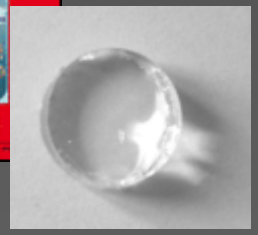
M. Signoretto Dip. di Scienze Molecolari e Nanosistemi

Innovative organic and inorganic hybrid nanomaterials for DDS

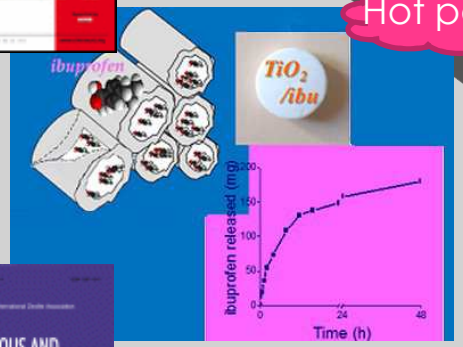
Drug Delivery Systems (DDS)

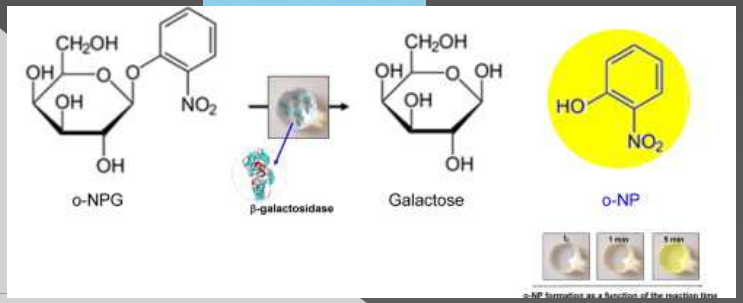
Structure-Directing Agents for the Synthesis of TiO2 -Based Drug-Delivery Systems

Hybrid Organic–Inorganic Silica Gel Carriers with Controlled Drug-Delivery Properties

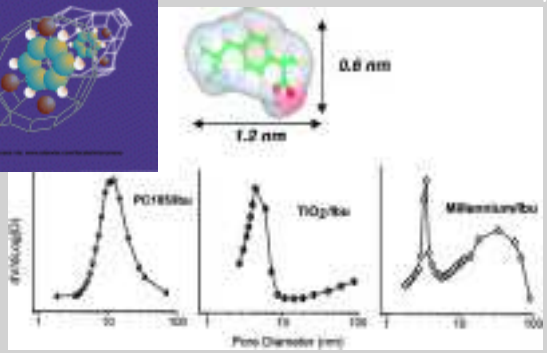


Hot paper



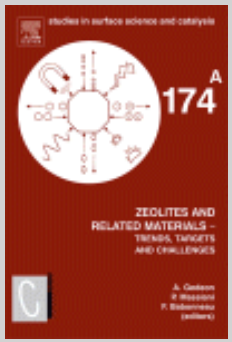


β-Galactosidase entrapment in silica gel matrices for a more effective treatment of lactose intolerance

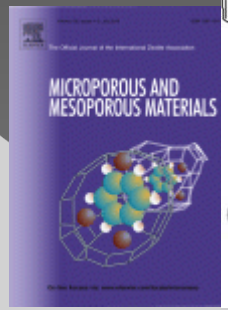


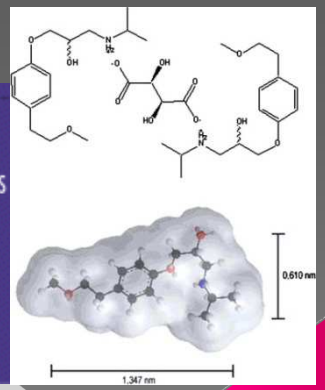
Effect of textural properties on the drug delivery behaviour of nanoporous TiO_2 matrices

