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Review article

Mesoporous silica materials: From physico-chemical properties to enhanced dissolution of poorly water-soluble drugs

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ABSTRACT

New approaches in pharmaceutical chemistry have resulted in more complex drug molecules in the quest to achieve higher affinity to their targets. However, these 'highly active' drugs can also suffer from poor water solubility. Hence, poorly water soluble drugs became a major challenge in drug formulation, and this problem is increasing, as currently about 40 of the marketed drugs and 90% of drug candidates are classified as poorly water soluble. Various approaches exist to circumvent poor water solubility and poor dissolution rate in aqueous environment, however, each having disadvantages and certain limitations.

Recently, mesoporous silica materials (MSMs) have been proposed to be used as matrices for enhancing the apparent solubility and dissolution rate of different drug molecules. MSMs are ideal candidates for this purpose, as silica is a "generally regarded as safe" (GRAS) material, is biodegradable, and can be readily surface-modified in order to optimize drug loading and subsequent release in the human body. The major advantage of mesoporous silica as drug delivery systems (DDSs) for poorly water soluble drugs lies in their pore size, pore morphology, and versatility in alteration of the surface groups, which can result in optimized interactions between a drug candidate and MSM carrier by modifying the pore surfaces. Furthermore, the drug of interest can be loaded into these pores in a preferably amorphous state, which can increase the drug dissolution properties dramatically.

The highlights of this review include a critical discussion about the modification of the physico-chemical properties of MSMs and how these physico-chemical modifications influence the drug loading and the subsequent dissolution of poorly water soluble drugs. It aims to further promote the use of MSMs as alternative strategy to common methods like solubility enhancement by cyclodextrins, micronization, or microemulsion techniques. This review can provide guidance on how to tailor MSMs to achieve optimized drug loading and drug dissolution.

1. Introduction: poorly water-soluble drugs – a threat or an opportunity?

Oral delivery is the preferred route of administration of drugs due to comfort for the patient, low cost, and a patient compliance. To obtain a pharmacological effect of a drug in the body, the drug needs to be available in the therapeutic range at the target site. For oral administration, this is achieved when a sufficient high amount of drug is dissolved in the gastro-intestinal (referred to as GI)-tract, absorbed, and distributed via the blood stream to reach the target. Hence, three processes including timely disintegration in the GI tract, appropriated drug dissolution in GI fluids, and sufficient drug permeation through the GI wall are mainly governing the pharmacological action of an orally administered drug.

Most of the drug candidates recently presented to the global drug market suffer from poor water solubility, so-called poorly water soluble drugs (PWSD) [1]. Accordingly, while being highly potent in vitro, these drugs lack therapeutic efficacy in vivo, mainly because of not reaching a high enough concentration in the site of absorption, i.e., GI lumen. Enhancing the dissolution of the drug in the GI is therefore a challenge in drug discovery [2]. New trends in combinatorial chemistry and novel drug design have resulted in drugs with higher lipophilicity,

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poorer water solubility, and higher molecular weight, all of which not being beneficial for oral absorption. Apart from the aforementioned problems, drugs that can form stable crystals are an emerging challenge for pharmaceutical researchers as well. Newer drug molecules possess several functional groups, which makes them able to crystallize into stable crystals with high melting points [3]. These drugs are not necessarily lipophilic, but the energy needed to overcome the forces attaching the drug molecule within the crystalline lattice is higher compared to the metastable or amorphous ones, thus making the dissolution in GI fluids more difficult.

In order to find the best solutions for the oral bioavailability concerns, the BCS classifies drugs intended for oral administration into 4 different groups based on the aqueous solubility/dissolution as well as the intestinal epithelium permeability [4]. In class 1, drugs with both, high permeability and high solubility are found; those with high permeability but low solubility are assigned to class 2; drugs with low permeability, but high solubility are classified as class 3, and finally, class 4 houses the drugs with both low solubility and low permeability. Based on the Noyes-Whitney equation, the dissolution rate is directly proportional to solubility, it is not considered as an independent determinant in BCS. The US Food and Drug Administration (FDA) determines solubility as dose-dependent drug solubility in 250 mL water at a pH ranging from 1 to 7.5. Permeability is determined as the gastrointestinal absorption of > 90% of the orally administered dose or in reference to the intravenous injection. Unfortunately, most of the data regarding solubility and permeability for drugs are not freely available or accurate, making it difficult to predict or model the BCS grouping based on molecular features of the drug.

According to the IUPAC definition, solubility is determined as “the analytical composition of a mixture or solution which is saturated with one of the components of the mixture or solution, expressed in terms of the proportion of the designated component in the designated mixture or solution” [5]. The solubility of a chemical substance depends on various parameters, mainly including the chemical nature of the solute, solvent, and co-existing agents within the dissolution medium, temperature and pressure. Commonly, solubility is expressed as mass per unit volume. The United States Pharmacopeia (USP) uses descriptive terms like freely soluble or practically insoluble to express the extent a drug can be dissolved in a solvent. These terms describe how many parts of solvent are required to solubilize one part of solute [6].

