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Review

Salt disproportionation: A material science perspective

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ABSTRACT

While screening the counter-ions for salt selection for an active pharmaceutical substance, there is often an uncertainty about disproportionation of the salt and hence physical stability of the final product formulation to provide adequate shelf life. Several examples of disproportionation reactions are reviewed to explain the concepts of *pHmax*, microenvironmental *pH*, and buffering capacity of excipients and APIs to gain mechanistic understanding of disproportionation reaction. Miscellaneous factors responsible for disproportionation are examined. In addition to the dissolution failure due to the formation of less soluble unionized form, various implications of the disproportionation are evaluated with specific examples. During lead optimization and early stages of development, when only a limited amount of material is available, use of predictive tools like mathematical models and model free kinetics to rank order the various counter-ions are discussed in detail. Finally, analytical methods and mitigation strategies are discussed to prevent the disproportionation by detecting it during early stages of drug development.

Contents

Abbreviations: WHO, World Health Organization; API, active pharmaceutical ingredient; FDA, US Food and Drug Administration; RH, relative humidity; HCl, hydrochloride; PPI, proton pump inhibitor; NaCMC, croscarmellose sodium; ssNMR, solid state nuclear magnetic resonance; TSPd, tribasic sodium phosphate dodecahydrate; HPLC, high performance liquid chromatography; HDPE, high density polyethylene; HBr, hydrobromide; FTIR, Fourier transform infrared spectroscopy; ATR, attenuated total reflectance; DSC, differential scanning calorimetry; TGA, thermogravimetric analysis.

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1. Introduction

Salt formation of ionizable compounds (anionic, cationic or zwitterionic) is a well-known strategy to improve poor aqueous solubility of drugs (Kumar and Trivedi, 2017). In addition, a number of other properties such as ease of isolation, dissolution, hygroscopicity, crystal purity and habit, melting point, possibility of hydrate and polymorph formation, processability, and stability can be optimized using salt formation (Paulekuhn et al., 2007; O'Connor and Corrigan, 2001a, 2001b; Berge et al., 1977; Gould, 1986; Agharkar et al., 1976; Li et al., 2005; Stahl and Wermuth, 2008; Farag Badawy et al., 1999; Stephenson et al., 2011; Serajuddin, 2007). Change in solubility and dissolution of a compound may also influence its bioavailability and toxicity profile (Berge et al., 1977; Lin et al., 1972a, 1972b; Gwak et al., 2005). A number of pharmaceutically acceptable counter-ions, approved by the US Food and Drug Administration (FDA), are being used by the pharmaceutical industry for the purpose of salt formation, (Paulekuhn et al., 2007; FDA). For the sake of simplicity, chloride and sodium were counter-ions of choice for weakly basic and weakly acidic drugs respectively (Paulekuhn et al., 2007). But with more challenging molecules, this trend has been gradually replaced by the use of variety of other counter-ions like salts of sulfonic acids (Saal and Becker, 2013; Elder et al., 2010a, 2010b). Trend in the salt forms approved by FDA indicates that majority of the marketed ionizable drug compounds are weak base (Serajuddin, 2007).

Based on '*Acceptable Daily Intake*' of food additives and processing aids assigned by WHO and their '*Generally Regarded as Safe*' status in the USA, Stahl and Wermuth divided the salts into three categories on the basis of counter-ion used (Stahl, 2002). The first category includes salt counter-ions that have rampant use because of their physiological prevalence, such as hydrochlorides and sodium salts. The second category of salts contains counter-ions that are not typically natural in occurrence, but have low toxicity and good tolerability, e.g. sulfonic acids. The last category includes counter-ions having intrinsic property for specific industrial applications. For example, sweet cyclamate salts to mask the bitter taste of many novel APIs. Counter-ion selection is based upon the acidity or basicity of the ionizable functional group on the drug molecule. The "Rule of 3", which states that the pK_a difference ($\Delta\, pK_a$) between pK_a of counter-ion and that of ionizable group of free form should be 3 or more, is the guiding principle for successful salt formation (Bastin et al., 2000; Bowker, 2002). Principles of salt formation are explained in detail in the literature and readers may refer to a comprehensive review by Abu Serajuddin (Serajuddin, 2007).

