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Mini Review

Solid Dispersions: Improved Solubility and Sustained Release

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Abstract

Sustained-release dosage forms are aimed at improving patient compliance by reducing the frequency of dosing. They allow to reduce the total dose, ensure a uniform and prolonged concentration of the drug in the systemic circulation, and minimize side effects, which ultimately leads to a better response to the treatment. In pharmaceutical practice, the use of polymers may be the first choice to prolong the release of a drug from its dosage forms, including matrix tablets, microcapsules, multilayer tablets, etc. Although the use of polymers in the form of solid dispersion aim to enhance the solubility of non-soluble or poorly soluble drugs, this term may be used to refer to the systems consisted of soluble or poorly soluble drugs and release -controlling polymers and prepared by the different methods known for preparing solid dispersions. in the literature there are different studies devoted to preparing sustained release systems on the base of solid dispersions. The purpose of this work is to provide a brief overview of solid dispersions and the prospect of their use to provide sustained release dosage forms.

Keywords: Solid dispersion, Polymer, Sustained release, Dissolution rate, Solubility

Introduction

The definition of Solid Dispersions (SDs) has been introduced in deferent ways, but in general they can be defined as systems in which the drug is dispersed at the molecular level in a biologically inert matrix or carrier, which can be sugar, a wax-based system, or, more commonly, a polymer [1]. The main goal of obtaining SD is to improve the solubility and, consequently, the bioavailability of poorly soluble drugs [2].

Classification of Solid Dispersions

SDs can be classified according to different parameters, including carrier type and molecular arrangement. According to the carrier type four generations of SDs are distinguished [3-5]:

1) In the first generation the crystalline carrier, like sugar or urea, is used.

2) In the second generation, the drug is molecularly dispersed in an inert polymer matrix where natural, semi-synthetic or synthetic polymers may be used.

3) The carriers used in SDs of third generation, can be a copolymer or a mixture of polymers and surfactants, improving the drug release profile due to the surface activity of the carrier or self-emulsifying ability, which in turn can reduce drug recrystallization and improve SD stability.

4) The fourth generation, known as controlled release SD, is basically aims to enhance the solubility of poorly soluble drugs

using water swellable or insoluble polymers such as HPC, Eudragit RS/ RL, EC, etc.

SDs also may be classified based on their molecular arrangement, or the correlation of their stability and solubility, to six groups, including C-C, C-A, A-C, A-A, M-C, and M-A [6-8]:

1) Classes C-C and C-A, refer to SDs in which the drug is present in a crystalline state and the carrier is crystalline or amorphous, respectively. Thus, these two classes are considered stable but less soluble. Class C-C is a eutectic mixture, while C-A is a glass suspension.

2) In classes A-C and A-A, the amorphous drug is dispersed in a crystalline or amorphous vehicle, which increases the solubility of the drug but reduces its stability. A-C is an amorphous precipitation in crystalline matrix while class A-A is a glass suspension.

3) When the drug is molecularly dispersed in a crystalline or amorphous carrier, we obtain M-C and M-A classes, which have improved drug dissolution characteristics with great physical stability. While M-A is a glass solution, M-C may be continuous or discontinuous, substitutional or interstitial solid solution.

It is worth noting that SDs can sometimes be classified into more than one group, for example, when a crystalline drug dispersed in an amorphous polymer is partially converted to amorphous, then SD will be a mixed system of C-A and A-A.

Solid Dispersions for Sustained Release

Recently, sustained release systems based on SDs have been increasingly developed and become the object of many studies. These systems provide various potential advantages in terms of bioavailability and long-lasting drug release, providing the benefits of both SDs and sustained-release delivery systems while largely avoiding the risk of burst release [9]. This can be achieved by directly preparing SDs with release-controlling polymers, or by preparing SDs with solubility-enhancing carriers, and then formulating them with release-controlling polymers. Here are some examples of the use of SD technology to produce sustained drug release systems.

In 2015 *Neha, et al*. prepared metoclopramide sustained release SDs using Eudragit RLPO and Eudragit RSPO by solvent evaporation method. The resulted SDs prolonged the drug release up to 12 h with increasing bioavailability and with increased half-life than pure metoclopramide [10]. In 2016 *Nguyen, et al*. successfully prepared SDs of isradipine, a calcium channel blocker, with PEG 6000/ HPMC 4000 by melting method. HPMC 4000 was then also added to the resulting SDs and tableted. The result was a sustained release system with an increased rate of dissolution of a poorly soluble drug [11]. In a study conducted by *Shergilla, et al*. in 2016, SDs of disulfiram, the anti-alcoholism drug with a cytoytoxicity in different type of cancers, were prepared with Kolliphor1 P 188 and P 237 by hot melt method, and these SDs were blended with Kollidon®SR or HPMC and tableted. The dissolution studies showed that SD-loaded tablets provided not only sustained release but also an enhanced dissolution of disulfiram [12]. In 2019, the antipsychotic drug risperidone was formulated into SDs with ß cyclodextrin and HP- ß cyclodextrin by kneading method and co-precipitate method in ratios 1:1, 1:2 (drug: carrier). Dissolution studies of SDs showed that SD prepared by co-precipitate method in ratio 1:2 with ß cyclodextrin had the best dissolution profile, so it was then loaded into tablets which were prepared by direct compression with varying amounts of HPMC K4, HPMC K15, or HPMC K100 as release control polymers. Tablets with 15% HPMC K100 showed the best profile dissolution than other prepared formulas [13].

