further sulfate salts have been approved for injectable dosage forms. The third anion in frequency of occurrence ranking is acetate with an average fraction of 5.8% and a peak value of 26.3% during the 1987–1991 period. During the following

period, from 1992 to 1996, there were no further FDA-approved acetate salts. On the other hand, during the last two periods 1997–2001 and 2002–2006 the relative fraction of acetates increased to 14.3% and 16.7%. Frequent usage of mesylates over the past 10 years, with a relative frequency of occurrence of 21.4% during the 1997–2001 period and 16.7% during the 2002–2006 period, is apparent from Table 6. This is in strong contrast to the period from 1982 to 1996 in which no mesylate salts were approved for injectable dosage forms. In contrast to API salts containing anionic counterions intended for oral formulations, a trend toward a broader variety of anions cannot be observed for injectable formulations.

Distribution of Cationic Counterions Used in Injectable Formulations. In category II, 38 of the 40 APIs used in injectable formulations and approved over the past 25 years are sodium salts. Beyond the sodium salts, there is only one tromethamine salt approved in 1989 and one lysine salt approved in 2006. A summary together with the 63 salt forms approved before 1982 is given in Table 7.

Comparison with Analysis of Data from the Cambridge Structural Database. Haynes, Jones, and Motherwell searched the Cambridge Structural Database (CSD) for the

occurrence of salts with pharmaceutically acceptable counterions.²³ It is mentioned that the CSD is a database that is not limited to pharmaceuticals. Rather, it contains many substances used in other industries, such as pigments. The analysis of Haynes et al. was published in 2005, covering a time span of more than 80 years. Haynes et al. received 6021 hits for anions and 587 hits for cations. A hit represents one structure of an organic salt found in the CSD. Because of the fact that the CSD is not a database exclusively comprising APIs, it is difficult to obtain pharmaceutically relevant trends in salt selection from this database.

Haynes et al. searched the CSD for salt forms containing pharmaceutically acceptable counterions. For this search they used 69 different anions and 21 different cations. However, since the authors faced difficulties in determining charges and the bonding type of metal atoms, they were unable to differentiate appropriately between ionic and covalent compounds. This problem forced the authors to omit all compounds containing metal atoms. Because metal cations are the most frequently used cationic counterions in the Orange Book, a comparison of the data between the Orange Book and CSD for cations is not meaningful.

As a consequence, only the results for anionic counterions are compared with the Orange Book data. The comparison of the relative occurrence of anions used as counterions for the formation of salts shows large differences between the CSD and the Orange Book analysis. As one example, bromides used for formation of salts account for a much higher share in the CSD (23.3%) than in the Orange Book (4.6%). In contrast to this observation, the results for chlorides agree quite well: 47.7% in the CSD and 53.4% in the Orange Book. The maleate, mesylate, and sulfate fractions in the CSD are distinctly lower than in the Orange Book: 1.3% (CSD) versus 4.2% (Orange Book) for maleates, 1.1% (CSD) versus 4.2% (Orange Book) for mesylates, and 2.7% (CSD) versus 7.5% (Orange Book) for sulfates.

The ratio of salts formed with anionic counterions to salts formed with cationic counterions in the CSD analysis is about 10 to 1. The respective ratio obtained from the Orange Book is roughly 3 to 1. This reflects the large fraction of compounds left out by neglecting substances containing metal cations in the CSD analysis. Nonsalt forms of API were not considered in the CSD analysis.

The CSD analysis for cationic counterions loses pharmaceutical relevance by using a database that includes non-API substances and leaves out metal cations as counterions. Surprisingly, the analysis for anionic counterions gives the right order of magnitude for most anions. Nevertheless, examples such as the bromide salts show that the CSD results are not sufficiently reliable. In conclusion, analysis of a very general database like the CSD cannot be expected to and does not yield results relevant in a pharmaceutical environment.

Comparison with Analysis of Data from Martindale. Berge, Bighley, and Monkhouse published a review article about pharmaceutical salts in 1977.¹ In this article, the distribution of counterions at that time was presented. Their list was based on Martindale's "The Extra Pharmacopoeia", 26th edition, from 1974. The authors listed 80 different anions and 21 different cations used as counterions for formation of pharmaceutical salts. At that time, 53 anions and 14 cations were classified as FDA-approved. The distribution of counterions obtained in this analysis is comparable to the average values from the Orange Book compilation obtained 30 years later. This can be derived from the data summarized in Table 8. The good agreement is

Table 8. Comparison of Orange Book (2006) Data with Data from Berge, Monkhouse, and Bighley (1993 and 1974)

| counterion | Martindale, 1974 (%) | Martindale, 1993 (%) | Orange Book, 2006 (%) |
|------------|----------------------|----------------------|-----------------------|
| bromide | 7.6 | 5.7 | 4.6 |
| chloride | 47.7 | 48.9 | 53.4 |
| maleate | 3.0 | 3.1 | 4.2 |
| mesylate | 2.0 | 3.2 | 4.2 |
| sulfate | 7.8 | 6.1 | 7.5 |
| calcium | 10.5 | 12.2 | 6.9 |
| potassium | 10.8 | 9.8 | 6.3 |
| sodium | 62.0 | 57.7 | 75.3 |

not surprising because the trend toward a broader variety of counterions first started to have a notable impact on distributions around the mid-1990s. Because of the large number of APIs approved before that point in time, the average distribution is still dominated by drug products approved earlier.

There is a second publication by the same authors on this topic.³ This analysis is based on Martindale's "The Extra Pharmacopoeia", 30th edition, from 1993. It lists 112 different anions and 38 cations. Some of the counterions have not been newly introduced for formation of API salts but simply listed with the respective trivial names. This leads to multiple references of the same counterion. Another circumstance leading to the increased variety of anionic and cationic counterions at this time is the fact that quite a lot of counterions were used in only one case. Although the database changed considerably from 1974 to 1993, results are still in quite good agreement for the most important counterions and compare well with the data from our Orange Book analysis. Some examples of important counterions are given in Table 8.

One must keep in mind that the Orange Book only contains drug products approved in the U.S. In contrast, the "Martindale Extra Pharmacopoeia" contains drug products from all over the world. A further reason for differences between both databases is the way salt forms and formulations are counted, e.g., if salt forms used in drug products containing more than one API are considered as separate use of the counterion.

Conclusions

This contribution proves that there is a trend away from using a small selection of counterions for formation of pharmaceutical salts toward a much broader variety of ions. This trend started in the 1990s and has accelerated significantly during recent years. The separate analysis for APIs used in oral and injectable dosage forms confirms that trends in the choice of counterions depend on the route of administration.

The comparison with data from other databases indicates the importance of the choice of the data source. Only pharmaceutical databases will give pharmaceutically relevant results reflecting the specific needs for development of new drugs. The data from the Orange Book agrees well with data from older pharmaceutical sources; this is exemplified by comparison with data from Martindale's "The Extra Pharmacopoeia". Finally, it is speculated that the trend toward more diversity in pharmaceutical salts will be even more pronounced in the near future, as increasingly challenging molecules are selected for predevelopment and clinical development.

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