During the drug discovery phase, salts are often formed as a means of crystallization or isolation of drug at the end of a synthetic pathway. During lead optimization, salt formation is important to achieve the optimum aqueous solubility of the drug candidate, so as to achieve sufficiently high exposure and observe any toxic effects in animals to establish its margin of safety (Stephenson et al., 2011). Usually early stage formulations for "first-in-human" use are quite simple e.g. drug in capsule or drug in bottle. However for the commercial development, physical and chemical stability of the active drug ingredient (API) must be ensured typically over a shelf life of a minimum of two years (Baertschi et al., 2011).

During manufacturing of a solid dosage form, an API along with other excipients is generally subjected to harsh processing conditions such as wet granulation, drying, roller compaction, compression, etc. Due to these processing conditions, coupled with reaction with formulation excipients, an API salt may disproportionate, i.e. dissociate and revert back to the less soluble, unionized form (Stephenson et al., 2011). Salt disproportionation, a proton exchange process involving an acid-base reaction, leads to changes in chemical composition of the API. It can adversely affect the product stability and performance e.g. loss of potency, slow dissolution and reduced bioavailability (Merritt et al., 2013; Rohrs et al., 1999; Zannou et al., 2007; Gu et al., 2004). The numerous implications of salt disproportionation are discussed in more detail in Section 5.

Disproportionation reactions are predominantly observed in dissolution studies, where the salt undergoes physical transformation in solution state and crystallize back into a less soluble free form. However, salt disproportionation in the solid state has also been reported (Stephenson et al., 2011). In solid state reactions, moisture almost always plays an important role (Carstensen, 2000). Presence of water at API-excipient interface may plasticize and increase the mobility of the surface species, and may facilitate intermolecular interactions (Ahlneck and Zografi, 1990). Even in the solid state, salt disproportionation is considered to be a solution-mediated process, where microenvironmental/surface *pH* of pharmaceutical solids is believed to play an important role (Stephenson et al., 2011; Serajuddin, 2007; Merritt et al., 2013; Pudipeddi et al., 2008). The current understanding of salt disproportionation is based on *pHmax* of the drug, i.e. point of maximum solubility and microenvironmental *pH* of the drug relative to its *pHmax* (Stephenson et al., 2011; Hsieh et al., 2015).

Microenvironmental *pH* has been defined in the literature as hydrogen ion activity in noncrystalline regions such as adsorbed water layers or water plasticized amorphous domains (Badawy et al., 2008). A number of salts have been reported to be chemically unstable due to microenvironmental *pH* created by the counter-ion (Badawy, 2001; Guerrieri et al., 2010; Hailu and Bogner, 2009). The equations used to calculate the pH of solution containing salts of weakly acidic/basic drugs (Florence and Attwood, 2006) may also be used to estimate the microenvironmental *pH*.

For a salt between a weak base and a strong acid,

$$pH = \frac{1}{2}pK_w + \frac{1}{2}pK_a + \frac{1}{2}logC \quad (1)$$

For a salt of a weak acid and a strong base,

$$pH = \frac{1}{2}pK_a - \frac{1}{2}logC \quad (2)$$

For a salt of a weak base and a weak acid,

$$pH = \frac{1}{2}pK_w + \frac{1}{2}pK_a - \frac{1}{2}pK_b \quad (3)$$

where, K_a is the dissociation constant for weak acid, K_b is the dissociation constant for weak base, K_w is the dissociation constant of water, and C is the concentration of drug in mol/L.

In a multi-component formulation, in addition to the API, excipients can significantly influence the microenvironmental *pH* by their acidity/basicity. Basic excipients can elevate, while acidic excipients can reduce the microenvironmental *pH*, and can impact the stability of the API in solid dosage form (Serajuddin and Jarowski, 1985; Badawy and Hussain, 2007; Govindarajan et al., 2006; Scheef et al., 1998). Excipients may also modulate the microenvironmental *pH* in biopharmaceuticals and hence affect the protein stability (Wittayanukulluk et al., 2004).

Measurement of microenvironmental pH in solid-state is challenging. In a solid dosage form, two different approaches have been used to empirically determine the microenvironmental *pH* – (i) the slurry experiments, where excess solid is suspended in water and *pH* of saturated solution is measured, (ii) by diffuse reflectance visible spectroscopy of the ionization of indicator dyes, mixed with the formulation (Govindarajan et al., 2006). The role of microenvironmental *pH* relative to *pHmax* in inducing salt disproportionation will be explained in the following section.