Advanced Drug Delivery Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Screening for new pharmaceutical solid forms using mechanochemistry: A practical guide☆

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ARTICLE INFO

Article history:
Received 30 November 2016
Received in revised form 21 April 2017
Accepted 1 May 2017
Available online xxxx

Keywords:
Grinding methods
Crystal
Polymorphism
Multicomponent solid
Polymer
Seeding

ABSTRACT

Within the pharmaceutical industry, and elsewhere, the screening for new solid forms is a mandatory exercise for both existing and new chemical entities. This contribution focuses on mechanochemistry as a versatile approach for discovering new and alternative solid forms. Whilst a series of recently published extensive reviews exist which focus on mechanistic aspects and potential areas of development, in this review we focus on particular practical aspects of mechanochemistry in order to allow full optimisation of the approach in searches for new solid forms including polymorphs, salts and cocrystals as well as their solvated/hydrated analogues. As a consequence of the apparent experimental simplicity of the method (compared to more traditional protocols e.g. solvent-based methods), the high efficiency and range of conditions available in a mechanochemical screen, mechanochemistry should not be considered simply as an alternative method when other screening methods are not successful, but rather as a key strategy in any fully effective solid form screen providing reduced effort and time as well as the potential of requiring reduced amounts of material.

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Contents

1. Introduction

After the publication of a series of examples in the pharmaceutical field, including the ritonavir case [1], pharmaceutical scientists are fully aware of the importance of solid state structure on the physical, chemical, mechanical and biopharmaceutical properties of a drug [2]. Additionally, even if the identification of new solids has been performed thoroughly and a specific form selected for development it is also

☆ 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.2017.05.001
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Please cite this article as: D. Hasa, W. Jones, Screening for new pharmaceutical solid forms using mechanochemistry: A practical guide, Adv. Drug Deliv. Rev. (2017), http://dx.doi.org/10.1016/j.addr.2017.05.001

important to ensure that the selected solid remains unchanged in the final dosage form [3]. For these reasons, screening for new solid forms and studying their stability are essential practices for all existing and new chemical entities.

Approaches to screening can be computational and experimental, with computational methods being mostly predictive i.e. aiming to identify all possible three-dimensional arrangements which a specific drug can adopt in the solid state. Such crystal structure prediction (CSP) methods address some of the main challenges in solid state chemistry including the "continuing scandal that it is still impossible to predict the structure of a simple crystal" [4], the propensity of a molecule to polymorphism [5–7] and the possibility of including two or more molecules in the same crystal lattice forming a cocrystal [8,9], a salt [10] or a solvate [11]. CSP methods, however, cannot establish the exact experimental conditions required to produce a particular hypothetical form [12] and as a result are not intended as a substitute for a full experimental screening program. On the other hand, experimental screening for new solid forms does not follow a universally agreed screening strategy, and no single approach appears to guarantee the discovery of all the possible crystal forms.

Traditionally, the screening for new solid forms of pharmaceuticals has been performed using solution based methods such as solvent evaporation, antisolvent addition, cooling crystallization and slurrying: experimental variations on these methods include change in the solvent type, temperature (heating/cooling rate), solvent/antisolvent mixtures, concentration, rate of addition, etc. [13]. Such variations would be included in various "high-throughput" approaches [14–16]. Additionally, other screening approaches would include as examples supercritical fluid technologies [17], sono-crystallization (ultrasound-assisted crystallization) [18], microfluidic approaches [19] and the application of high pressure during crystal nucleation and growth [20].

This review focuses on mechanochemistry as a highly-efficient screening method, minimising the amount of solvent involved and thereby aligning to green and sustainable chemistry. It will highlight the various approaches including equipment, protocols and variations in experimental conditions.

A formal definition of mechanochemistry is the discipline that deals with "chemical reactions involving reagents in any aggregate state that are induced by the input of mechanical energy" [21]. The most frequent use of such a description, however, is in relation to solid-state processes and reactions initiated by any type of mechanical treatment, or involving reagents that are preliminarily activated mechanically [22]. The great potential of mechanochemistry has been recorded in the past by several distinguished scientists. For example, in 1820 Faraday demonstrated the reduction of AgCl to pure Ag by grinding in a mortar and pestle a mixture of AgCl and Zn [23], while Carey Lea studied the decomposition of silver halides [24]. The current application of mechanochemistry has been further extended to a very large number of inorganic [25] and organic [26] processes.