1. One-step synthesis of silica gel used in controlled release of drug



2. Ibuprofen delivery behaviour on MCM-41: influence of organic groups amount



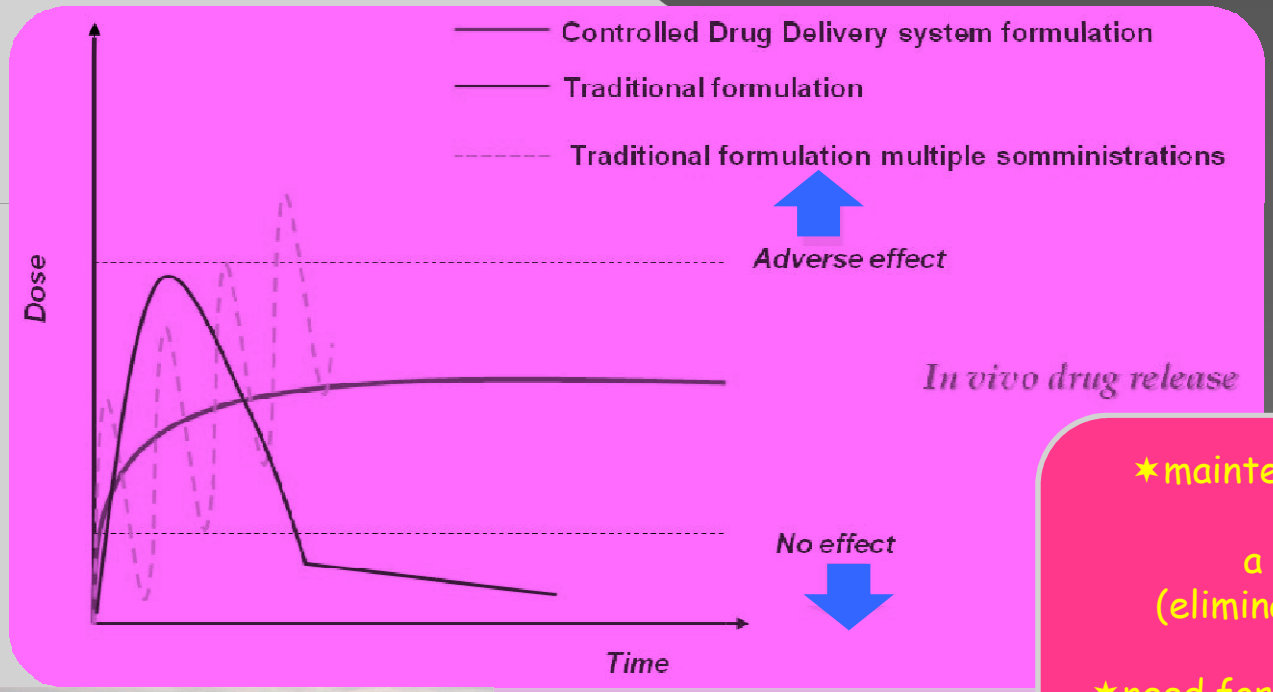


Controlled release of metoprolol tartrate from nanoporous silica matrices

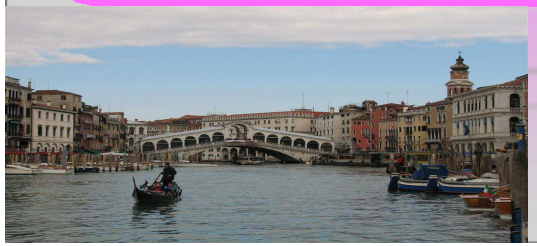
Drug Delivery Systems (DDS)

Traditional Pharmaceutical Forms → Immediate and total transfer of the active molecule to the organism

