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Co-delivery of SN38 and curcumin by Pluronic micelles for synergistic therapy of colorectal cancer

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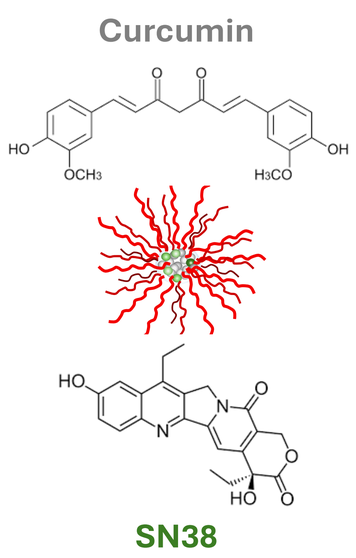
INTRODUCTION

Chemotherapy based on application of drug combination has emerged as an appropriate solution for addressing the colorectal cancer heterogeneity by targeting multiple complementary cellular pathways involved in tumorigenic processes (1). Polymer nanomicelles based on amphiphilic A-B-A (hydrophilic-hydrophobic-hydrophilic) Pluronics® have attracted attention due to the ability to solubilize and stabilize hydrophobic drugs and increase their accumulation in tumors through passive or active mechanisms (2). Here, we explore their ability to encapsulate SN38 and curcumin for combined colorectal cancer therapy.

MATERIALS AND METHODS



Mixed Pluronic® Micelles Preparation

- P123:F127 8:1 w/w, 30 mg/ml; thin film hydration (72h at room temperature)
- different feed ratios of SN38 (2 and 5 µg/ml) and curcumin (50, 150, 350, 500, 750 and 1050 µg/ml) used to account for differences in IC_{50} and loading capacities of free drugs

Micelle Characterization

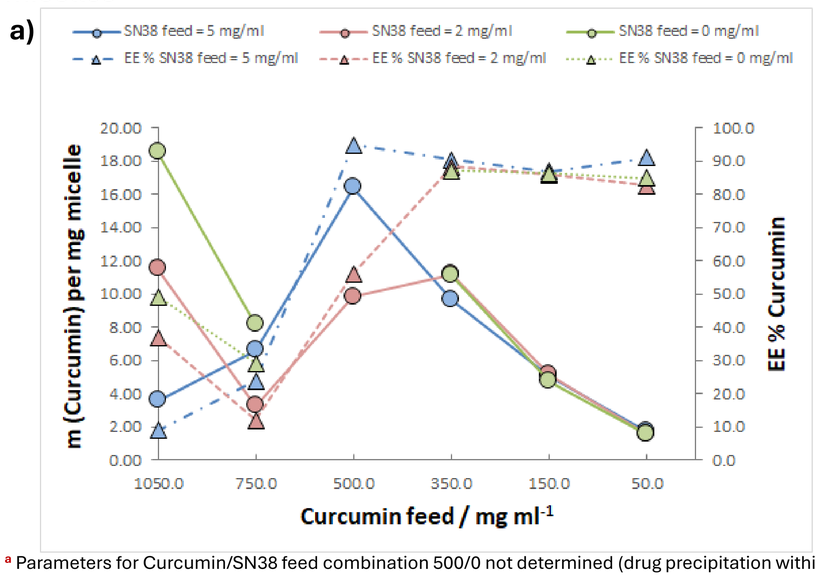
- colloidal properties (size, PDI)
- encapsulation efficiency (EE%): HPLC

***In vitro* activity**

- **free drugs**
  - synergistic activity against colorectal cancer cell line LoVo: SynergyFinder Plus (3)
- **encapsulated drugs**
  - 2D model (LoVo)
  - heterogeneous 3D spheroids (HCT116, human pulmonary microvascular endothelial cell HPMEC, HIF fibroblasts, and donor macrophages) (4)

