Advanced Drug Delivery Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design☆

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ARTICLE INFO

Article history:
Received 18 November 2016
Received in revised form 20 March 2017
Accepted 21 March 2017
Available online xxxx

Keywords:
Pharmaceutical
Cocrystal
Salt
Intermolecular interactions
multicomponent crystals
Physicochemical properties
Bioavailability
Pharmacokinetics

ABSTRACT

As small molecule drugs become harder to develop and less cost effective for patient use, efficient strategies for their property improvement become increasingly important to global health initiatives. Improvements in the physical properties of Active Pharmaceutical Ingredients (APIs), without changes in the covalent chemistry, have long been possible through the application of binary component solids. This was first achieved through the use of pharmaceutical salts, within the last 10–15 years with cocrystals and more recently coamorphous systems have also been consciously applied to this problem. In order to rationally discover the best multicomponent phase for drug development, intermolecular interactions need to be considered at all stages of the process. This review highlights the current thinking in this area and the state of the art in: pharmaceutical multicomponent phase design, the intermolecular interactions in these phases, the implications of these interactions on the material properties and the pharmacokinetics in a patient.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Polymorphs: Advances and Challenges".

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http://dx.doi.org/10.1016/j.addr.2017.03.003
0169-409X/

1. Introduction

In the making of new medicines, it is important to optimise and control the quantity of an active drug which is delivered to the body, organ system, or tissue in question. Appropriate quality is achieved by strict control of the manufacturing route of the medicine, to meet its designated attributes, and the solid state chemistry of the drug molecule. This is done in order to ensure reproducible delivery of the drug to the right place at the right time to treat the disease. Alterations to the solid-state chemistry of drug molecules are common within the pharmaceutical industry as they enable modification of the physical properties of a drug, without changing the pharmacology of the active pharmaceutical ingredient (API) through modification of covalent bonds. Addition of second components to alter the APIs physical chemistry has been commonplace within the pharmaceutical industry for well over a quarter of a century in the form of pharmaceutical salts [1]. More recently, i.e. for around a decade [2], it has also been common practice to include pharmaceutical cocrystals in the search for the optimum properties [3–7]. There have been many excellent reviews on the intermolecular interactions [8], growth [9], manufacture [10] and utility of cocrystals in this time [11–13], along with significant advances to accompany them. There has been seeming reticence within the industry to turn the potential of cocrystals into products however. This issue has been partially blamed on a number of key perceived problems: regulatory uncertainty, problems with manufacture at scale and a lack of *in vivo* confirmation of the promise of these systems in the lab [14]. This review will address these points from the perspectives of the intermolecular interactions within these phases, their properties pertinent to manufacture and their *in vivo* pharmacokinetics. Although not the focus of this review it is of note that recently the regulatory opinion of cocrystals has changed in the eyes of the FDA [15]. It is also important that the EMA [16] see the utility of these phases as their defining trait. With this in mind this review will focus on the following areas; intermolecular interactions, their implications on design towards robust manufacturing and their pharmacokinetics.

2. Intermolecular interactions in multicomponent crystals

2.1. Classification of multicomponent crystals

In the pharmaceutical context the basis of the utility of cocrystals and salts lies in the alterations they impart on the intermolecular interactions within the crystalline state and their potential to change *in vivo* solution behaviour through altered dissolution. Both cocrystals and salts have been seen to improve many manufacturing and biopharmaceutical properties within API materials, so knowledge of which characteristics to seek, using what chemical design strategy, is of great utility to the pharmaceutical industry and the patients it serves. It is commonly accepted that the bonding behaviours within salts and cocrystals lie along similar, though different, chemistry, but a specific tension is added within the confines of the pharmaceutical sector due to regulatory necessity. It has been suggested that cocrystals and salts offer new intellectual property opportunities [17]. Filing a patent requires some degree of definition of the disclosed phase however, as does the need to submit information about a new phase to regulatory agencies [15,16]. This inherently drives an agenda which is sometimes more prescriptive, in terms of defining the nature of the phase, than the chemistry which controls it. Initially there was reticence to see salts and cocrystals as part of the same continuum [18], but that has changed over the last decade as more data has emerged. Recently a Venn diagram approach has been proposed by de Gelder and co-workers to describe the differing phases and can be seen in Fig. 1 (although the solid/liquid at 293.15 K, 10^5 Pa distinction between solvents and coformers represents a chemically arbitrary division) [19].

This depiction of bonding behaviours is a progression from the cartoon depiction of the solid form chemistry that has previously been used to describe these phases [12]. A version of such a cartoon can be seen in Fig. 2. Here it is also evident that significant crossover is possible within cocrystal and salts. As it is clear that understanding the molecular level architectures within API phases are essential for appropriate form designation, Section 2.2 will focus on examples of the relevant interactions. It also follows that without discovery of novel phases there is nothing to define, so this section will also deal with molecular level design strategies for the discovery of new drug phases (Section 2.3) before discussion of property based design.

2.2. Understanding Intermolecular interactions within salts and cocrystals

In order for any multicomponent crystal to form there must be some kind of interaction between the molecules or ions that make up the crystal. For the system to be thought of as multi-component (*i.e.* a cocrystal or salt of any of the types shown in Fig. 2 C to H) such interactions are of a non-covalent and hence supramolecular type. While the energy and geometry of the interactions between two isolated (gas phase) molecules are relatively amenable to calculation and hence relatively well understood, the three dimensional, close-packed nature in crystals makes understanding the ways in which they are held together considerably more challenging. Ultimately, computational crystal structure prediction (CSP) methods may well hold the key to a holistic understanding of the full spectrum of intermolecular interactions in crystals. Indeed it is only through a full understanding of the contribution to the overall stability of all of the long and short range contacts made by a given molecule in a crystal that it will be ultimately possible to reliably predict the most stable crystal structure. Even then, nucleation and growth considerations may mean that the most stable structure is not experimentally accessible and hence an understanding of intermolecular interactions at all stages along the crystal formation pathway is really what is required. Such information remains beyond the scope of even the very powerful CSP methods currently available [20] although it is noteworthy that recent Cambridge Blind Tests have produced some remarkable successes [21]. In the case of multi-component systems the CSP challenge is even more daunting because of the additional degrees of freedom and hence possible structures enabled by the presence of a second component [22] and in practical terms the understanding of multi-component crystals is often based on empirical data gathering and rationalisation. However, experience in common association modes coupled with empirical rules [23–25] and carefully targeted calculations can give insight into likely cocrystal and salt formation. A good example is the deliberate engineering of ternary (three-component) cocrystals based on observations of the best hydrogen bond donor/best acceptor pairings [26]. More recently a combined

Please cite this article as: D.J. Berry, J.W. Steed, Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design, Adv. Drug Deliv. Rev. (2017), http://dx.doi.org/10.1016/j.addr.2017.03.003