In contrast to the solubility which is basically a ‘thermodynamic’ parameter, dissolution(most precisely expressed as dissolution rate) is a ‘kinetic’ one defined as the rate of mass transfer of the solute from the bulk solid state to the solution (a solute-in-solvent molecular dispersion) thus expressed as mass per unit time. Intrinsic dissolution rate (IDR) is a parameter frequently used in pharmaceutical industries and, according to USP, is defined as the dissolution rate of pure substances under the condition of constant surface area.

Permeability describes the ability of a drug to overcome cellular barriers to reach the systemic circulation. Permeability is usually expressed as a rate (normally in the order of 10^{-6} cm/s). The permeability increases inversely with the molecular weight but directly with the drug lipophilicity [7]. The permeability of drugs can be estimated by the lipid-to-water partition coefficient (known as logP), where P is the octanol-to-water concentration ratio of the drug. The logP is one of the five rules from Lipinski “rule of five” which evaluates, if a drug can be delivered orally [8].

Recently, Lindenberg et al. have categorized drugs on the list of Essential Medicines of the World Health Organization. They found that out of 130 orally administered drugs, 61 could be classified with certainty, and from these, 21 (34%) belong to class 1, and 10 (16%) belong to class 2. To class 3 and 4, 24 (40%) and 6 (10%) belong, respectively. Only 8% of the new drug candidates have high shown both solubility and high permeability. Class 1 example molecules are metoprolol, propranolol, and theophylline. For these drugs, there is no rate-limiting step for oral absorption. Formulating class 2 drugs, like cyclosporine or itraconazole aims for dissolution enhancement to achieve relevant amounts to be absorbed in the GI tract. Class 3 drugs like atenolol or cimetidine are highly soluble, but can hardly permeate. Permeation enhancers like fatty acids or bile salts can partially overcome this limitation. Class 4 drugs are the most challenging drugs to formulate, and mostly, these molecules need to be redesigned.

Poor water solubility influences significantly a number of stages during the drug development and pre-clinical studies. A compound with aqueous solubility < 100 μg/mL is usually considered to have a dissolution-limited resorption. Simply increasing the drug amount in the oral dosage form however may lead to several problems. First, formulating a tablet with a high amount of drug may lead to poor powder properties. The powder might become sticky, have poor flowing properties, and higher costs in the development stage due to increased consumption of the drug. In in vitro screening, poor water solubility might result in precipitation and false outcomes can have consequences like underestimated activity and toxicity. In vivo, the high drug load could cause local irritations in the GI-tract and lead to lesser compliance, and ultimately, still not high enough plasma concentrations would result in limited therapeutic action.

With these significant hurdles hampering the efficient development of the majority of new drug candidates, new and more efficient approaches for overcoming the poor aqueous solubility and low dissolution rates are of critical importance. For class 2 drugs, a variety of techniques exist to enhance their water solubility. Currently, 40% of the marketed drugs and even 90% in the discovery status are poorly water-soluble [9,10]. This challenge can partially be overcome with an array of drug delivery technologies.

One such promising approach that has received increased acceptance and awareness with regard to its potential use as dissolution enhancers in pharmaceutical formulations is using MSMs for the encapsulation of PWSDs. This notion has culminated in the first-in-human proof-of-concept study published at the end of 2016 [11]. This type of material possesses a range of controllable properties that can be utilized for the benefit of preserving the loaded drug in its amorphous form within the porous structure, consequently leading to enhanced dissolution behavior. The course of action further results in protection of the drug molecules from oxidation, hydrolysis and other degradation processes by restriction of access from the surrounding environment [12]. We will highlight in the following how the properties of MSMs can be rationally controlled, followed by how these material properties can be utilized in the formulation of PWSDs.

2. Methods for solubility and dissolution enhancement: an overview

Solubility and/or dissolution rate can be improved by physical, chemical, or other modifications on the drug molecules. A large variety of techniques exist to overcome poor water solubility of the drugs [13]. Physical modification includes manipulation of the particle size, using different polymorphs of a drug, or solid solutions. Chemical modifications include variation of the pH, derivatization, or salt formations, among others. These approaches can be grouped into solubility improvement on the molecular level, solubility improvement on the colloidal level, and solubility improvement on the particle size level, as depicted in Fig. 1. On the molecular level, solubility can be improved by using co-solvents, using salt-forms of the drug, creating prodrugs, or using cyclodextrins. On the colloidal level the solubility is increased by emulsions, microemulsions, or lipid based water-free formulations. The solubility enhancement on the particulate level includes nanosizing, or by the creation of metastable polymorphs.

2.1. Cyclodextrins

Cyclodextrins are used in a wide variety of drug formulations, including liposomes, microparticles, nanoparticles, and others [14].