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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 Database[20] 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

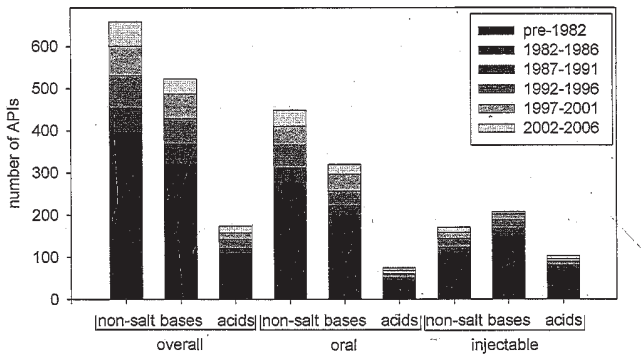


Figure 1. Classification and distribution of species in the Orange Book according to their type of charge and administration route.

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%.

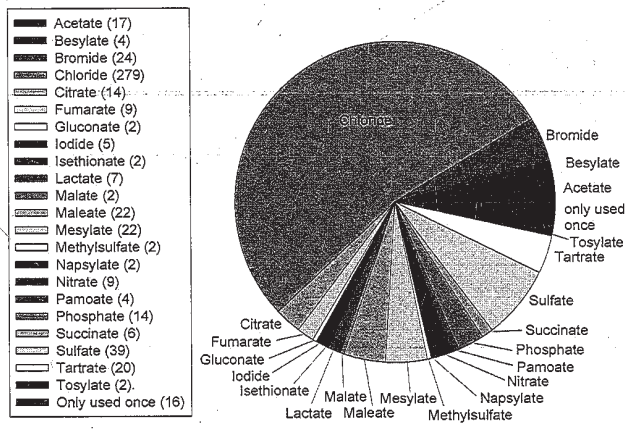
There appears to be some tendency for "fashions" in anionic counterion selection, with certain counterions showing a noticeably higher occurrence during one period compared to their overall usage. For example, nitrates represented 8.0% of anionic counterions during the 1982–1986 period. The average usage 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

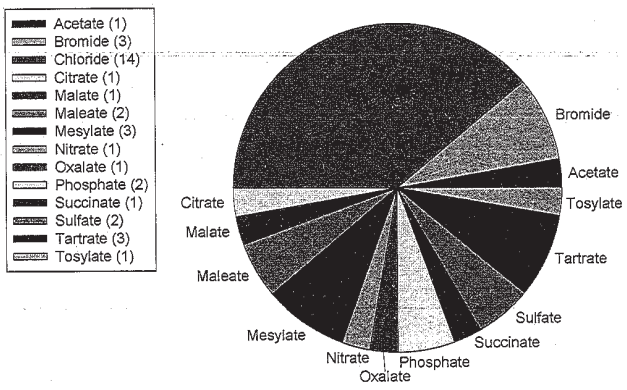
Table 2. Distribution of Anions Used in APIs of Category I

	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	
besylate	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
chlortheophyllinate	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.

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





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