1-2012

A survey of Top 200 Drugs—Inconsistent Practice of Drug Strength Expression for Drugs Containing Salt Forms

Daniel Prohotsky
St. John Fisher College, dlp02075@students.sjfc.edu

Fang Zhao
St. John Fisher College, fzhao@sjfc.edu

Publication Information

Prohotsky, Daniel and Zhao, Fang (2012). "A survey of Top 200 Drugs—Inconsistent Practice of Drug Strength Expression for Drugs Containing Salt Forms." *Journal of Pharmaceutical Sciences* 101.1, 1-6.

A survey of Top 200 Drugs—Inconsistent Practice of Drug Strength Expression for Drugs Containing Salt Forms

Abstract
Many ionizable drugs are developed and marketed as salt forms. However, there are no clear US regulatory guidelines on drug strength labeling for salts. The strengths of some drugs are expressed as salts and some as free acids/bases. This study surveyed the top 200 US drugs to assess the common practice in industry. The top 200 drugs prescribed in the United States were included in this survey. The drugs containing active pharmaceutical ingredient (API) salts were selected for analysis. Generic or combination products with redundant API salts were excluded. The package insert of each selected drug was reviewed, and the information on drug strength expression was extracted and categorized. Out of the top 200 drugs, 59 unique API salts were identified. The drug strengths were expressed as salts for 32 drugs (54%) and as free acids/bases for 27 drugs (46%). The survey results revealed the inconsistent practice among the industries regarding the drug strength expression for salts. Non-harmonized labeling practice can lead to confusions, potential calculation/dosing errors, and complications in labeling new products. The authors recommend the US Food and Drug Administration to standardize the labeling format for salts and preferably express the drug strengths based on the free acid/base forms. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association.

Disciplines
Pharmacy and Pharmaceutical Sciences

Comments
This is the author's manuscript version of the article. The final published version of this article is available through the publisher: https://doi.org/10.1002/jps.22735

A Survey of Top 200 Drugs – Inconsistent Practice of Drug Strength Expression for Drugs Containing Salt Forms

by

Daniel L. Prohotsky and Fang Zhao[1]

Wegmans School of Pharmacy, St. John Fisher College, 3690 East Avenue, Rochester, NY 14618

[1] Corresponding author. Email address: fzhao@sjfc.edu; Phone: 585-385-5296

ABSTRACT

Purpose. Many ionizable drugs are developed and marketed as salt forms. However, there are no clear US regulatory guidelines on drug strength labeling for salts. The strengths of some drugs are expressed as salts and some as free acids/bases. This study surveyed the top 200 US drugs to assess the common practice in industry.

Methods. The top 200 drugs prescribed in US were included in this survey. The drugs containing API salts were selected for analysis. Generic or combination products with redundant API salts were excluded. The package insert of each selected drug was reviewed, and the information on the drug strength expression was extracted and categorized.

Results. Out of the top 200 drugs, 59 unique API salts were identified. The drug strengths were expressed as salts for 32 drugs (54%) and as free acids/bases for 27 drugs (46%).

Conclusion. The survey results revealed the inconsistent practice among the industry regarding the drug strength expression for salts. Non-harmonized labeling practice can lead to confusions, potential calculation/dosing errors, and complications in labeling new products. The authors recommend the FDA and industry to standardize the labeling format for salts and preferably express the drug strengths based on the free acid/base forms.

KEY WORDS

Regulatory science, preformulation, formulation, physicochemical, physicochemical properties, Acid/Base

INTRODUCTION

Many drug molecules are weak acids or bases, and they can form stable salts with the suitable counter ions [1-2]. For various reasons, the salt forms are often chosen as the API (active pharmaceutical ingredient) forms for the development and commercialization of the drug products [1-2]. Based on a recent study, 51.4% of the 1356 drugs in the US Orange Book Database are formulated with the salt forms [3].

