T4066

Selective Delivery of Anticancer Drugs: Folate-appended Cyclodextrins

Tamás Sohajda, Milo Malanga and Lajos Szente
CycloLab Cyclodextrin R&D Ltd

CONTACT INFORMATION: sohajda@cyclolab.hu

2017 AAPS ANNUAL MEETING & EXPOSITION

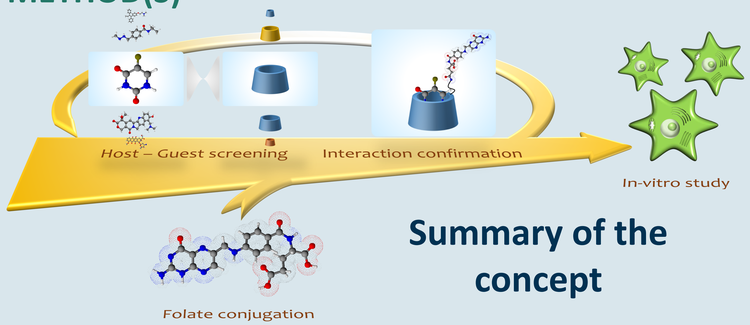
PURPOSE

The conjugation of drug delivery systems with folate groups is a widely applied and successful strategy for achieving selectivity towards cancer cells [1-2]. Cyclodextrins (CDs) are universal host-molecules able to interact with a large variety of anticancer drugs. The combination of these two functional moieties, folate as selective targeting unit and cyclodextrin as tunable host-molecule may create the next generation of anticancer products. A general strategy for the targeted delivery of anticancer drugs based on folate-appended cyclodextrins was developed in this work.

OBJECTIVE(S)

The main objectives at this stage of the study were to identify the CDs that are the most suitable hosts for several target anticancer APIs by high throughput screening, prepare the folate-appended analogs and verify the complex formation and efficacy by in vitro techniques.

METHOD(S)



Summary of the concept

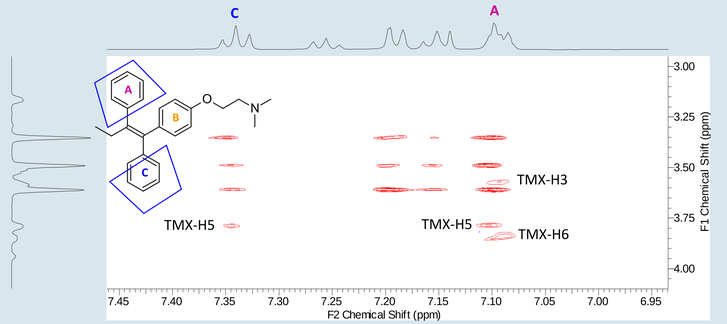
A library of anticancer drugs (10 compounds) were screened by capillary electrophoresis (CE) with various cyclodextrins (21 derivatives) in order to evaluate host-guest matches. Hosts of the most promising pairs (αCD, βCD, permethyl-βCD and sulfobutylether-βCD) were appended with folate groups in a green synthetic method. The interactions were confirmed by CE and 2D-NMR techniques.

RESULT(S)

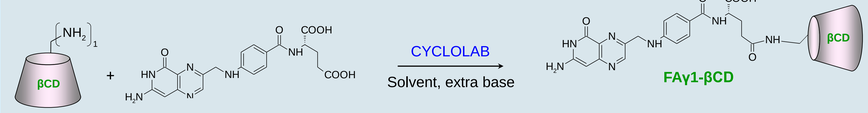
Among the library of selected anticancer drugs, BCD, GCD and TRIMEB formed stable complexes with tamoxifen, and SBECD with doxorubucin and docetaxel based on the CE study (K: 500-10000 M^{-1}, see table below). The inclusion of the host-guest systems was confirmed by ROESY (see Tamoxifen (TMX)-TRIMEB interaction on the right).

	Tamoxifen	Fluorouracil	Doxorubicin	Docetaxel	Finasteride	Pomalidomide
ACD	42	150	127			
BCD	**1440**	-	112			
GCD	**1300**	110	200			
RAMEB	130	50	50			
TRIMEB	**600 (pH=6)**	-	92			
HPACD	450	78	99			
HPBCD DS:4.5	-	25	60			
HPGCD DS:4.5	-	-	120			
DIMEB 50	520	75	245			
SBEBCD DS:6	-	-	**8000**	**9584**	< 5	< 5

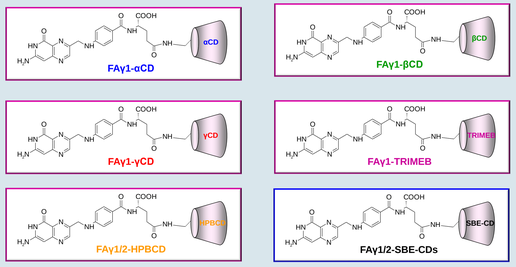
Affinity of selected cyclodextrins towards anticancer agents



Folate-appended cyclodextrins were prepared, isolated by reversed phase chromatography and characterized by HPLC-MS, NMR and CD spectroscopy. As proof of concept, the best performing inclusion complexes are under testing on tumor cells.



Synthetic scheme for the folate conjugation



Library of available folate appended CDs

CONCLUSION(S)

The presented and established drug delivery platform combines the advantages of cyclodextrins and targeted delivery using a folate moiety. Due to the flexibility and variation of potential CD hosts, the platform is universally applicable to deliver various anticancer drugs having affinity for inclusion complexation by CDs with high efficiency. Since several types of cyclodextrins are already safely used in over 60 pharma formulations, the acceptance of these new folate appended CDs as drug delivery systems shall not pose a problem.

REFERENCE

[1] R. Onodera, K. Motoyama, A. Okamatsu, T. Higashi, H. Arima, Scientific Report, 2013, 3, 1104.

[2] Z. Tofzikovskaya, A. Casey, O. Howe, C. O'Connor, M. McNamara, J. Incl. Phenom. Macrocycl. Chem ., 2015, 81, 85-94

CycloLab The Cyclodextrin Company