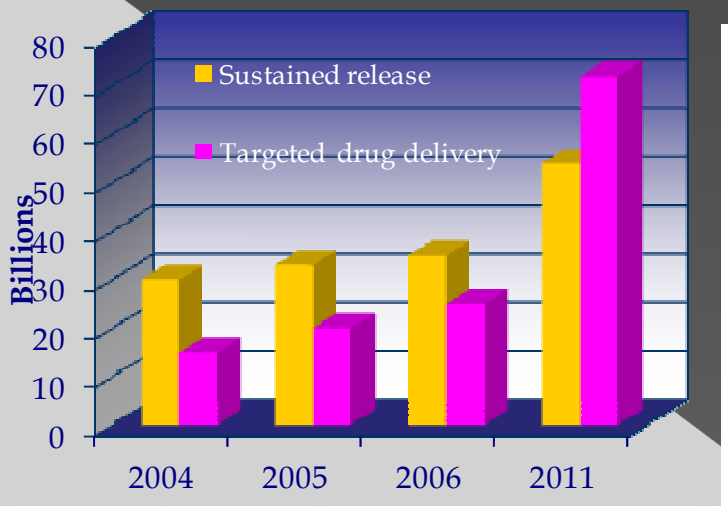
Controlled Drug Delivery Systems → Control the rate, period and modality of drug delivery and target specific area of the body

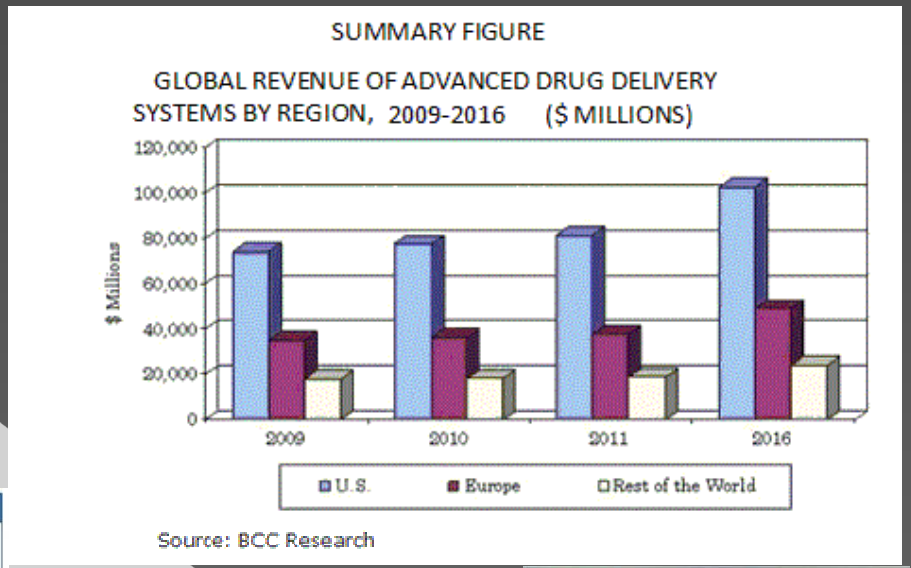


- ✶maintenance of drug levels within a desired range (eliminating both under-and overdosing)
- ✶need for fewer administrations
- ✶optimal use of the drug
- ✶increased patient compliance