Currently, the US labeling requirements for drug products do NOT specify how the drug strengths are expressed for salt forms, as evidenced by the relevant sections from the Code of Federal Regulations (CFR) and United States Pharmacopoeia (USP) below.

Excerpts from CFR [4]

> (a)(2) *Drug names, dosage form, route of administration, and controlled substance symbol.* The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in §600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration.
>
> (a)(8) *Dosage forms and strengths*. A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets) and whether the product is scored.
>
> (c)(4)*3 Dosage forms and strengths*. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:
> (i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and
> (ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

Excerpt from USP [5]

> **10.40.10 Amount of Ingredient Per Dosage Unit**

> The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage on the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

As a result, the strengths of some drugs are expressed as the salt forms and some as the free bases/acids. In other words, it is not possible for anyone to accurately interpret the strength of a salt drug simply based on the drug product title and the strength. To obtain such information, one has to read the "Description" section of the FDA-approved drug labeling which is also known as the "package insert" and will be referred as such throughout the rest of this article. In the Description section, the manufacturer typically provides some clarification on the strength expression of the salt. Alternatively, this information can be searched for in the Orange Book [6] or the Drugs@FDA database [7]. However, these publications do not accompany the drug products, and most users are not aware of this feature.

In 2006, FDA amended its regulations governing the content and format of the package insert [8]. The changes were intended to make it easier for the health care practitioners to access, read, and use the prescribing information. However, the strength expression issue mentioned above was not addressed. To make matters worse, the Description section was moved from the beginning of the document to the middle, making it more difficult for an average user to obtain the information needed to interpret the drug strengths correctly.

Non-harmonized labeling practice can lead to unnecessary confusion and mistakes among pharmaceutical scientists and health care practitioners. This study was

initiated in order to survey the current practice in pharmaceutical industry regarding the strength expression for drugs which are marketed in their salt forms.

METHODS

This survey included the top 200 drugs in the US market based on the number of prescriptions dispensed in 2010 [9]. The package inserts of all 200 drugs were obtained from DailyMed [10] for analysis. The drugs which did not contain API salt forms were first eliminated. Potassium chloride products, quaternary ammonium salts, and proteins were also excluded. The remaining drugs were then sorted to remove duplication. Multi-source generic products containing the same API salt were counted as one entry; only the highest ranking product was included in the data table. Combination drug products were included if they contain at least one API salt which was not present as a single drug product in the top 200 list. For example, hydrocodone/APAP was included, because hydrocodone (bitartrate salt) was not available as a single drug product. Amlodipine besylate/benazepril, on the other hand, was not included, because each of the two API salts was available as a single drug product in the top 200 list. Hydrocodone bitartrate and codeine phosphate were present in several different combination products, and only the highest ranking product for each drug was included in the data table.

Once the non-salt and duplicate drugs were eliminated, the remaining drugs were categorized into two groups: salts of weak acids and salts of weak bases. The Description section of the package insert of each drug was carefully reviewed to identify whether the strength of drug was expressed as the salt or free acid/base.

RESULTS

The survey results are summarized in Figure 1. Out of the top 200 drugs prescribed in 2010, 59 unique API salts were identified. Thirteen of the 59 drugs were salts of acids; the drug strengths were expressed as the free acids for 7 drugs and as the salts for 6 drugs. Forty-six drugs of the 59 drugs were salts of bases; the drug strengths were expressed as the free bases for 20 drugs and as the salts for 26 drugs. The data on the 59 individual drugs are presented in Tables 1 and 2 for acidic and basic drugs, respectively. Overall, 54% products were labeled based on the salt forms and 46% based on free acid/base forms.

In addition to the percent distributions, three noteworthy observations are included below.

Amlodipine besylate/benazepril hydrochloride was a combination capsule product (rank 136). The capsule strengths were expressed as the free base for amlodipine besylate but as the salt for benazepril hydrochloride [10].

