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Review

Overview of milling techniques for improving the solubility of poorly water-soluble drugs

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ABSTRACT

Milling involves the application of mechanical energy to physically break down coarse particles to finer ones and is regarded as a "top–down" approach in the production of fine particles. Fine drug particulates are especially desired in formulations designed for parenteral, respiratory and transdermal use. Most drugs after crystallization may have to be comminuted and this physical transformation is required to various extents, often to enhance processability or solubility especially for drugs with limited aqueous solubility. The mechanisms by which milling enhances drug dissolution and solubility include alterations in the size, specific surface area and shape of the drug particles as well as milling-induced amorphization and/or structural disordering of the drug crystal (mechanochemical activation). Technology advancements in milling now enable the production of drug micro- and nano-particles on a commercial scale with relative ease. This review will provide a background on milling followed by the introduction of common milling techniques employed for the micronization and nanonization of drugs. Salient information contained in the cited examples are further extracted and summarized for ease of reference by researchers keen on employing these techniques for drug solubility and bioavailability enhancement.

1. Introduction

The process of drug dissolution is critical to the therapeutic efficacy of a medicinal product regardless of its route of administration. Dissolution involves the transfer of a solid drug into solution in the surrounding physiological fluid. The rate of dissolution of a drug is affected by factors embodied in the Noyes–Whitney equation [1]. The extent to which drug dissolution proceeds under prevailing physiological conditions is governed by its aqueous solubility. Drug solubility is defined as the amount of drug that passes into solution when an equilibrium is established between the drug solute in solution and any excess, un-dissolved drug to produce a

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saturated solution at a specified temperature [2]. The solubility and dissolution rate of a drug are often positively correlated. The bioavailability of a drug is defined as the rate and extent to which a dissolved drug is absorbed and becomes available at its target site of action [3]. The bioavailability of a drug is thus dependent not just on its dissolution and solubility characteristics, but also on its membrane permeability and associated absorption-related degradation.

Currently, the pharmaceutical industry faces considerable challenges associated with the increasing number of poorly water-soluble drugs coming through the drug discovery pipeline [4,5]. Despite promising pharmacological activity, many of these drug candidates fall under class II of the Biopharmaceutics Classification System (BCS), characterized by high membrane permeability but low aqueous solubility [6]. These drugs exhibit erratic or incomplete absorption often leading to unsatisfactory drug exposure *in vivo* and poor bioavailability. Biopharmaceuticals and biotechnology-derived therapeutic agents face similar challenges [7]. For BCS class II drugs, the dissolution step is the rate-determining factor in drug absorption. Pharmaceutical scientists are constantly seeking new approaches to facilitate and enhance the solubility and thus dissolution rate of BCS class II drugs. Current strategies employed to improve the apparent solubility of a drug include the use of: (i) co-solvents (e.g. low molecular weight polyethylene glycols and propylene glycol) in combination with water to dissolve the drug; (ii) complexing agents (e.g. cyclodextrins and its derivatives) to form water-soluble inclusion complexes of the drug [8] or (iii) hydrophilic excipients (e.g. polyvinylpyrrolidones and high molecular weight polyethylene glycols) as drug carriers for the preparation of solid dispersions in which the drug is dispersed molecularly or as ultrafine crystals [9]. Alternatively, the drug molecule may be modified chemically by the syntheses of suitable pro-drugs [10] or salt forms of the drug that often exhibit greater aqueous solubility than the parent molecule. However, drug precipitation is a common threat faced by some of these formulations [11]. Precipitation may arise from excess drug coming out of solution when a previously supersaturated drug solution is diluted upon administration. For oral formulations, drug precipitation maybe triggered by the changing pH environment of the gastro-intestinal tract. To ensure that a drug stays in solution up till the point of absorption, lipids and oils have been employed as drug carriers. Lipid formulations of drugs basically comprise drugs dispersed, but more often, dissolved, in lipids or oils. These formulations improve drug bioavailability by exploiting the innate lipid digestion and absorption mechanisms in the body. Depending on the chemical nature of the lipid, the formulation may also self-emulsify in the gastro-intestinal tract to facilitate lipid digestion and maximize drug absorption. The advantage of lipid formulations is that the drug is maintained in a solubilized state prior to absorption. A comprehensive reference on oral lipid-based formulations can be found in the book edited by David J. Hauss [12]. The key advantages and disadvantages of the different strategies employed to improved drug dissolution and bioavailability are highlighted in Table 1.

2. Milling

Apart from the techniques aforementioned, another strategy employed to improve solubility and ultimately, bioavailability of poorly water-soluble drugs is milling. The terms milling,

Table 1 – Key advantages and disadvantages of common strategies employed to improve drug dissolution and bioavailability.

Technique	Advantages	Disadvantages
Use of co-solvents	• Simple technique • Lower costs involved • Applicable for a wide range of drugs	• Toxicity of solvents • Risk of drug precipitation *in-vivo* • Limited to liquid formulations
Complexation using cyclodextrins	• Improves the chemical stability of the drug • May potentially enhance drug absorption by modification of lipid barrier	• Successful complexation depends on both chemical and geometrical properties of drug molecule • Large amounts of cyclodextrins may be required due to low complexation efficiencies • Higher costs involved
Solid dispersions	• Creates fine drug particles without excessive application of energy • Fine particles are readily wetted with minimal risk of agglomeration • Wide range of hydrophilic polymers are available as drug carriers	• Preparation method is difficult to scale up • Amorphous drug forms created are physically unstable and may convert to crystalline forms during storage, accelerated by moisture absorption by the hydrophilic carrier
Chemical modification (e.g. prodrugs)	• Prodrugs may enable drug targeting and improve drug stability	• Toxicity potential of prodrugs • Fate of prodrugs is difficult to predict *in-vivo* due to biological variations in the way they are handled in the body
Lipid formulations	• Exploits the innate lipid digestion mechanisms of the body to enhance drug bioavailability • Emulsifiable lipid formulations further enhance lipid digestion and drug bioavailability • Diversity of lipid excipients allow formulation flexibilities • Lower risks of drug precipitation *in-vivo*	• Amount of lipids typically present in the formulation may be insufficient to trigger an appropriate physiological response to enhance drug bioavailability • Quality control of lipid-based formulations is challenging due to the complex and diverse physicochemical properties of lipids and the lack of standardized testing methods