With specific regard to pharmaceutical materials, mechanochemistry is a relatively new technique and a significant growth of interest has been observed over the last three decades. Although being quite recent, several independent studies have demonstrated mechanochemistry to be effective and often superior to other approaches for the discovery of additional solid forms — indeed a recent extensive review by Tan et al. [27] has highlighted the great efficiency of mechanochemistry as a screening method and several other areas where it is likely to emerge.

This review has particular focus on the various experimental variations available in mechanochemistry, and relates the outcomes to operational variables such as components, temperature, solvents, additives, etc. Indeed, mechanochemistry offers suitable conditions for the discovery of less stable forms as the apparent equilibrium reached in specific conditions often does not correspond to the thermodynamic equilibrium but is rather related to the experimental conditions used. This is particularly evident during liquid-assisted mechanochemistry, where the main driving force for the formation of a new solid form (i.e. supersaturation) is always present (the amount of liquid added to the mechanochemical reaction is usually at the microliter scale) and therefore other experimental conditions will affect the kinetics of crystallization. Such variables are able to cover a wide range of crystallization space thereby increasing the probability of discovering different crystalline forms: a correct use of this versatility positions mechanochemistry as an important technique in pharmaceutics.

1.1. Specialised mechanochemical devices

The development of mechanochemistry as a chemistry discipline can be divided into four stages namely 1) "inadvertent" mechanochemistry representing the primitive use of mechanical energy (making fire by friction, grinding herbs in a mortar and pestle etc.), 2) recognition of mechanochemistry, starting from the middle of 19th century as a series of scientists became aware of mechanochemistry as an efficient technique for promoting reactions in the solid state, 3) development of mechanochemistry where the first extensive investigations on the chemical effects of mechanical action were performed, and the availability of efficient equipment from specialised companies, and 4) the modern period where mechanochemistry was applied to different emerging areas including pharmaceuticals. Stage 4 represents additionally the development of advanced mechanochemical techniques (Fig. 1) [28].

The term "mechanochemistry", introduced first in the 19th century [28], embraces a broad range of methods such as hydrostatic loading, controlled blow, pressure and shear, grinding, etc. [21,25]. Specifically, with regard to the mechanochemical preparation of pharmaceutical solids (recently defined as "medicinal mechanochemistry" [27]) grinding, however, represents the most frequent operation for the solid state preparation of cocrystals, salts and polymorphs [21,25,27]. The simplest method of grinding consists of using a mortar and pestle where the reactant materials (the amounts typically vary around the milligram scale) are mechanically ground for a specific amount of time (generally minutes [29]) in the presence or absence of a catalyst. Grinding in a mortar and pestle represents the "genesis" of mechanochemistry since the first documented mechanochemical experiments were performed this way [28]. The main limitations of this method are related to 1) the low amount of material produced and low throughput, and 2) a difficulty in quantifying power input (the energy input will clearly depend on the human operator, and will likely, therefore, be low and irregular, and will be difficult to operate continuously for >25–30 min). The experimental conditions also generally result in direct contact with air which may cause solvent evaporation (in the case where reactant are ground in the presence of small amounts of a liquid - discussed later) or an unknown effect of moisture on the course and speed of the process (Fig. 2).

Significantly higher control on the experimental conditions and the type of forces generated can be obtained by using "an automatic mortar and pestle" which was first developed by the company Retsch in 1923 (Fig. 1) [28]. The ideal mechanochemical device would be able to transfer the maximum amount energy to the loaded reactants. In this context, not all grinders are equal [30]: ball mills represent the most efficient devices for transferring high mechanical energy amounts to the loaded material in a relatively short time [31]. In these devices mechanical energy is transferred by the mill body to the loaded mixture in the form of pulses through a series of grinding media. Ball mills include tumbling ball mills, planetary mills, vibrational mills etc. The mechanical action in ball mills takes place through both shear and normal stresses and their relative importance varies in different types of ball mills. Most interest for polymorph screening and production of pharmaceutical multicomponent crystals such as cocrystals and salts, however, are the planetary and vibrational/shaker mills.

A standard version of the vibrational mill has two jars (frequently of steel) which are secured in a clamp (Fig. 2) and vibrated energetically

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