In the package insert of rosuvastatin calcium tablet (rank 16), it was not explained whether the tablet strengths were expressed as the salt or the free acid [10]. Additional information was obtained from the Drugs@FDA database [7], which verified that the tablet strengths were expressed as the salt.

An error was noted in TEVA's package insert of benazepril hydrochloride (rank 174), a generic product of Lotensin® from Novartis. The excerpts from the two package inserts are shown below for comparison [10]. The term "hydrochloride" was apparently omitted by mistake in TEVA's document, which could be misleading for product strength interpretation.

Excerpt from TEVA's Package Insert:

> Benazepril hydrochloride is supplied as tablets containing 5 mg, 10 mg, 20 mg, and 40 mg of benazepril for oral administration.

Excerpt from Novartis's Package Insert:

> Lotensin is supplied as tablets containing 5 mg, 10 mg, 20 mg and 40 mg of benazepril hydrochloride for oral administration.

DISCUSSION

The molecular formula of a salt is different from that of the free acid/base due to the presence of the counter ion. In some cases, the counter ion can account for a significant fraction of the total formula weight. For example, escitalopram is marketed as the oxalate salt [10]. The MW of escitalopram (free base) is 324, and the MW of escitalopram oxalate is 414. The counter ion in this case is 21.7% of the salt. Fentanyl citrate (not in top 200 list) represents an extreme case, where the citrate ion accounts for 36.3% of the total salt weight.

Currently, the US regulatory labeling requirements do not specify how the strengths are labeled for drugs which are salts. The manufacturer can express the drug strength as the salt form or as free acid/base. If the manufacturer chooses to express the strength as the salt form, it is implied that the active moiety content is the labeled strength multiplied by the weight fraction of the drug in the salt form. For example, the package insert of metoprolol tartrate [10] states:

> *Metoprolol tartrate USP, is a selective beta1-adrenoreceptor blocking agent, available as 50- and 100-mg tablets for oral administration… Metoprolol tartrate USP is (±)-1-(Isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) salt… Metoprolol tartrate USP is a white, practically odorless, crystalline powder with a molecular weight of 684.82.*

In this case, the MW of metoprolol (free base) is 267 (not given in the package insert). The free base weight fraction is calculated to be 78.0%. Therefore, a 100 mg strength metoprolol tartrate tablet contains only 78 mg metoprolol.

If the manufacturer expresses the strength as the free base/acid form, the equivalent strength terms are described explicitly in the package insert. Below is an example from the escitalopram oxalate package insert [10]:

> *The molecular formula is $C_{20}H_{21}FN_2O \bullet C_2H_2O_4$ and the molecular weight is 414.40. Lexapro® tablets are film-coated, round tablets containing escitalopram oxalate in strengths equivalent to 5 mg, 10 mg, and 20 mg escitalopram base.*

Based on the survey data of the top 200 US drugs described in the Results section, there is no clear trend or consensus among industry regarding the strength labeling for salts. About 54% of the salt drugs are labeled as salts and the remaining as free acids/bases. This inconsistent labeling practice can lead to confusion among pharmaceutical scientists and health care practitioners.

The misinterpretation of the salt vs. free forms can lead to calculation errors, which can impact many critical activities. For example, the strengths of all escitalopram oxalate products are expressed as the free base [10]. If a pharmacist uses the escitalopram oxalate drug substance to compound 15 mg strength capsules, he will need 19 mg escitalopram oxalate per capsule. However, if the pharmacist misinterprets the strength expression as the salt, he will use only 15 mg escitalopram oxalate per capsule, and the final capsule strength will be 21.7% sub-potent. A similar error can occur if an analytical scientist uses the escitalopram oxalate material to prepare a standard solution without adjusting the calculations to account for the weight of the oxalate.

Non-harmonized labeling practice of the salts among industry can also complicate the strength labeling of new products based on alternative forms or combinations of existing drugs. Two examples are discussed below.