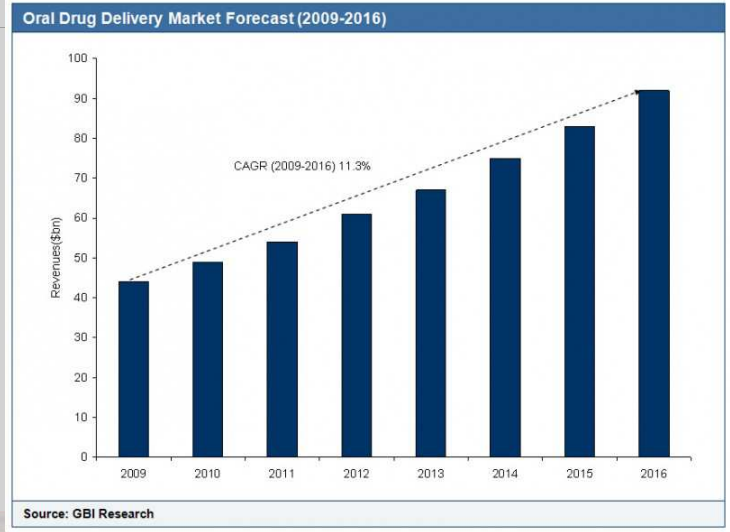


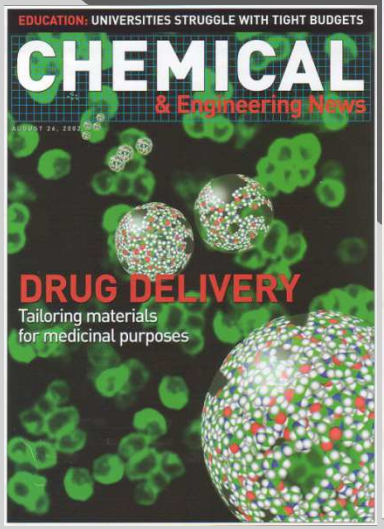
Drug Delivery Systems





Source: BCC Research





Formulation

active principle

excipients

Drug delivery systems

Traditional pharmaceutical forms

matrix

bio-compatible materials

mechanically strong

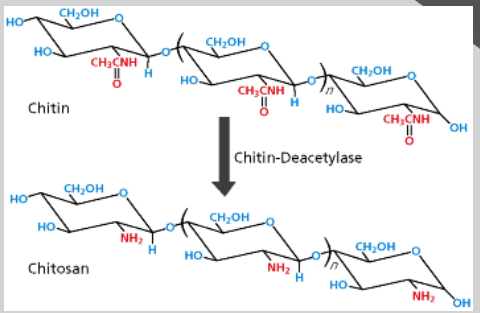
IDEAL MATRIX

comfortable for the patient

simple to administer and remove

Bio-degradable Polymeric materials Bio-compatible

natural



(a) The structure of the chitin monomer.

(b) Chitin forms the exoskeleton of arthropods.

(c) Chitin is used to m… a strong and flexib… surgical thread.

Based on natural materials
Collagen
Starch
Chitosans
Gelatin
Alginates
Dextrans

Based on synthetic polymers
N-VP
Poly(vinyl alcohol)
Polyphosphazenes
Poly(ethylene oxide-b-poly(propylene oxide))
Copolymers
PL(G)A/PEO/PL(G)A copolymers
PVA-g-PLGA graft-polymers
PEGT-PBT copolymers (PolyActive)
MA-oligolactide-PEO-oligolactide-MA

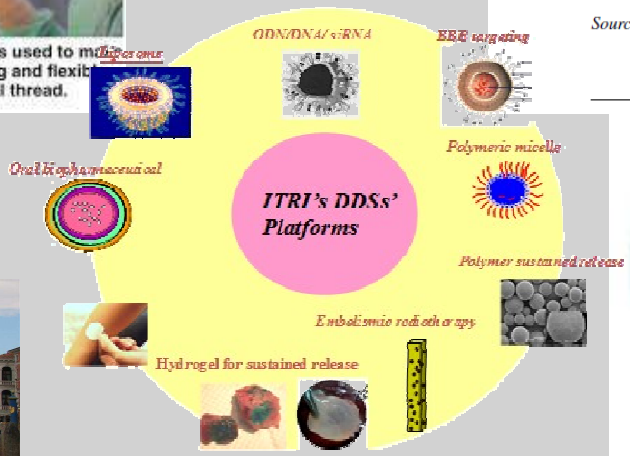
Responsive polymers
Methacrylates (pH-dependent swelling)
PNIPAM (LCST)
PEO-PPO-PEO (Pluronics)
PEO-PPO-PAA graft-copolymer (LCST)
PLGA-PEO-PLGA (LCST)

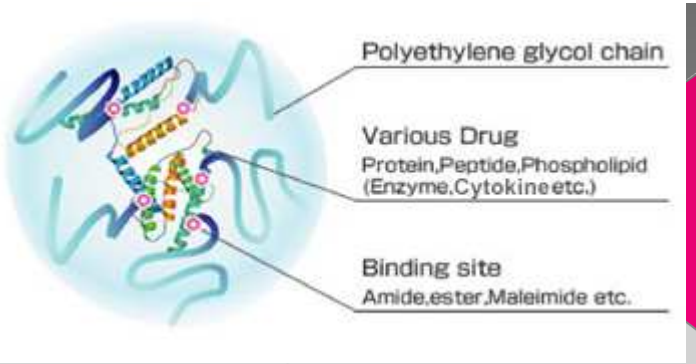
Source: Jill Wechsler, *Pharm. Technol.*, Advanst… March 2002, p. 144.

