European Journal of Pharmaceutics and Biopharmaceutics 107 (2016) 142–150

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

A novel solubilization technique for poorly soluble drugs through the integration of nanocrystal and cocrystal technologies

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ARTICLE INFO

Article history:
Received 8 November 2015
Revised 6 June 2016
Accepted in revised form 3 July 2016
Available online 5 July 2016

Chemical compounds studied in this article:
Carbamazepine (PubChem CID: 2554)
Indomethacin (PubChem CID: 3715)
Furosemide (PubChem CID: 3440)

Keywords:
Cocrystal
Nanocrystal
Crystal engineering
Solubilized formulation
Poorly soluble drug
Absorption improvement

ABSTRACT

The aim of the present study was to develop a novel solubilization technique consisting of a nanococrystal suspension by integrating cocrystal and nanocrystal formulation technologies to maximize solubilization over current solubilizing technologies.

Monodisperse carbamazepine–saccharin, indomethacin–saccharin, and furosemide–caffeine nanococrystal suspensions, as well as a furosemide–cytosine nano-salt suspension, were successfully prepared with particle sizes of less than 300 nm by wet milling with the stabilizers hydroxypropyl methylcellulose and sodium dodecyl sulfate. Interestingly, the properties of resultant nano-cocrystal suspensions were dramatically changed depending on the physicochemical and structural properties of the cocrystals. In the formulation optimization, the concentration and ratio of the stabilizers also influenced the zeta potentials and particles sizes of the resultant nano-cocrystal suspensions. Raman spectroscopic analysis revealed that the crystalline structures of the cocrystals were maintained in the nanosuspensions, and were physically stable for at least one month. Furthermore, their dissolution profiles were significantly improved over current solubilization-enabling technologies, nanocrystals, and cocrystals.

In the present study, we demonstrated that nano-cocrystal formulations can be a new promising option for solubilization techniques to improve the absorption of poorly soluble drugs, and can expand the development potential of poorly soluble candidates in the pharmaceutical industry.

1. Introduction

Nearly 40% of the marketed drugs and up to 70% of the drug candidates in current pharmaceutical development have been reported to exhibit poor aqueous solubility, which can complicate drug development due to the potential risks of low oral bioavailability and exposure issues in pharmacological and toxicological studies [1–3]. Hence one of the key challenges in pharmaceutical development is resolving the solubility, dissolution, and absorption issues of poorly soluble compounds through suitable crystal engineering technologies or absorption-enhanced formulations, which can improve the efficiency of drug delivery to the target tissue. Several methods for improving solubility or dissolution-limited drug absorption have been developed, from crystal engineering approaches such as salt and cocrystal formation, to absorption-enhanced formulations such as amorphous solid dispersions and nanoparticles [4–9].

Cocrystals are defined as multi–component crystals, based on stoichiometric relationships, which are mainly combined through nonionic interactions without the transfer of protons [10–12]. Cocrystals have attracted significant interest from the pharmaceutical industry because of their broad benefits, including advantageous physicochemical properties such as solubility, dissolution, melting point, and physical and chemical stabilities, compared to the corresponding single component crystals [13–18]. Therefore, the cocrystal technology has been widely used to improve the oral absorption of poorly soluble compounds. On the other hand, several studies have suggested that the dissociation of the cocrystal formers (CCFs) during dissolution, resulting in the precipitation of active pharmaceutical ingredients, is one limitation of cocrystals [13,19,20]. Therefore, a rational design of cocrystals and an appropriate CCF screening system are important to achieving the desired properties in drug products [21–23].

Abbreviations: ACT, acetamide; BCS, biopharmaceutical classification system; CAF, caffeine; CBZ, carbamazepine; CCF, cocrystal former; CYT, cytosine; DH, dihydrate; FSD, furosemide; GCDC, glycochenodeoxycholate; HPMC, hydroxypropyl methylcellulose; IMC, indomethacin; NIC, nicotinamide; PVDF, polyvinylidene difluoride; SAC, saccharin; SDS, sodium dodecyl sulfate.

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http://dx.doi.org/10.1016/j.ejpb.2016.07.006
0939-6411/

Nanocrystal formulation is another promising way to improve oral bioavailability because of the rapid dissolution rate owing to increased surface area of drug particle [7,24,25]. The key advantages of nanocrystal formulations over amorphous solid dispersions are their superior physical and chemical stabilities, due to the lower energy of the crystalline state than the amorphous [6]. Nanocrystal is a suitable formulation to successfully enhance the bioavailability of drugs where the dissolution rate is the rate limiting step in the absorption; however, it is not adequate to drugs whose saturation solubility is the rate limiting step because saturation solubility of drugs is not significantly improved by nanonization according to the Ostwald–Freundlich equation in typical particle size range of nanocrystals, 100–200 nm [26,27]. In general, nanocrystals are prepared by top-down or bottom-up approaches. Bead milling is one of the most universal top-down methods used in the pharmaceutical industry: the drug particles are nanonized with stabilizers such as polymers and surfactants in aqueous media using high-shear media mills [24,28]. However, there is another limitation of nanocrystals in the top-down preparation: the crystallinity of the milled drug is gradually decreased and it becomes physically destabilized during the milling process [29,30]. Drug compounds having fragile crystalline structures tend to transform to the amorphous state and undergo particle aggregation, thereby decreasing the usefulness of nanocrystal formulations.

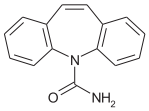
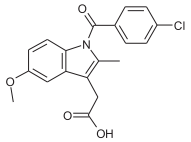
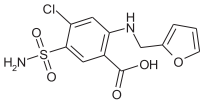
Taken together, although both cocrystal and nanocrystal formulation technologies have been widely used in the pharmaceutical development of poorly soluble drugs, the synergistic effects due to the integration of these technologies have not been well investigated. In fact, the solubilization effect or physical stability of each technology, cocrystal or nanocrystal, is occasionally insufficient for absorption improvement and pharmaceutical development due to their limitations shown above. Therefore, more promising solubilization technique that can overcome the limitation and maximize the solubilization potential with acceptable stability over each of nanocrystal and cocrystal is highly required. A new proposal in the present study is based on the integration of cocrystal into nanocrystal, nano-cocrystal formulation, that can potentially overcome the limitation of nanocrystal in solubility improvement and physical stabilization during wet milling by crystal modification. De Smet et al. reported that itraconazole–adipic acid nano-cocrystal suspension having particle diameter of 549 nm could be prepared by the wet milling of physical mixture of itraconazole and adipic acid with Tween 80, and the dissolution and oral absorption of the nano-cocrystal was equal to or greater than those of amorphous formulations [31]. Meanwhile, the exhaustive characterizations on the nano-cocrystal properties with various combinations of cocrystals and its feasibility in pharmaceutical development were not fully accomplished. The present study aimed to develop the nano-cocrystal formulations having particle diameter less than 300 nm that showed acceptable physical and chemical stability for pharmaceutical development, compared to the single-component nanocrystal formulations. Universal wet milling procedure using cocrystals as a starting material with stabilizers was employed to meet the target particle size required, considering scalability as well. The target particle diameter was set based on experimental in vitro and in vivo performance of nanocrystal formulations. Required particle diameter of nanocrystals to reveal the oral absorption improvement was empirically less than 300 nm at minimum [32,33]. To comprehend a variety of drug properties, neutral, acidic and amphoteric poorly soluble drugs carbamazepine, indomethacin (BCS class II compounds) and furosemide (BCS class IV compound), respectively, and their cocrystals or salts were selected as the model compounds to demonstrate the formulation of nano-cocrystal suspensions [21,22,34–37]. The structures and physicochemical properties of these model drugs are provided in Table 1. The particle sizes, zeta potentials, dissolution, and physical stabilities of the nano-cocrystal suspensions were compared to those of single-component nanocrystals.

2. Material and methods

2.1. Materials

Anhydrous carbamazepine (CBZ, ⩾97.0% purity, form III) and indomethacin (IMC, ⩾98.0% purity, form γ) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Furosemide (FSD, ⩾99.0% purity, form I) was purchased from Tokyo Chemical Industry, Ltd. (TCI, Tokyo, Japan). Carbamazepine dihydrate (CBZ DH) was prepared by recrystallization of CBZ from mixture of ethanol and water according to the procedure previously reported [38]. The CCFs saccharin (SAC), caffeine (CAF), acetamide (ACT), urea, and nicotinamide (NIC) were purchased from Wako, and cytosine (CYT) was purchased from TCI. All organic solvents used in the preparation of the cocrystals were purchased from Wako, as was the surfactant sodium dodecyl sulfate (SDS). Hydroxypropyl methylcellulose (HPMC, TC–5E grade) was kindly gifted by the

Table 1
Structures and physicochemical properties of carbamazepine (CBZ), indomethacin (IMC) and furosemide (FSD).

		CBZ	IMC	FSD
Structure				
Molecular weight		236.27	357.79	330.74
clogP[a]		1.9	4.3	2.3
Crystal form		Form III	Form γ	Form I
Melting point (°C)[b]		182	159	203
Solubility at 37 °C (μg/mL) ± S.D., n = 3	JP1 (pH 1.2)	263 ± 11	0.7 ± 0.1	17 ± 0
	JP2 (pH 6.8)	266 ± 17	762 ± 2	>1000
	GCDC/JP2	631 ± 11	>1000	>1000
BCS class		II	II	IV

JP1: 1st dissolution fluid (pH 1.2) in the Japanese Pharmacopoeia.
JP2: 2nd dissolution fluid (pH 6.8) in the Japanese Pharmacopoeia.
GCDC/JP2: 20 mM glycochenodeoxycholate in JP2 (pH 6.8).
[a] clogP was calculated by ACD/Percepta.
[b] Melting points were quoted from the literatures [22,35,37].