Metoprolol was first developed and marketed as a tartrate salt. The strengths of the metoprolol tartrate products (tablets and iv injections) were labeled based on the salt [10]. The metoprolol succinate salt was later developed as the API form for the extended release oral tablets. Due to the pre-existing tablet strengths based on the tartrate salt form, the new metoprolol succinate tablets were labeled based on the tartrate salt to maintain consistency (see excerpt from package insert [10] below).

> *Metoprolol succinate extended-release tablets are a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended release tablets... The tablets contain 23.75 mg, 47.50 mg, 95 mg and 190 mg of metoprolol succinate equivalent to 25 mg, 50 mg, 100 mg and 200 mg of metoprolol tartrate USP, respectively.*

It is perplexing that the strength of a metoprolol succinate tablet does not reflect the quantity of metoprolol succinate in the tablet but rather the equivalent quantity of metoprolol tartrate. In other words, a 25 mg metoprolol succinate tablet contains only 23.75 mg metoprolol succinate which is equivalent to 25 mg metoprolol tartrate. This confusing situation could have been avoided if the strengths of the original metoprolol tartrate tablets had been labeled based on the free base.

The second example involves amlodipine besylate and benazepril hydrochloride. Both drugs were initially marketed as individual oral tablet products. The amlodipine besylate tablets were labeled based on the free base [10], and the benazepril hydrochloride tablets were labeled based on the salt [10]. The combination products of these two drugs were later developed and marketed. Due to the pre-existing single drug

products, the strengths of the combo capsules were expressed as the free base for amlodipine besylate and as the salt for benazepril HCl (see excerpt from package insert [10] below).

> *Amlodipine besylate and benazepril hydrochloride capsules are a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated in six different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5 mg, 5 mg or 10 mg of amlodipine, with 10 mg, 20 mg or 40 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg and 10/40 mg.*

Based on the issues and examples described above, it should become evident that a more consistent strength labeling practice should be promoted for pharmaceutical salts to avoid unnecessary confusion and errors. The authors recommend the approach to express the strengths of salts based on the free acid/base forms. This approach states the exact quantity of the active moiety of the drug in the dosage form. It eliminates potential labeling issues when new forms of the same drug are developed and marketed at a later date.

It is also worthwhile to emphasize that while this survey focused only on the marketed drug products, the recommendation above needs to be implemented for clinical trial materials to achieve the desired outcomes for future marketed products.

Even with a standardized labeling approach, scientists and pharmacists still need to understand the relationship between salts and their free base/acid forms to perform calculations accurately for sample/dosage preparations. Therefore, it is important to provide the necessary training to entry level scientists and pharmacists. In addition, it is recommended that the manufacturers describe the strengths for both the salt and free

acid/base forms in the package insert to avoid any potential confusion. For example, clopidogrel bisulfate (Plavix®) is marketed as 75 and 300 mg strengths tablets. Even though the strengths are expressed as the free base, the package insert [10] states the strengths for both the salt and the free base without ambiguity:

> *Plavix for oral administration is provided as either pink, round, biconvex, debossed, film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or pink, oblong, debossed film-coated tablets containing 391.5 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.*

CONCLUSIONS

A survey of the top 200 US drugs revealed the inconsistent practice of strength expression for drugs which were marketed as salts. The strengths were expressed as the salt forms for 54% drugs and as the free acid/base forms for the remaining 46% drugs. Non-harmonized labeling practice can lead to unnecessary confusion among pharmaceutical scientists and healthcare practitioners. The confusion on drug strengths and forms can result in potential errors in calculations and dosing, especially when the drugs are to be compounded extemporaneously prior to use. This inconsistent labeling practice can also complicate the strength labeling when new products of existing drugs are developed, such as new salts and combination products. The authors recommend the FDA and industry to standardize the labeling format for salts and preferably express the drug strengths based on the free acid/base forms.

ACKNOWLEDGMENTS

The authors would like to acknowledge Mr. Daniel Stein and Dr. Srini Venkatesh for their helpful review and comments.