In 2020, gliclazide SDs were obtained by solvent evaporation method in three ratios 1:1, 1:2, 1:3 (drug: HP cyclodextrin). SDs were then processed into tablets, which were prepared by wet granulation using HPC and HPMC K100M as release control polymers. The dissolution studies showed that the dissolution rate of the drug from the SDs was higher than that of the pure drug, with up to 99.9% of the drug released from the tablets over a long period of time up to 16 hours [14]. In 2020, donepezil hydrochloride, the highly water-soluble reversible inhibitor of acetylcholinesterase, was formulated in SDs with HPMC K100 or stearic acid as carrier, by co-grinding method and fusion method in ratios 1:1, 1:2, 1:3 (drug: carrier). Then SDs in 1:2 ratio obtained by fusion method with stearic acid and with HPMC K100 by co-grinding method were incorporated in oral gels with Na alginate or Na CMC as gelling agents. It turned out that formulation obtained with stearic acid SDs showed the best result in the term of prolonged drug release and stability of the gel. So, it may be said that stearic acid SDs loaded oral gels are suitable for the control release of water suitable drugs with required stability during storage [15].

In 2020, *Sulthana, et al*. [16] prepared sustained release tablets based on the SDs of elvitegravir, a poorly soluble drug used in the treatment of HIV-infections. SDs were prepared using urea, PEG 6000 and mannitol in ratios 1:1, 1:2, 1:3 (drug: carrier) by fusion methods, and by solvent evaporation method in the same ratios with urea and mannitol. Dissolution studies showed that the drug was released from all prepared SDs in 20 minutes, but the highest dissolution rate was from SD prepared with HPMC in the ratio 1:3, which was then formulated into tablets. Tablets were prepared by direct compression with 10% and 20% of EC, HPMC or guar gum as release-prolonging agents. The best result of dissolution studies of tablets was with the formulation containing 20% guar gum, in which the drug entirely released in 12 hours [16]. In 2021, donepezil hydrochloride was formulated in SDs with different hydrophobic carriers, namely EC, Eudragit RSPO, and compritol® 888 using hot-melt extrusion technology. SDs were prepared with compritol® 888 and Eudragit RSPO in the ratios of 1:1, 1:2, 1:3, 1:4 (drug: polymer), and with EC in ratios 1:1, 1:3, 1:4 in addition to a formulation of 1:1:1 (drug: EC: compritol® 888) and 1:2:0.1 (donepezil: EC: mannitol). Also, two formulations (donepezil: compritol® 888: mannitol) were prepared in two ratios 1:2:0.1 and 1:2:0.075, where Mannitol was added to SDs as a pore former, to improve drug release profile. Tablets were obtained from compritol® 888 SDs by direct compression with or without MCC. Dissolution studies showed that the best dissolution profile was with SD prepared with compritol® 888 and mannitol in ratio 1:2:0.075, which showed an entire stable release within 10 hours [17]. 1n 2022, nifedipine was formulated in

SDs with PVP k 30 in the ratios 1:2, 1:4, 1:6, 1:8, 1:10 (drug: polymer) using solvent evaporation method. The highest dissolution rate was with the SD prepared in ratio 1:8, which was then used as a core to prepare sustained release microcapsules by emulsion solvent method and modified emulsion solvent method with a coat consisted of Eudragit RS100 as a polymer, acetone as a polymer solvent and N-hexane as a vehicle. Dissolution studies showed that all prepared microcapsules showed a sustained-release profile in phosphate buffer (pH=7.2) with a maximum release of 97.22 % within 12 hours for the microcapsules prepared in ratio 1: 4 (core: coat) by emulsion solvent method [18].

Conclusion

Solid dispersions are a good choice not only to solve the problem of poor drug solubility, but also to modify the drug release, and, in particular, to achieve sustained drug release. Solid dispersions themselves may be sustained release systems or formulated into a variety of sustained release dosage forms such as microcapsules, tablets, capsules and even gels. Selecting suitable carriers from the available wide range of polymers with varying characteristics from soluble to insoluble as well as swelling polymers provides the desired release profile for both poorly soluble and soluble drugs. Thus, it could be said that solid dispersions are a prospective technique for both enhancing solubility and prolonging release.

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Conflict of Interest

None.

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