RESULTS

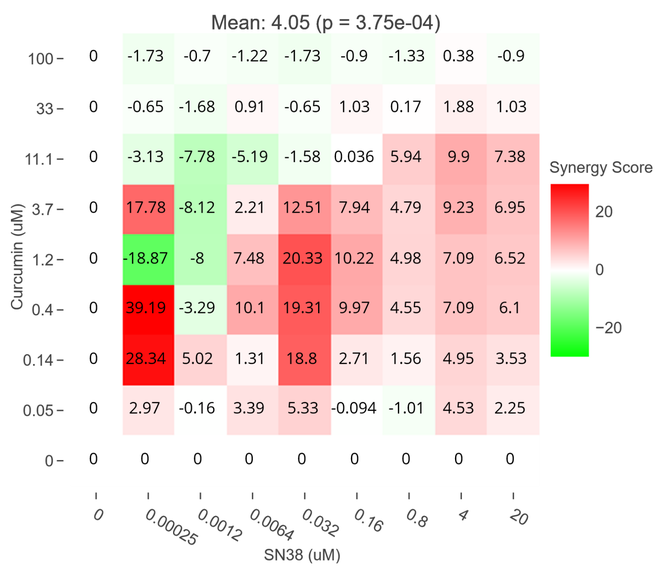
Figure 1. Characterization of curcumin/SN38-loaded P123-F127 micelles: a) Influence of curcumin and SN38 feed concentrations on co-encapsulated curcumin solubilization and encapsulation efficiency;[a] b) Influence of curcumin and SN38 feed concentrations on co-encapsulated SN38 solubilization and encapsulation efficiency; insert: solubilization and encapsulation efficiency of SN38 (single drug)**; c) colloidal properties of freshly-prepared curcumin-SN38-loaded micelles;[b]** insert: colloidal properties of freshly-prepared SN38-loaded micelles



[a] Parameters for Curcumin/SN38 feed combination 500/0 not determined (drug precipitation within 4 days)

[b] colloidal properties of **empty micelles: size: 19.9 ± 0.22; PDI = 0.09 ± 0.02**

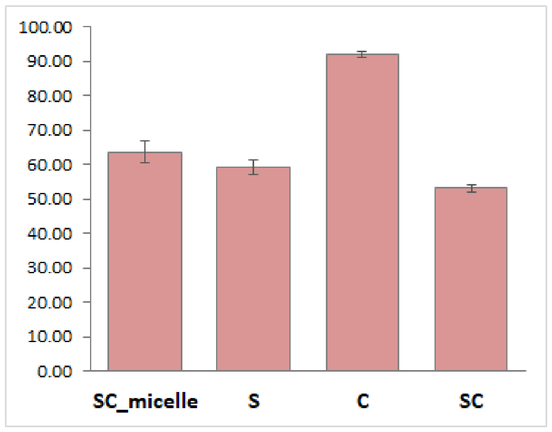
Figure 2. Loewe additivity synergy score map for curcumin/SN38 combination in LoVo cells



IC_{50} (SN38) = 0.03 µM; IC_{50} (curcumin) = 5.8 µm
RI[a] (SN38) = 50.2; RI (curcumin) = 44.2; CSS[b] = 71.7