REFERENCES

1. Stahl PH, Wermuth CG, Eds. 2002. Handbook of pharmaceutical salts: Properties, selection, and use. New York: Wiley-VCH, pp 1-17.

2. Stephenson GA, Aburub A, Woods TA. 2011. Physical stability of salts of weak bases in the solid-state. J Pharm Sci 100:1607-1617.

3. Paulekuhn GS, Dressman JB, and Saal C. 2007. Trends in active pharmaceutical ingredient salt selection based on analysis of the orange book database. J Med Chem 50:6665-6672.

4. Code of Federal Regulations, Title 21: Food and Drugs, Part 201.57. Specific requirements on content and format of labeling for human prescription drug and biological products described in Part 201.56(b)(1). http://www.ecfr.gpoaccess.gov. Accessed on May 27, 2011.

5. United States Pharmacopeia and National Formulary, USP 32/NF 26. 2010. United States Pharmacopeial Convention, Inc., Rockville, MD.

6. Orange Book: Approved drug products with therapeutic equivalence evaluation. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed on Jun 17, 2011.

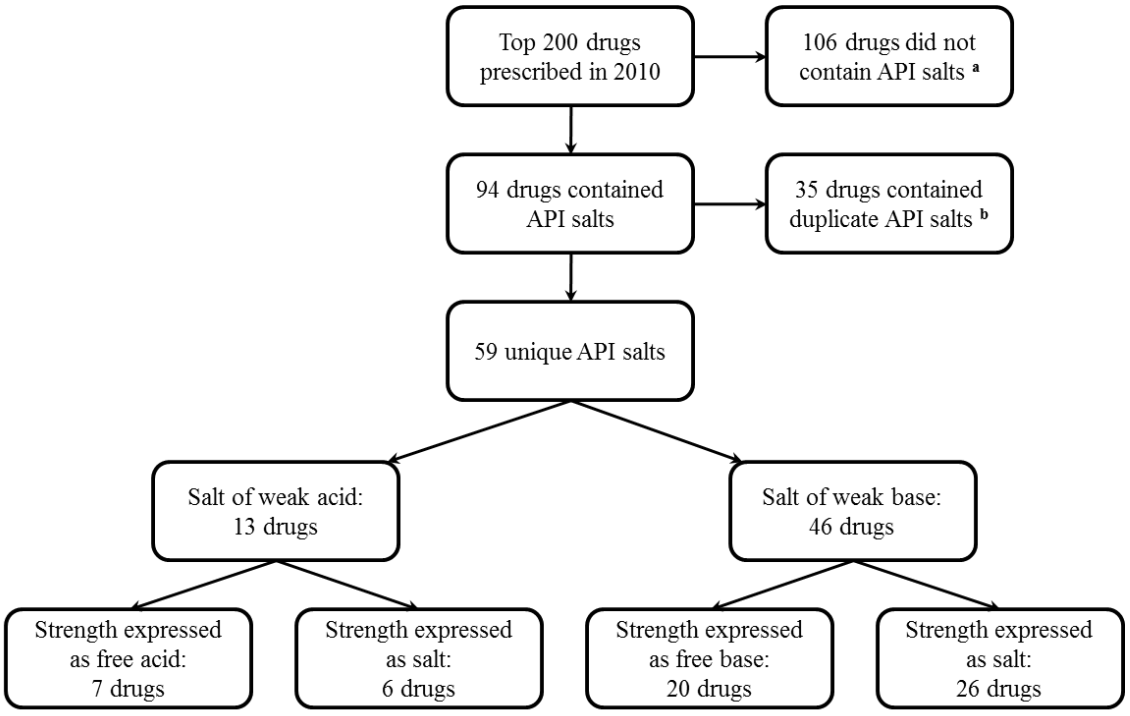
7. Drugs@FDA, FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed on Jun 17, 2011.

8. FDA Docket No. 2000N-1269. Requirements on Content and Format of Labeling for human prescription drug and biological products. http://www.fda.gov/OHRMS/DOCKETS/98fr/00n-1269-nfr0001-01.pdf. Accessed on Jun 1, 2011.

