



Amphiphilic drugs as surfactants to fabricate excipient-free stable nanodispersions of hydrophobic drugs for cancer chemotherapy

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ABSTRACT

Nanoformulations have been extensively explored to deliver water-insoluble drugs, but they generally use exotic new materials, for instance, amphiphilic block copolymers, which must first go through extensively clinical trials and be approved as drug excipients before any clinical uses. We hypothesize that using clinical amphiphilic drugs as surfactants to self-assemble with and thus solubilize hydrophobic drugs will lead to readily translational nanoformulations as they contain no new excipients. Herein, we show the first example of such excipient-free nanodispersions using an amphiphilic anti-tumor drug, irinotecan hydrochloride (CPT11). CPT11 self-assembles with its insoluble active parent drug, 7-ethyl-10-hydroxy camptothecin (SN38), into stable and water-dispersible nanoparticles, increasing SN38's water solubility by thousands of times up to 25 mg/mL with a loading efficiency close to 100%. The versatility of this approach is also demonstrated by fabricating nanodispersions of CPT11 with other water-insoluble drugs including paclitaxel (PTX) and camptothecin (CPT). These nanodispersions have much increased bioavailability and thereby improved anti-cancer activities. Thus, this strategy, using clinically proven amphiphilic drugs as excipients to fabricate nanodispersions, avoids new materials and makes readily translational nanoformulations of hydrophobic drugs.

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1. Concept and hypothesis

Small molecular cytotoxin based anti-cancer drugs are still the main arsenal in fighting against cancer. However, most drugs are poorly water-soluble and the number of insoluble drug candidates in drug discovery is still increasing with almost 70% of new drug candidates [1]. Furthermore, their off-targeted intoxication to healthy cells causes severe adverse effects [2–4]. Hence, great efforts have been made to formulate these insoluble drugs for easy administration [5] using nanocarriers including polymers, liposomes and dendrimers [6,7]. These nanocarriers are also expected to improve drugs' pharmacokinetics via the enhanced permeability and retention effect [8]. Many such nanomedicines indeed show substantially reduced adverse effects, and several are already in clinical use and many more are in clinical trials [7]. For instance, 7-ethyl-10-hydroxycamptothecin (SN38) is a very potent inhibitor of topoisomerase I inhibiting growth of various tumor cells [9], but is poorly soluble in aqueous solution with a water solubility of about 11 µg/mL [10]. It is also insoluble in most pharmaceutically acceptable solvents and excipients including ethanol, polysorbate 80 and

cremophor, making it difficult to prepare suitable formulations for clinical use. So nanoparticles (e.g. SN38-loaded poly-lactide-co-glycolic acid [11]), polymer–drug conjugates (e.g. EZN-2208 [12]), and liposomal formulations (e.g. LE-SN38 [10]) of SN38 have been attempted to solve this challenge. Among them, EZN-2208 and NK012 (amphiphilic prodrugs) have entered the Phase II clinical trial, while some including SN2310 [13] (a lipophilic prodrug), DTS-108 [14] (a peptidic prodrug) and IMMU-130 [15] (an antibody–drug conjugate) are in the Phase I trial [16]. For example, EZN-2208 is a multi-arm 40 kDa PEG conjugate of SN38 via a glycine linker with an SN38 loading of 3.7% (wt/wt) and water solubility of 6.7 mg/mL. After extensive clinical trials, though well tolerated, it did not show expected therapeutic efficacy but unanticipated side effects, like neutropenia [17]. Up to date there is still no commercial SN38 formulations in clinics.

Given a large number of nanomedicine systems reported to date, only few have entered clinical use [18]. One major bottleneck to clinical translation is that current nanomedicines often use new carrier materials or chemical modifications to drug molecules. These new materials or new molecules themselves need intensive clinical trials and final FDA approvals to be used as new excipients; particularly, the carriers may go through a more difficult path through the clinic [18]. Furthermore, the fabrications of the nanomedicines are often too complicated to establish proper manufacture process for scaling up [19].

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Motivated by our previous work that amphiphilic prodrugs could self-assemble into nanoparticles/nanocapsules for drug delivery [20], we hypothesized that directly using clinically proven amphiphilic drugs as surfactants to fabricate nanomedicines would avoid using non-clinically proven materials and thus facilitate their clinical translation. Herein, we demonstrated this concept that using CPT11 as the sole excipient to solubilize SN38 or other highly hydrophobic drugs. CPT11 is a clinically used water-soluble drug with a protonated tertiary amine head. Its hydrophobic moiety may interact with hydrophobic drugs such as SN38 like an amphiphilic surfactant to form stable nanodispersions (Supporting information, Fig. S1).

2. Experimental methods

SN38/CPT11 nanodispersions were prepared using an anti-solvent method. A typical procedure is as follows: SN38 (10 mg) and CPT11 (10 mg) were dissolved in 150 μL of dimethyl sulfoxide (DMSO), and then DI water (10 mL) was added into the solution with vigorous stirring or ultrasonication for 5 min (ultrasonic cleaner, FRQ-1004HT, 200 W). The bluish solution was then loaded into a dialysis bag (MWCO 3500) and dialyzed against water for 10 h or freeze-dried directly to remove the organic solvent. This formulation is referred to as S1C1, which stands for the weight ratio of SN38 (S) to CPT11 (C) at 1 to 1. Other formulations at different ratios were prepared similarly (Supporting information). For in vivo experiments, the nanodispersions were prepared in 5% glucose or 0.9% sodium chloride injection medium.