Commercial Preparation of Drug–Polymer Combinations

Corporation	Drug	Polymer as a Matrix
Scios Nova and MIT	Gentamicin and carmustine	BIODEL delivery system (Polifeprosan)
DynaGen	Vaccine, immunogens	Sleeper system
KabiPharmacia and Berol Nobel	Drugs for blood disorders	Bioadhesive thermogel
Fidia	Antibiotics, antiseptics, and anti-inflammatories	HYAFF series (modified hyaluronic acids)
TheraTech	Systemic drug administration Wide variety of drugs	BHHA, biodegradable hydrogel HIPN(Heterogeneous interpenetrating polymer network)
Verex	Propranolol	POLiM(Polymers liquid hydrogel matrix)
Searle/Monsanto	Misoprostol	OLipHEX and pHEMS Polymer delivery system
Advanced Polymer Systems and Rhone-Poulenc Rorer	5-FU 2,4, (1H, 3H)-Pyrimidine-delivery system dione-5-fluoro	Microsponge based
Biosearch	Piloplex, a derivative of pilocarpine	Polymeric complex
Allelix and Glaxo	Corticosteroids	ALX 25 corticosteroid binding globulin (CBG)
(Alkermes)Enzytech	Therapeutic proteins OraLease, ProLease	Polymer-based delivery system

Source: Reprinted from *J. Control. Release*, 126, Ta, H.T., Dass, C.R., and Dunstan, D.E., Injectable chitosan hydrogels for localized cancer therapy, 205–216, Copyright (2008), with permission from Elsevier.

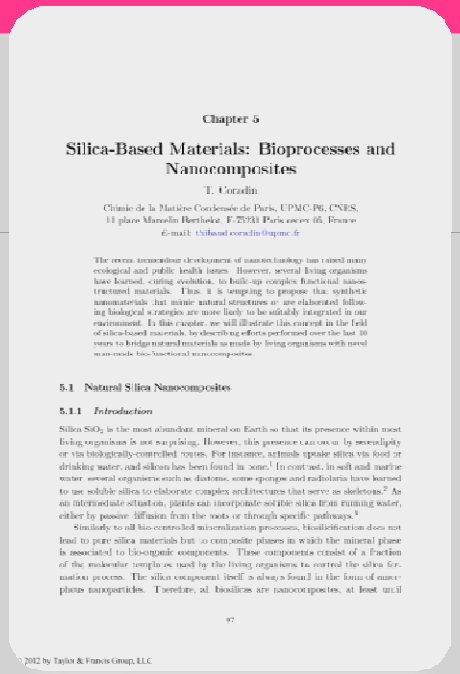




resistance to microbial attack
higher mechanical strength
enhanced thermal stability
negligible swelling in organic solvents
modulable textural properties

Inorganic materials

bio-compatible



Chapter 5

Silica-Based Materials: Bioprocesses and Nanocomposites

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The recent tremendous development of nanotechnology has raised many ecological and public health issues. However, several living organisms have learned, during evolution, to built-up complex functional nanostructured materials. Thus, it is tempting to propose that synthetic nanomaterials that mimic natural structures or are elaborated following biological strategies are more likely to be suitably integrated in our environment. In this chapter, we will illustrate this concept in the field of silica-based materials, by describing efforts performed over the last 10 years to bridge natural materials as made by living organisms with novel man-made bio-functional nanocomposites.

5.1 Natural Silica Nanocomposites

5.1.1 *Introduction*

Silica SiO_2 is the most abundant mineral on Earth so that its presence within most living organisms is not surprising. However, this presence can occur by serendipity or via biologically-controlled routes. For instance, animals uptake silica via food or drinking water, and silicon has been found in some.[1] In contrast, in soft and marine water, several organisms such as diatoms, some sponges and radiolaria have learned to use soluble silica to elaborate complex architectures that serve as skeletons.[2] As an intermediate situation, plants can incorporate soil-like silica from draining water, either by passive diffusion from the roots or through specific pathways.[3]

Similarly to all bio-controlled mineralization processes, biosilicification does not lead to pure silica materials but to composite phases in which the mineral phase is associated to bio-organic components. These components consist of a fraction of the molecular templates used by the living organisms to control the silica formation process. The silica component itself is always found in the form of monodisperse nanoparticles. Therefore, all biosilicas are nanocomposites, at least until

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9 Inorganic Nanostructures for Drug Delivery

Ying-Jie Zhu

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9.3 Nanostructured Calcium Carbonate and Calcium Phosphates as Drug Carriers 224
9.4 Magnetic Targeting Drug Delivery Systems 226
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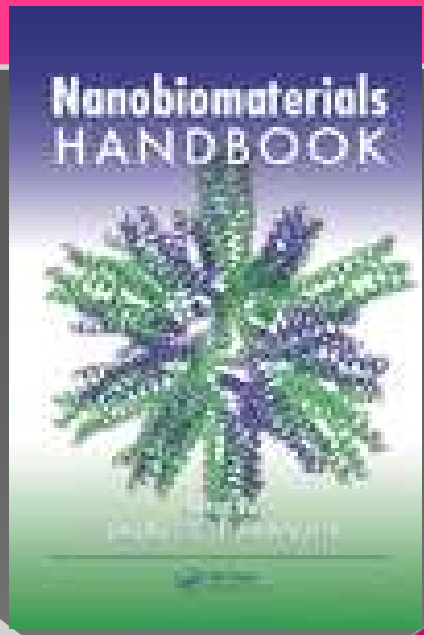
9.1 INTRODUCTION

Nanotechnology has had a significant impact on the development of drug delivery systems over the past decade, leading to the emergence of entirely new research fields [1]. For the pharmaceutical industry, novel drug delivery technologies represent a strategic tool for expanding drug markets, evidenced by the fact that sales of products incorporating sales delivery system account for approximately 15% of the current global pharmaceutical market. The demand for drug delivery systems in the United States alone is expected to grow by nearly 9% annually, to more than US$ 62 billion by 2007. Controlled drug delivery provides the ability to control the release rate of the drug and the delivery of the drug to a specific location in the body (i.e., targeting). Recently, some reviews on drug delivery were published [1–4]; however, these reviews focused primarily on polymeric systems.

Many organic materials such as polymers [5], liposomes, and micelles have been investigated as drug delivery carriers. However, unsolved problems regarding these organic systems continue to exist. These problems include low chemical stability, swelling, susceptibility to microbiological contamination, and inadequate control over the drug release rate. The release properties of many biodegradable polymer-based drug delivery systems are dependent on the hydrolysis-induced erosion of the carrier structure [2,3]. Such systems usually require the use of organic solvents for drug loading, which could sometimes trigger undesirable modifications of the structure or the function or both of the encapsulated molecules.

In contrast, many inorganic materials are nontoxic, biocompatible, hydrophilic, and chemically stable. These materials hold promise for the development of drug delivery systems, especially for controlled drug delivery. It is possible to produce the stable porous structures of inorganic materials, which can often be tailored to control the drug loading and the drug release rate. In addition, there is no swelling or porosity change under different pH values, which is a common problem encountered when using organic materials. Because of the abovementioned reasons, the research on inorganic nanostructures as drug carriers has gained momentum in recent years and is currently a fast growing field. In this chapter, the recent progress in nanostructured inorganic drug carriers and their drug delivery properties will be briefly reviewed. However, all the literature on this subject will not be reviewed; instead, only some related papers will be included in this chapter. This chapter is divided

