Development of Novel Hybrid Delivery Systems using SCF Technology for Enhanced Bioavailability of Antioxidant Compounds

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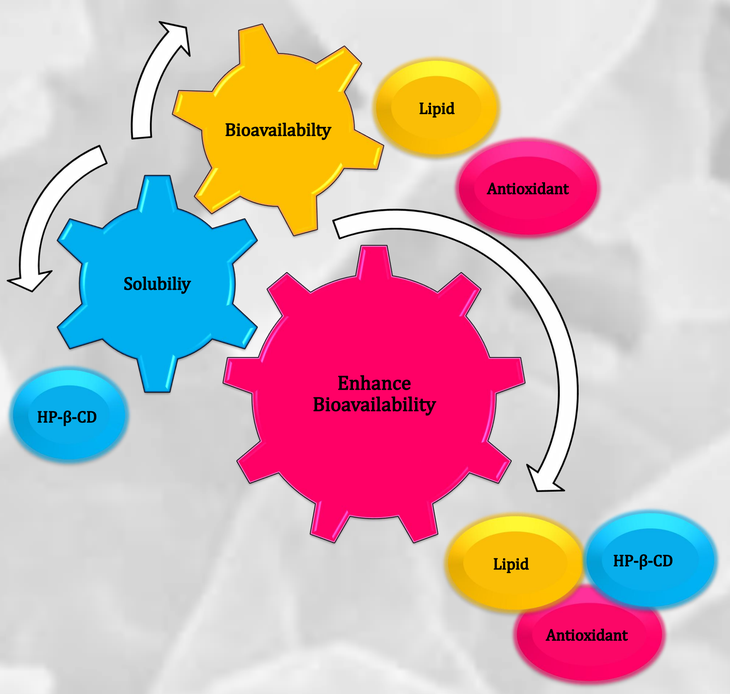
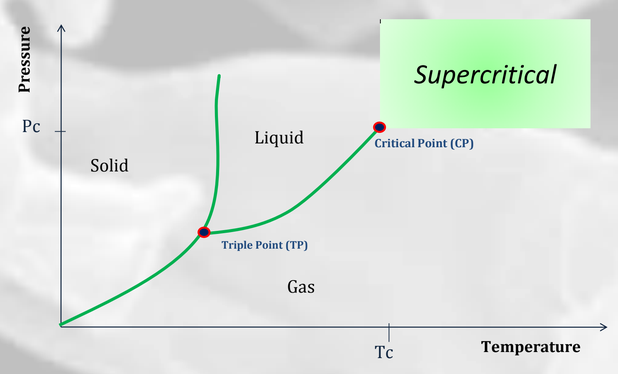
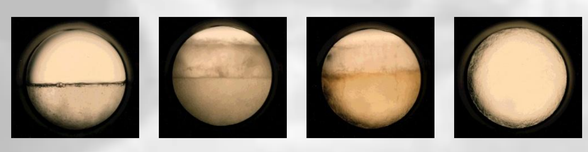
This work explores the possibility to prepare, using supercritical fluid technology, particulate hybrid delivery systems that allow improvement of bioavailability and controlled release of antioxidant bioactive compounds.

Hybrid delivery systems with improved properties are designed to meet specific challenges that the pharmaceutical industry is presently facing in the area of drug delivery[1,2].



SCF Technology





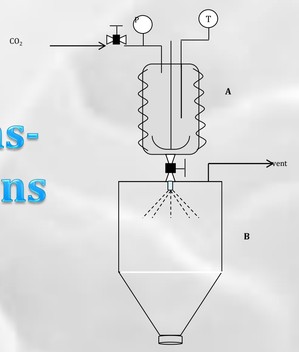
Clean Method

Alternative to conventional processes, carried out under conditions that have detrimental effects on the active principle and/or carriers materials

Drug Stability and bioavailability enhnacement

Formulation of particulate drug delivery systems, such as microparticles and nanoparticles, liposomes and inclusion complexes which can enhance the drug stability and bioavailability, and modulate the drug release profile.