9. Bartholow M. 2010. Top 200 Prescription Drugs of 2009. Pharmacy Times Website. http://www.pharmacytimes.com/publications/issue/2011/May2011/Top-200-Drugs-of-2010. Accessed on Jun 10, 2011.

10. DailyMed. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed on Jun 17, 2011.

Figure 1. Summary results of top 200 drugs to assess the current industry practice of drug strength expression for salts.



a. This category also included KCl products, quaternary ammonium salts, and proteins.
b. These drugs were generic or combination products.

Table 1. Drug strength expressions for salts of acidic drugs from the top 200 list.

Rank [a]	Drug [b]	Strength Expression As
4	Atorvastatin Calcium	free acid
5	Levothyroxine Sodium	salt form
9	Esomeprazole Magnesium	free acid
10	Montelukast Sodium	free acid
16	Rosuvastatin Calcium	salt form
36	Warfarin Sodium	salt form
48	Amoxicillin Trihydrate/ Potassium Clavulanate	free acid
53	Pravastatin Sodium	salt form
75	Alendronate Sodium	free acid
115	Penicillin V Potassium	free acid
142	Risedronate Sodium	salt form
152	Pantoprazole Sodium	free acid
187	Naproxen	salt form

a. The ranking information was obtained from Reference 9.
b. Some API salts were used in several generic or combination products. Only the highest ranking product was included for each API salt.

Table 2. Drug strength expressions for salts of basic drugs from the top 200 list.

Rank [a]	Drug [b]	Strength Expression As
1	Hydrocodone/APAP	salt form
8	Clopidogrel Bisulfate	free base
11	Metoprolol Tartrate	salt form
13	Escitalopram Oxalate	free base
18	Albuterol Sulfate	free base
19	Metformin HCl	salt form
20	Sertraline HCl	free base
22	Metoprolol Succinate	salt form (as tartrate salt)
24	Zolpidem Tartrate	salt form
25	Fluticasone propionate/ Salmeterol xinafoate	free base
29	Trazodone HCl	salt form
33	Tramadol HCl	salt form
35	Duloxetine Hydrochloride	free base
37	Amlodipine Besylate	free base
42	Quetiapine Fumarate	free base
43	Promethazine HCl	salt form
52	Pioglitazone	free base
56	Fluoxetine HCl	free base
64	Donepazil Hydrochloride	salt form
66	APAP/Codeine	salt form
70	Ciprofloxacin HCl	free base
77	Venlafaxine Hydrochloride	free base
79	Sildenafil Citrate	free base
83	Citalopram Hydrobromide	free base
93	Cyclobenzaprine HCl	salt form
95	Methylphenidate HCl	salt form

96	Fexofenadine HCl	salt form
98	Propoxyphene-N/APAP	salt form
104	Memantine Hydrochloride	salt form
118	Sitagliptin Phosphate	free base
120	Amitriptyline Hydrochloride	salt form
121	Clonidine Hydrochloride	salt form
125	Lisdexamfetamine Dimesylate	salt form
128	Oxycodone Hydrochloride	salt form
150	Doxycycline Hyclate	free base
157	Tamsulosin Hydrochloride	salt form
161	Paroxetine Hydrochloride	free base
163	Buprenorphine Hydrochloride / Naloxone Hydrochloride	free base (both actives)
165	Enalapril Maleate	salt form
174	Benazepril Hydrochloride	salt form
175	Olanzapine Pamoate	free base
179	Tolterodine Tartrate	salt form
183	Amphetamine Salts	salt form
188	Ranitidine Hydrochloride	free base
191	Diltiazem Hydrochloride	salt form
197	Verapamil Hydrochloride SR	salt form

a. The ranking information was obtained from Reference 9.
b. Some API salts were used in several generic or combination products. Only the highest ranking product was included for each API salt.