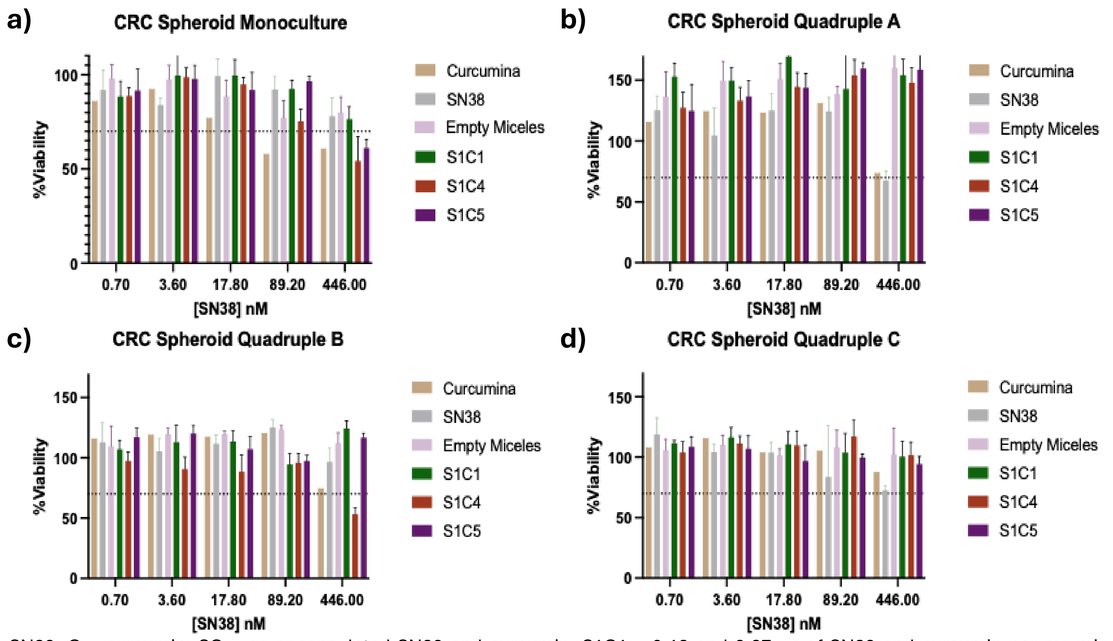
[a] relative inhibition of monotherapy; [b] combination sensitivity score of SN38/curcumin

Figure 3. *In vitro* activity of co-encapsulated SN38/curcumin in 2D LoVo CRC model[a]



[a] S = SN38; C = curcumin; SC = SN38/curcumin; SC_micelle contains 0.03 µM SN38 and 1.2 µM curcumin in 0.3 mg/ml micelle (0.038 and 1.21 µg of SN38 and curcumin per mg micelle, respectively); the combination of loaded drugs corresponds to synergy score 20 (Figure 2); corresponding drug concentrations were used for free drugs; Alamar test was used to evaluate cell viability.

Figure 4. *In vitro* activity of co-encapsulated SN38/curcumin in mono (a) and quadruple (b-d) 3D HCT116 CRC model[a]



[a] S = SN38; C = curcumin; SC = co-encapsulated SN38 and curcumin; S1C1 = 0.13 and 9.37 µg of SN38 and curcumin per mg micelle, respectively; S1C4 = 0.1 and 14.23 µg of SN38 and curcumin per mg micelle, respectively; S1C5 = 0.086 and 7.79 µg of SN38 and curcumin per mg micelle, respectively; SN38 concentrations were used for normalization; CellTiter assay was used to evaluate the viability of spheroids.

CONCLUSIONS

To exploit fully the advantages of nanomicelles for simultaneous delivery of combination chemotherapy, they must encapsulate the correct ratio of drugs while considering their respective biological potential and the physicochemical characteristics. In the case of SN38/curcumin combination, the ratio could be regulated by specific drug feeds to obtain stable nanomicelles that possess synergistic activity against LoVo CRC 2D model. In the more complex 3D *in vitro* model based on human HCT116 CRC cells, endothelial cells, and fibroblasts, as well as donor macrophages, response to co-encapsulated and free individual or combined drugs reflect complex interplay of cell model and cell types, tested drug ratio, and above all the presence of specific donor macrophages.

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LITERATURE
(1) Guo W, Song Y et al., Sci Rep. 2020, 10: 7832. https://doi.org/10.1038/s41598-020-64828-1
(2) Jarak I, et al., Eur. J. Med. Chem. 2020, 206:112526. DOI: 10.1016/j.ejmech.2020.112526
(3) Zheng S, et al, Genom. Proteom. Bioinform. 2022, 20: 587. doi:10.1016/j.gpb.2022.01.004.
(4) Carvalho et al, Adv. Ther. 2023, 6:2200282. https://doi.org/10.1002/adtp.202200282