Particles from Gas-Saturated Solutions (PGSS®)[3]



A: High-pressure stirred vessel,
B: collector with nozzel,
TIC: temperature control.

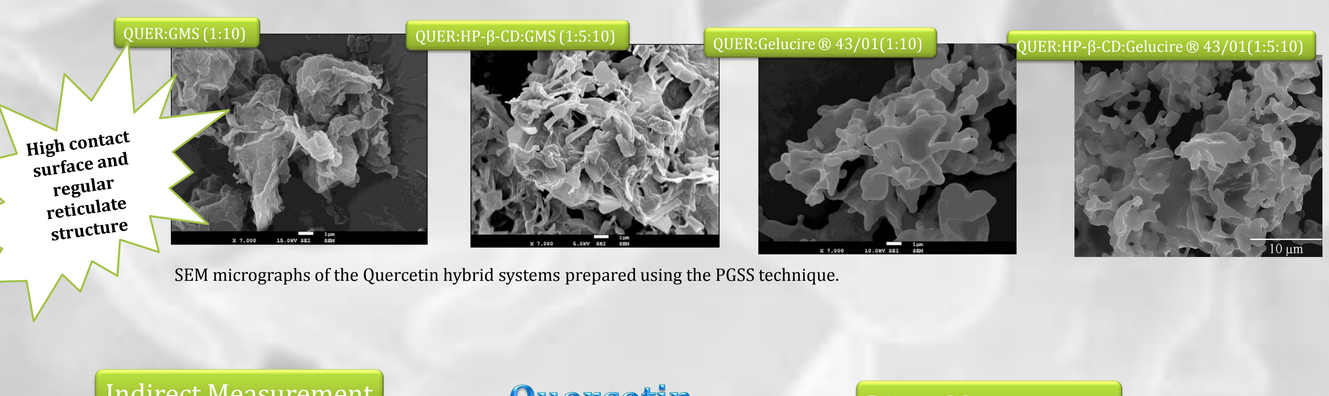
CO_2 is fed to a high pressure stirred vessel containing the carriers and the antioxidant compound, quercetin. The operating conditions are adjusted according to previous studies[4] in order to have a melted product under CO_2 atmosphere. After a certain stirring equilibration time, the mixture is depressurized though a nozzle and the particulate solids collected.

Results & Discussion

Systems Prepared

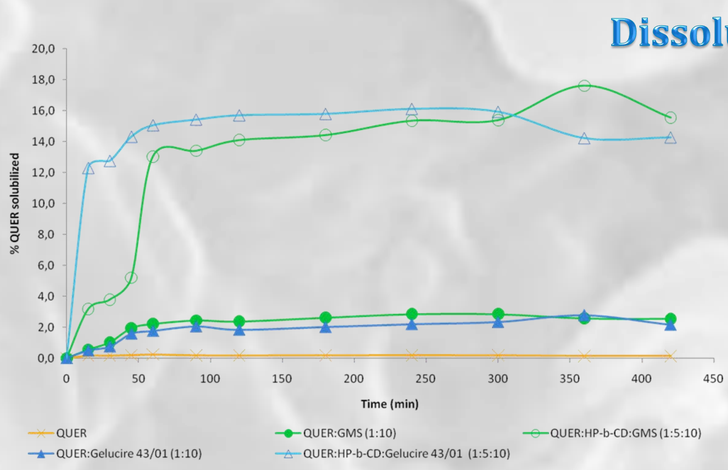
	Mass proportion	Molar Ratio	Lipid HLB	Contact Time (h)	T (ºC)	P (bar)	Teorical Drug load (%)	Drug Load (%)	Entrapment Efficency (%)
QUER:GMS	1:10	1:8	4	2	70	130	9,09	9,51 : 0,3	104,65 ± 3,27
QUER:HP-b-CD:GMS	1:5:10	1:1:8					6,25	6,71 : 0,05	107,43 ± 0,79
QUER:Gelucire® 43/01	1:10	1:4	1	2	70	130	9,09	6,45 : 0,07	70,95 ± 0,82
QUER:HP-b-CD:Gelucire® 43/01	1:5:10	1:1:4					6,25	6,26 : 0,39	100,16 ± 6,17

SEM



SEM micrographs of the Quercetin hybrid systems prepared using the PGSS technique.

