HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajps

Original Research Paper

Pharmaceutical salts: Theory, use in solid dosage forms and *in situ* preparation in an aerosol

Timothy Scott Wiedmann [a,*], *Amir Naqwi* [b]

[a] *Department of Pharmaceutics, University of Minnesota, 308 Harvard St SE, Minneapolis, MN 55455, USA*
[b] *MSP Corporation, Shoreview, MN 55126, USA*

ARTICLE INFO

Article history:
Received 22 April 2016
Received in revised form 20 May 2016
Accepted 7 July 2016
Available online 16 July 2016

Keywords:
Solubility
Salt
Aerosol
Inhalation
Solubility product

ABSTRACT

In this article, the theoretical foundation for salts is given with an emphasis on the amount of drug in solution. Consideration is given for the solubility of the non-ionized form, acid dissociation constant and solubility product, which are the limiting constraints. For dissolution of nonionized drugs, the surface pH differs from the bulk pH, giving rise to a lower than expected rate. For salts, theoretical considerations are relatively complex, and an experimental approach to estimating the surface pH is more likely to be of value in predicting the dissolution rate. General guidelines are described for screening, preparing and characterizing drugs as salts, which critically depend on the goal of the product development. Thereafter, our work involving the preparation of salts as a means to generate aerosols from a solution is provided. The solubility of six structurally related compounds was determined in four acids. Thereafter, the amount of the compound in solution was determined as a function of pH, using the acid that provided the highest solubility. Because the pH required to achieve the needed concentration for aerosol generation was low, ammonia vapor was introduced into the air stream to neutralize aerosol droplets. Solvent was then removed from the aerosol by a silica column. The resulting aerosol had a concentration of 96 μg/l and a mass median particle size of 1.8 μm. The reported pharmacokinetic study substantiated the feasibility of evaluating its safety and efficacy of inhalation administration in the rat model.

1. Introduction

1.1. *Prevalence and importance of salts*

The formation of salts is invaluable for the preparation of safe and effective dosage forms of many drugs [1–3]. Whether the drug products are solutions or solids, the use of a salt provides a higher concentration in solution than the free acid or free base (nonionized forms). Typically, salts readily undergo crystallization, and the resulting material facilitates subsequent processing. Thus, the salt is often the preferred form for isolating and purifying the drug. Historically, the number of available salts was rather limited; however, today there is a wide

* *Corresponding author.* Department of Pharmaceutics, University of Minnesota, 308 Harvard St. SE, Minneapolis, MN 55455, USA. Fax: +1 612 626 2125.
E-mail address: wiedm001@umn.edu (T.S. Wiedmann).
Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2016.07.002

Table 1 – List of compounds available for preparing salts [4].

Cations		Anions	
Aluminum	Acetate	Glutamate	Mucate
Arginine	Aspartate	Glycolate	Napsylate
Benzathine	Benzenesulfonate	Glycollylarsanilate	Nitrate
Calcium	Benzoate	Hexanoate	Octanoate
Chloroprocaine	Besylate	Hexylresorcinate	Oleate
Choline	Bicarbonate	Hydrabamine	Pamoate
Diethanolamine	Bitartrate	Hydroxynaphthoate	Pantothenate
Ethanolamine	Bromide	Iodide	Phosphate
Ethylenediamine	Camsylate	Isethionate	Polygalacturonate
Histidine	Carbonate	Isethionate	Propionate
Lithium	Chloride	Lactate	Salicylate
Lysine	Citrate	Lactobionate	Stearate
Magnesium	Decanoate	Malate	Subacetate
Meglumine	Edetate	Maleate	Succinate
Potassium	Estolate	Mandelate	Sulfate
Procaine	Esylate	Mesylate	Tartrate
Sodium	Fumarate	Methylbromide	Teoclate
Triethylamine	Gluceptate	Methylnitrate	Tosylate
Zinc	Gluconate	Methylsulfate	Triethiodide

range of chemical entities that are recognized as being safe, which can be used in the preparation of drug products (cf Table 1) [4,5].

In addition to solubility and manufacturing, the salt is typically a more stable form of the drug. This too is an important advantage for developing a product with a long shelf-life. Although non-ionized drugs often exist in multiple polymorphic forms, the number for salts appears limited. This may be an inherent property of the ionic bond, but it should also be recognized that relatively little effort has been expended in the search for different polymorphic forms of salts [6]. As such, there may be an untapped potential, because as it has been noted, the number of polymorphic forms appears to be function of the time expended in searching for them.

In this article, the theoretical foundation for salts is given with an emphasis on the observed increased amount of drug in solution. Here, consideration is given for the solubility of the non-ionized form, acid dissociation constant and solubility product, which are the limiting constraints. The salient features of the pH dependence of the dissolution of nonionized and ionized drugs and their salts are given. Some general guidelines are reviewed for screening and characterizing drugs as salts for development of products. Thereafter, our work involving the preparation of salts as a means to generate aerosols from a solution is provided. Here, *in situ* neutralization was needed to allow the drug to be evaluated for safety and efficacy in a rat model of a respiratory disease.

1.2. *Definitions*

In 1923, Johannes Nicolaus Brønsted (Denmark) and independently Martin Lowry (England) formulated a definition of an acid and a base [7]; an acid (generically HA) gives up or donates a proton (hydrogen ion, H^+) and a base (B) accepts a proton. This may be written as:

Acid: $HA \rightleftharpoons H^+ + A^-$

Base: $B + H^+ \rightleftharpoons BH^+$

It can be noted that A^- acts as a base in the reverse reaction and is thus called a conjugate base, just as BH^+ acts as an acid and is referred to as a conjugate acid. These form a conjugate acid–base pair. That is:

$$\text{Acid} \rightleftharpoons \text{Base} + H^+$$

Water is amphoteric, acting as both an acid and a base, and is often the source of the hydrogen ions as well as hydroxide ions in pharmaceutical systems. The Brønsted–Lowry model explains the dissociation of water into hydronium and hydroxide ions:

$$H_2O + H_2O \rightleftharpoons H_3O^+ + OH^-$$

This is a type of disproportionation reaction, in which identical components react to form two different species. The corresponding equilibrium constants follow the usual convention and are as follows with the assumption of ideality:

Acid dissociation constant, $K_a = [H^+][A^-]/[HA]$

Base dissociation constant, $K_b = [BH^+][OH^-]/[B]$

For water,

$$K_w = [H^+][OH^-]$$

In these expressions, the concentration of water is assumed constant and incorporated into K_w, K_a, and K_b. Finally, for a given conjugate acid–base pair, it is noted that: