Mesoporous silica for use as a supergeneric development compound

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Introduction

Today's pharmaceutical industry promotes innovation as an instrument to create competitive advantage. The overall focus of pharmaceutical science is shifting heavily towards the generic market sector – with an outlook of limited financial investment, short development timelines and lower risk of failure. In response to these parallel trends towards innovation and generic drugs, the idea of using "supergenerics" for drug product development and life cycle management is gaining ever more recognition.

The use of mesoporous silica particles (monographed and GRAS-status) appears to be a promising technology for the development of supergenerics in the pharmaceutical industry, as these particles demonstrate high potential to overcome poor solubility and improve oral absorption for BCS class II and IV APIs [1]. Based on the following case studies looking at 1) improved dissolution 2) dose reduction, and 3) a combinatorial application approach, we want to highlight the benefits of using mesoporous silica when developing supergeneric formulations.

Experimental Methods

Materials

For model APIs, please see Table 1. Dilatrend® 25 mg (Roche, Basel, Switzerland) and Atacand®Plus (AstraZeneca, London, UK) were purchased from the Engel Apotheke, pharmacy, Darmstadt, Germany. Parteck® SLC 500, phosphate buffer compounds, and acetone were obtained from Merck KGaA, Darmstadt, Germany. SIF® Powder is a complex of taurocholate and lecithin, and was purchased from Biorelevant.com, UK (lot 01-1210-05), to make FaSSIF biorelevant media. All other chemicals were of analytical grade and purchased commercially without further purification.

Substance	Trial	Manufacturer/ Supplier	Loading Method
Carvedilol (CAR)	1 & 2	TOKYO Chemical Co., LTD, Tokyo, Japan	A
Hydrochlorothiazide (HCT)	3	Boehringer Ingelheim, Ingelheim, Germany	B
Candesartan cilexetil (CAN)	3	Jiangxi Synergy Pharmaceutical Co., Ltd., Jiangxi, China	A

Table 1: Model APIs

Methods

Drug Loading

The respective API(s) were dissolved (alone or simultaneously) in acetone and loaded 30 % (w/w) onto the porous silica powder by the (A) solvent impregnation [2] or (B) suspension method [3] as outlined in Table 1. The resulting loaded silica was then dried overnight (T = 50 °C) in a vacuum drying oven (Heraeus Vacutherm, Thermo Fisher Scientific Inc., Waltham, USA) to remove the residual solvent. Successful loading was verified by NMR spectroscopy (Bruker Avance III, 500 MHz NMR spectrometer, Bruker Corporation, Billerica, USA), and the amorphous state of the APIs was confirmed by DSC analytics (DSC 821e, Mettler-Toledo GmbH, Giessen, Germany).

Dissolution

USP dissolution apparatus 2 with a paddle (Sotax AT7, Sotax GmbH, Aesch, Switzerland) was used to study the dissolution at 37 °C and 75 rpm together with biorelevant test media to simulate gastric intestinal conditions. The volumes were 1,000 mL (Trial 1), 500 mL (Trial 2), and 900 mL (Trial 3). Analysis was performed via online UV measurement (240 nm, Trial 1 & 2) or HPLC (LaChrom Elite, VWR International GmbH, Darmstadt, Germany), for Trial 3 [4]). Samples were tested in triplicate.

Results and Discussion

In Trial 1, the weakly basic model compound CAR was fully amorphously loaded to 23 % (w/w) (verified by DSC analysis, see Figure 1, and NMR spectroscopy) onto Parteck® SLC 500. Compared to crystalline CAR, the CAR loaded Parteck® SLC 500 dissolved three times as much API (same concentration of 60 mg/L CAR) in the pH 6.8 phosphate buffer over 120 min (see Figure 2). The use of mesoporous silica particles to enhance the dissolution of a poorly soluble drug was thus successfully demonstrated.

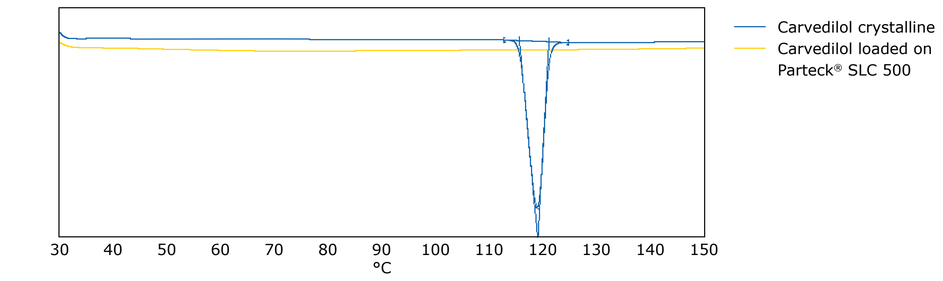

Figure 1: DSC analysis for CAR loaded on Parteck® SLC 500.

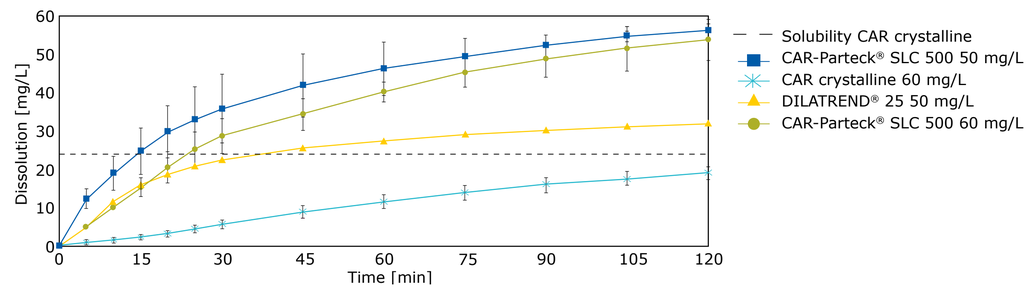

Figure 2: Dissolution of CAR in phosphate buffer pH 6.8.

For Trial 2, the amount of CAR was reduced to 50 mg/L for the dissolution test, corresponding to the market formulation Dilatrend® (Roche, Basel, Switzerland) which has a dose of 25 mg CAR. Dissolution was enhanced even more than in Trial 1, where a higher concentration of 60 mg was used (see Figure 2). Reducing the amount of Parteck® SLC 500 - loaded CAR thus increases dissolution further, so final formulations only need lower API concentrations.

For Trial 3, two weak acid model APIs, HCT and CAN, were simultaneously loaded onto Parteck® SLC 500 to a maximum of 30 % (w/w) total, with doses in line with the market combination (Atacand® Plus, 12.5 mg HCT and 8 mg CAN, AstraZeneca, London, UK). NMR spectroscopy and DSC analytics verified the loading amounts and the amorphous state of both drugs. Figure 3 shows the dissolution data in FaSSIF media for this combinatorial approach.

Both APIs showed superior stable dissolution compared to the respective crystalline drug, and in the case of CAN, twice the dissolution was seen after 90 min compared to the market formulation. For HCT, improved immediate release behavior between 5 and 15 min was observed with the loaded Parteck® SLC 500.

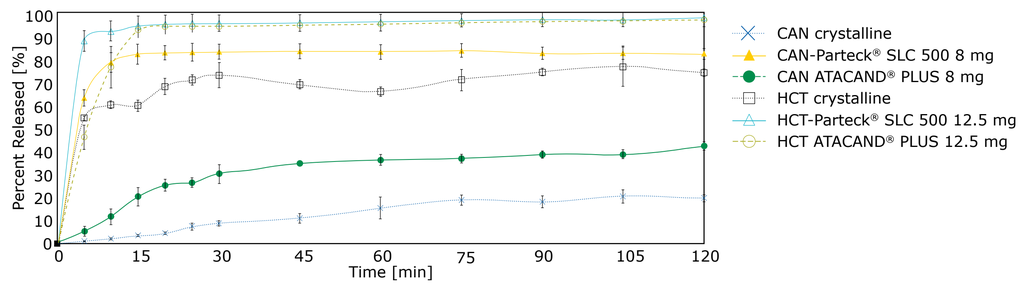

Figure 3: Dissolution of HCT and CAN in FaSSIF media.

Conclusion

These case studies demonstrate that the studied mesoporous silica-based Parteck® SLC 500 particles are a powerful tool for developing supergenerics in the pharmaceutical industry, as they allow formulators to create advanced drug delivery systems – such as by simultaneously loading two compounds in one process step, saving on handling and costs. Loading APIs onto an inert, safe silica carrier (monographed and GRAS-status) enhances dissolution, allowing for innovative and safe formulations.

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