PRE-FORMULATION STRATEGIES FOR AMPHIPHILIC CYCLODEXTRIN NANOSYSTEMS

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INTRODUCTION

Cyclodextrins (CDs) have sparked widespread interest as drug delivery systems due to their unique molecular structure, attractive properties, and remarkable versatility. Beyond their traditional role as host molecules, CDs can be chemically modified into amphiphilic derivatives that can self-assemble into different types of nanocarriers. These amphiphilic CDs are specifically designed to overcome the limitations of natural CDs, thus expanding their therapeutic applications [1].

OBJECTIVES

Understand the structural features of cationic amphiphilic CDs and their self-assembly capacity.

Evaluate the drug encapsulation capacity and efficiency of CD-based nanoparticles.

METHODS

- Evaluation of a panel of amphiphilic cationic CDs to assess the impact of structural variations on self-assembly behavior.
- Optimization of formulation parameters (including probe sonication time and aqueous to organic phase ratios).
- Selection of the most promising systems for encapsulation of Curcumin.
- Evaluation of performance in terms of encapsulation efficiency, loading capacity, stability, and in vitro cytotoxicity.

REFERENCES

[1] Varan G, Varan C, Erdoğar N, et al. Amphiphilic cyclodextrin nanoparticles. Int J Pharm 2017;531:457-69.

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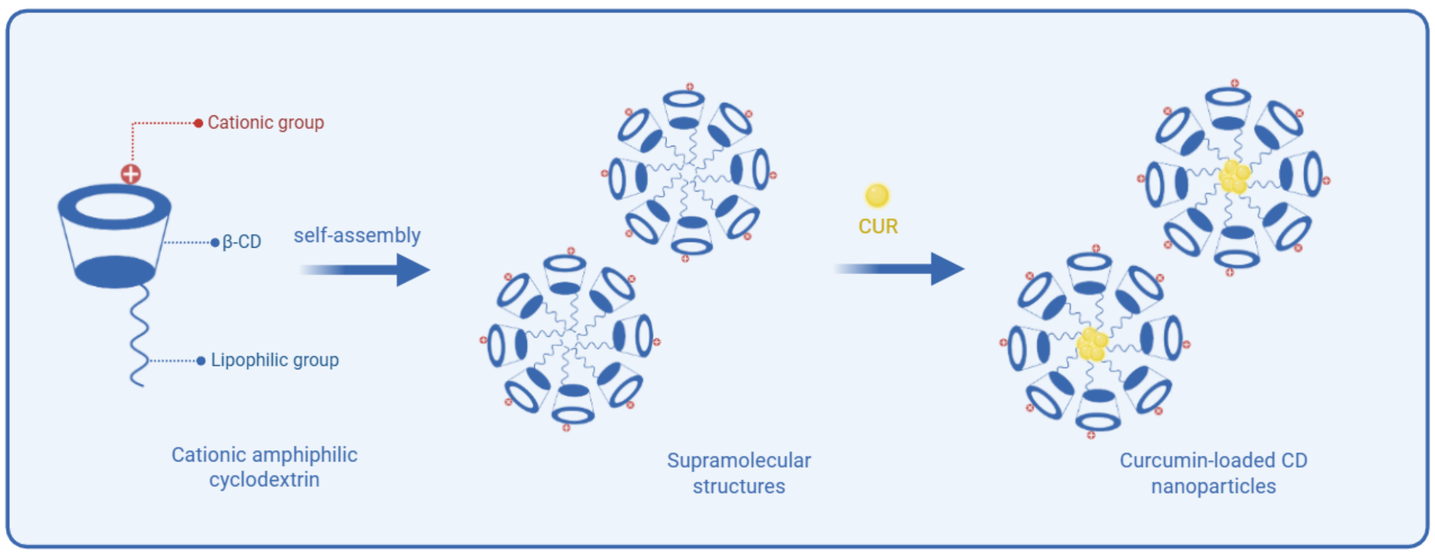

Figure 1. Cationic amphiphilic cyclodextrins: structural features, self-organization, and drug loading.

RESULTS

Among the evaluated cationic amphiphilic CDs, the C16 derivative bearing a single cationic chain exhibited the best overall performance (**Figure 1**). All CDs derivatives were further combined with different surfactants, namely Pluronic F127, Pluronic F68 and TPGS, among which TPGS showed the most promising results. Increasing TPGS concentration led to a progressive neutralization of the positively charged CDs, accompanied by a reduction in particle size and an increase in the polydispersity index (PDI) (**Table 1**). Complete charge neutralization was achieved at 10%. Regarding the preparation method, incorporation of TPGS into the organic phase, rather than the aqueous phase, improved the physical stability of the formulation, although both approaches initially yielded comparable particle sizes and PDI values. Additional formulation parameters, including probe sonication time and aqueous-to-organic phase ratio, are summarized in **Table 2**. The most suitable CD–CUR nanosystem was obtained using a Vaq:Vorg ratio of 1:2 and 8 minutes of probe sonication, resulting in an approximately eight-fold enhancement in the aqueous solubility of curcumin. Based on its superior encapsulation efficiency and storage stability, this formulation was selected for subsequent *in vitro* studies in LoVo cells. Although only modest effects on cell viability were observed, likely due to the low concentrations tested, a clear synergistic interaction between the CD and curcumin was observed.

Table 1. Effect of TPGS concentration on particle size, PDI, and zeta potential of nanoparticles properties (CD 0.5 mg/mL in CH_2Cl_2 in all formulations).

TPGS concentration (% w/v)	Particle size ± SD (nm)	PDI ± SD	Zeta potential (mV) ± SD
0	123.3 ± 3.54	0.30 ± 0.01	36.8 ± 2.01
0.1	75.9 ± 0.55	0.43 ± 0.01	25.7 ± 1.76
0.25	74.6 ± 0.91	0.59 ± 0.01	19.4 ± 2.66
0.5	59.8 ± 2.16	0.59 ± 0.03	17.4 ± 2.15

Abbreviations: PDI polydispersity index; SD standard deviation.

Table 2. Effect of the number of 1-min sonication cycles and aqueous/organic ratio during probe sonication at 0 °C (4-s pulses, 40% amplitude) on nanoparticle properties (CD 0.5 mg/mL and CUR 50 µg/mL in all formulations).

No. of 1-min cycles	Ratio (V_{aq}: V_{org})	Particle size ± SD (nm)	PDI ± SD
8	1:2	40.48 ± 0.47	0.283 ± 0.01
	1:1	63.41 ± 0.11	0.422 ± 0.02
5	1:2	47.08 ± 0.26	0.254 ± 0.01
	1:1	57.07 ± 0.90	0.365 ± 0.01
3	1:2	66.53 ± 0.86	0.467 ± 0.02
	1:1	58.22 ± 0.47	0.238 ± 0.01

Abbreviations: No number; V_{aq} aqueous phase volume; V_{org} organic phase volume; SD standard deviation.

CONCLUSION

Pre-formulation studies play a star role in rational pharmaceutical development, particularly when applied to promising drug delivery systems such as CDs. Within this framework, a systematic evaluation of amphiphilic CDs was undertaken to better understand their potential to encapsulate drugs with significant pharmacokinetic limitations.