3. Discovery and interpretation

CPT11 or irinotecan hydrochloride, a prodrug of SN38 and widely used as a first-line drug for treatments of many types of cancer, is insoluble in water at pH 5.7 (2 mg/mL), and no particles were detected by

DLS in the solution, but some large and undefined nanostructures formed as the solution pH increased to neutral (Fig. S2). SN38 is insoluble in water. Once water was added to its organic solution (e.g. DMSO solution), it quickly precipitated out (Fig. S3) and could not form any stable dispersion even in the presence of various surfactants, such as Tween 80 and Cremophor. However, when the same amounts of SN38 and CPT11 were dissolved in DMSO together and then water was added, unexpectedly, they formed stable nanodispersion (S1C1) without any precipitation even after removing DMSO by dialysis (Fig. S3) and no free SN38 was detected in the dialysate. The nanodispersion remained well dispersed for several months in 4 $^{\circ}\text{C}$ storage. Lyophilization of the solution produced S1C1 powders that were re-dispersed in water, but the particle size became much larger to 500 nm. Adding 6% D-trehalose as a cryoprotectant to the solution resolved the problem. Lyophilization of the nanodispersion solution with 6% D-trehalose produced a powder well re-dispersible in water, or 5% glucose, or 0.9% sodium chloride injection medium used in clinics, and the nanoparticle sizes remained unchanged (Fig. S4). The Z-average size of S1C1 nanodispersion was 79.7 nm with a PDI of 0.176 (Fig. 1A) and a zeta-potential of +31.3 mV in water, resulting from the protonated tertiary amine of CPT11. TEM and AFM images further proved the formation of uniform nanoparticles (Fig. 1B).

The nanodispersion could form even in the presence of a very small amount of CPT11; for instance, as low as 1 wt.% of CPT11 was sufficient to make a stable dispersion (S99C1). Thus, the nanodispersions could form in a very broad weight ratio range of SN38 to CPT11, from 1:0.01 to 1:5. Thanks to the nanodispersion, the concentration of SN38 could reach 25 mg/mL in water, increased by thousands of times to free SN38, which had not yet been achieved by other SN38 formulations so far.

This simultaneous formation of the SC nanoparticles can be ascribed to the strong interaction force between SN38 and its prodrug, CPT11 (Fig. S1). Though hydrophobic, SN38 is generally difficult to form

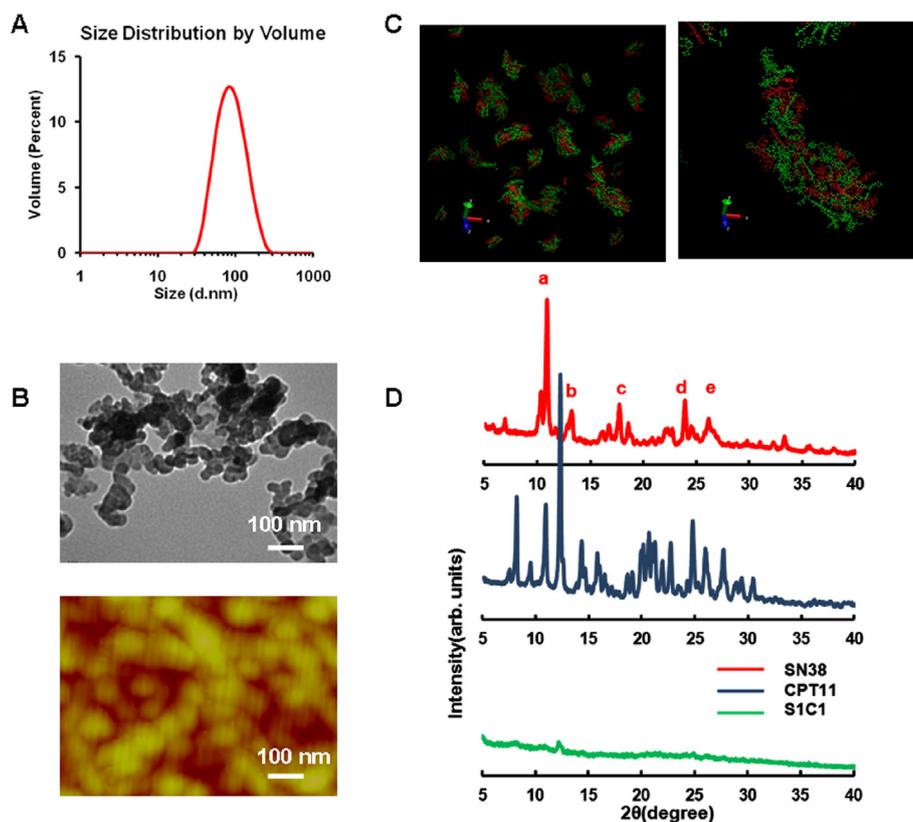


Fig. 1. Characterizations of nanodispersions. A) Particle size distribution of SN38/CPT11 nanodispersions (S1C1) measured by dynamic light scattering. B) Typical TEM (up) and AFM (down) images of S1C1 nanodispersion. Scale bar: 100 nm. C) Modeling of the self-assembly of S1C1, where CPT11 molecules are shown in red and SN38 molecules are in green. D) X-ray diffraction (XRD) diagrams of SN38, CPT11 and S1C1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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