ELSEVIER
DRUG DISCOVERY TODAY TECHNOLOGIES
Drug Discovery Today: Technologies
Vol. xxx, No. xx 2018

Editors-in-Chief
Kelvin Lam – Simplex Pharma Advisors, Inc., Boston, MA, USA
Henk Timmerman – Vrije Universiteit, The Netherlands

Different types, applications and limits of enabling excipients of pharmaceutical dosage forms

Barnabás Palcsó, Romána Zelkó*

University Pharmacy Department of Pharmacy Administration, Semmelweis University, Hogyes E. Street 7-9, H-1092 Budapest, Hungary

Along with the development of novel drug delivery systems the material science is also advancing. Conventional and novel synthetic or natural excipients provide opportunities to design dosage forms of the required features including their bioavailability. Emerging trends in the design and development of drug products indicate an increasing need for the functionality-related characterization of excipients. The purpose of this review is to provide an overview of different types of excipients in relation to their application possibilities in various dosage forms with special focus on the enabling excipients. The study also summarizes the applied excipient systems of research formulations and dosage forms available on the market.

Section editor: György T. Balogh – Compound Profiling Laboratory, Gedeon Richter Plc.

Introduction

The therapeutic compounds are never used alone, but are always used as part of a pharmaceutical formulation. The active ingredient of the pharmaceutical composition is generally present in a negligible amount relative to other substances that are most commonly used as excipients. The excipients, on the one hand, enable the delivery of the active ingredient, and on the other hand, ensure that the formulation meets the requirements of the medicines. They play a role in delivering the drug to the site of action, thereby providing efficacy. They are indispensable in the design of quality and safety, since with their help dosage forms of required properties can be formulated, which preserve the original quality until the expiry date. The excipients can be grouped according to their role in the pharmaceutical form. They may be carriers, promote a step-in production or provide release of the active substance to reach the site of the action. An excipient may have several functions.

It is known that in recent years among the drug candidates there are an increasing number of compounds with poor bioavailability, which is mostly due to their poor solubility [1]. Prediction of the bioavailability of a new compound is possible by classifying it into the appropriate class of BCS [2]. Because of the appearance of new drug candidates with poor dissolution belonging to BCS II class, more attention is being paid to formulations, which can improve the bioavailability of such compounds. These formulations can be referred as enabling formulations, as they allow drugs with low solubility to reach a level of concentration at the site of absorption that is suitable for the therapeutic goal. Accordingly, compounds of the delivery system that enhance the dissolution of such drug are enabling excipients. The hypothesis behind the use of such systems is that the poorly soluble BCS II drug is successfully dissolved, therefore its absorption profile may approach the well-dissolving BCS I [3–6]. Various tools are available to increase the solubility. Ideally, the BCS II

*Corresponding author: R. Zelkó (zelko.romana@pharma.semmelweis-univ.hu)

1740-6749/$ © 2018 Published by Elsevier Ltd. https://doi.org/10.1016/j.ddtec.2018.04.002

Please cite this article in press as: Palcsó B, Zelkó R. Different types, applications and limits of enabling excipients of pharmaceutical dosage forms, Drug Discov Today: Technol (2018), https://doi.org/10.1016/j.ddtec.2018.04.002

compounds are available as a soluble salt, polymorphic form or co-crystal [7–11]. It should be noted that significant solubility increase can be achieved by setting a suitable pH, which is most commonly used in the formulation of for parenteral solutions. For oral preparations, the pH adjustment with buffer systems is limited as the digestive system has a significantly greater buffering capacity than an oral formulation [12]. However, the effect of the various excipients on the pH of the drug molecule is not negligible [13].

In the absence of a highly soluble salt or crystalline formulation, the use of an enabling formulation will be necessary to ensure the release of the active ingredient in the digestive tract. The solubility of the BCS II drug can be increased by applying cosolvent, hydrotrope dissolution, micelle formation, and cyclodextrin complexes [14–21]. A common feature of these methods is that they can be used to dissolve the compound with poor solubility. The systems building up from active ingredient and excipient with secondary binding forces form true or colloidal solution in aqueous medium. Other groups of enabling formulations include heterogeneous systems, such as nanocrystalline nanosuspensions, crystalline or amorphous solid dispersions, microemulsions and self-emulsifying systems (SEDDS, SNEDDS). In the latter, the drug is dissolved, but an emulsion is formed from the formulation in the digestive system.