Dissolution Profile

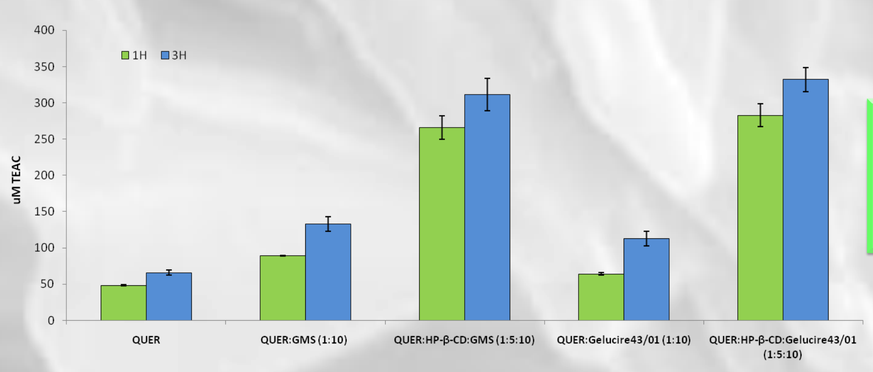


Performance evaluation of the Quercetin hybrid systems prepared using the PGSS technique in Simulated Intestinal Fluid (SIF) (pH 6.8) at 37ºC

The Hybrid Delivery Systems allowed to increase the amount of solubilized quercetin in the SIF.

Antioxidant Activity

The Oxygen Radical Absorbance Capacity (ORAC) assay was used to evaluate the antioxidant capacity of the samples obtained in the dissolution studies towards peroxyl radicals [5].



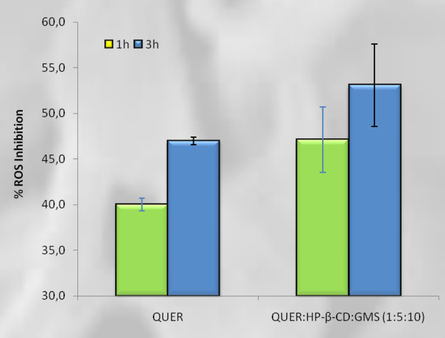
The antioxidant activity correlates with the release profile, i.e. the hybrid systems allow to improve the quercetin bioavailability

This assay measures the ability of the antioxidant species in the sample to inhibit the oxidation of fluorescein catalyzed by peroxyl radicals generated from AAPH. All data was expressed as micro molar of trolox equivalents antioxidant capacity (µM TEAC).

Quercetin Cellular Uptake

Indirect Measurement

Quercetin Intracellular Antioxidant Activity Caco-2 cells model

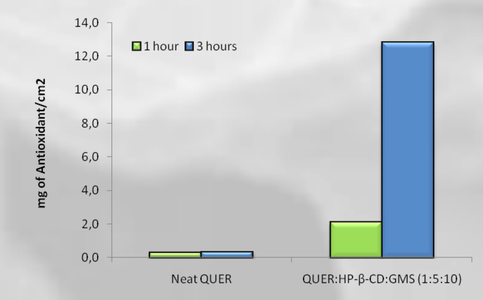


✓ @ 1 hour of oxidative stress induction - both systems can inhibit the ROS formation.

✓ @ 3h ROS inhibition slightly increases.

Direct Measurement

Caco-2 cells Extract (from cell lysis)



✓ With QUER:HP-β-CD:GMS (1:5:10) system a higher amount of quercetin was available intracellularly as it could be uptake by enterocytes

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