One of the first steps in the formulation of heterogeneous solubility enhancing systems may be the reduction in particle size, which is an important means of solubility increase itself. According to the Ostwald–Freundlich equation, particle size reduction results in elevated dissolution rate and can also improve the solubility of the drug [22,23]. The decrease of the particle size also means the growth of a specific surface which promotes the interaction of the poorly soluble drug with the aqueous medium, the formation of a saturated solution and ultimately the dissolution of the drug [24]. Level of saturation is crucial in terms of bioavailability, as the relation between supersaturation and precipitation can have a significant impact on the permeability of the drug. It has been found that absorption can be enhanced by greater supersaturation levels and also depends on the *in vivo* precipitation behaviour of the model compound, while precipitation presents limitation for the precipitation-induced transport enhancement [25–27]. By top-down and bottom-up technologies, nanocrystals of the poorly soluble drug can be formed, which produce colloidal dispersion in water [28]. Disintegrating processes requiring greater energy input include wet milling, colloid milling and high pressure homogenization [29]. Bottom-up techniques, include processes based on individual precipitation or solvent vaporization of the solutions of the active ingredients, are less energy-intensive [30]. The increased specific surface area is a metastable state for the particles because the attractiveness between the particles increases with the surface free energy, so the aggregation and agglomeration tendency of the particles increases. Depending on the type and conditions of the process, the active ingredient in the nanoparticles may also be present in crystalline and amorphous state, and therefore, by selecting the appropriate method and parameters, both states can be prepared. The amorphous state is characterized by instability, hygroscopicity, and aggregation tendency, but the apparent solubility of the compound also increases [31]. In practice, often surfactants are used to stabilize the particles of high surface area, which reduce surface free energy or the interfacial energy of the material, thus inhibiting aggregation [32]. Subsequently, with the given technique, a nanocrystalline formulation can be developed which can be found among marketed drugs (Rapamune®, Emend®, Tricor®). The solid dispersion system consists of at least two components, a hydrophilic matrix and a hydrophobic agent, where the matrix can be amorphous or crystalline [33]. The particle size and distribution of the active agent in the matrix can be different; it may be in a crystalline and amorphous dispersion as well as a molecularly dispersed form. In the latter case, it can be considered solid solution, but the methodological separation of each type is cumbersome. They can be made by melt extrusion, solvent vaporization, supercritical fluid method, freeze or spray drying [34–36]. Separate groups are represented by solid cyclodextrin complexes, which can be obtained by co-precipitation, kneading or neutralization as well as the above-mentioned ones [37]. For lipid-based systems, the poorly water-soluble drug can be dissolved in a mixture of two or more glyceride-type excipients in solubilized form in the gastrointestinal tract. The simplest formulations of this type include the active ingredient dissolved in simple triglycerides, which form a colloidal dispersion of mixed micelles in association with bile acids and lecithin in the intestine. In this case the drug is present in solubilized state inside the micelles. By adding a surfactant of appropriate amount and HLB value to the triglyceride mixture a self-emulsifying system (SEDDS) can be achieved, which also forms an emulsion in the aqueous medium under gentle agitation thus providing the solution of the active agent [38]. Depending on the size of the produced micelles, micro- and nanoemulsions (SMEDDS and SNEDDS) can be distinguished [39,40]. It is possible to produce solid self-emulsifying systems from liquid SEDDS or SNEDDS. This is usually achieved by using a high-specific surface carrier or solvent vaporization-based process [41]. It is important to note that the processes and materials used to increase the drug solubility cannot be sharply separated from each other. In order to improve the dissolution of an active ingredient, several methods can be used simultaneously; therefore, there is a great overlap with the applied excipients.

Different types of enabling excipients of pharmaceutical dosage forms

Fig. 1 summarizes the main groups of various enabling excipients, which are successfully applied in different pharmaceutical

Please cite this article in press as: Palcsó B, Zelkó R. Different types, applications and limits of enabling excipients of pharmaceutical dosage forms, Drug Discov Today: Technol (2018), https://doi.org/10.1016/j.ddtec.2018.04.002

Download English Version:

https://daneshyari.com/en/article/8411137

Download Persian Version:

https://daneshyari.com/article/8411137

Daneshyari.com