217



Release of active agent

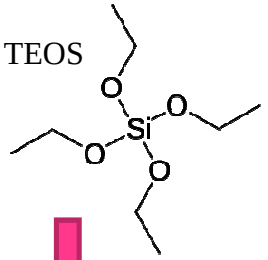
Matrix erosion

Diffusion through the matrix

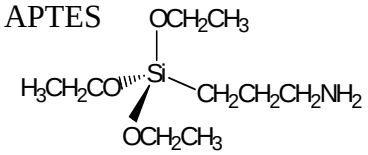
Interaction between matrix and drug molecules

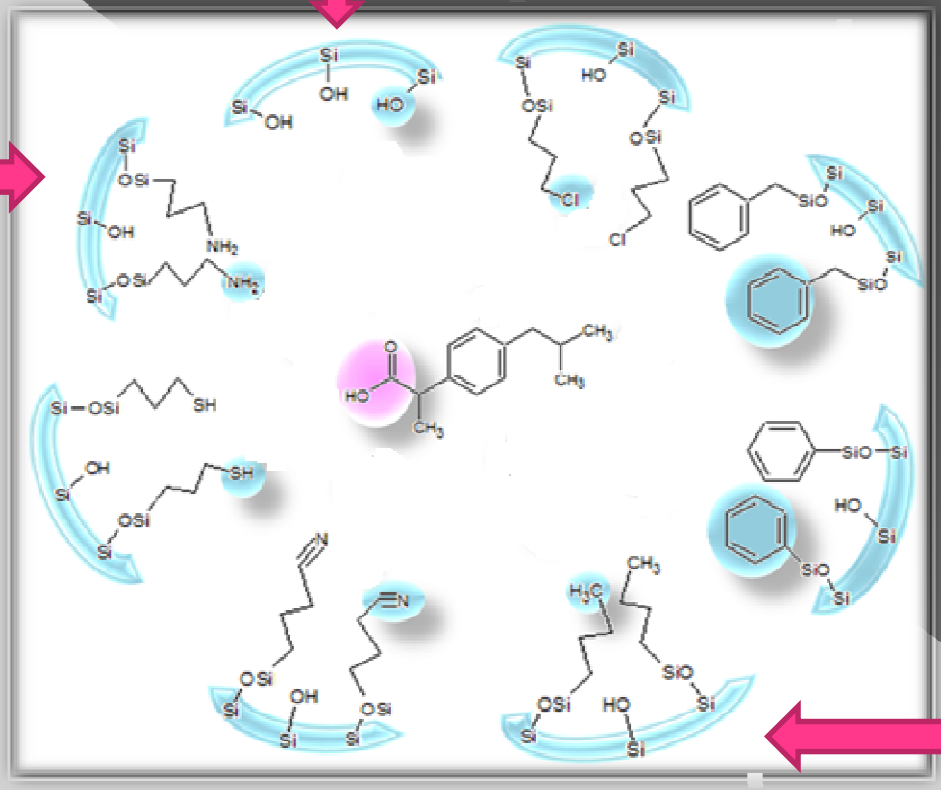
Silica functionalization

TEOS

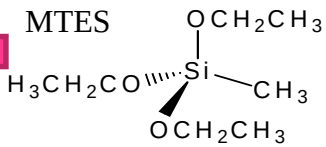


APTES





MTES



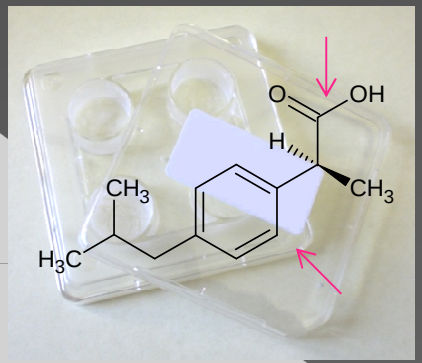
One-step synthesis of silica gel

Reagents + Drug *Sol* *Gel*

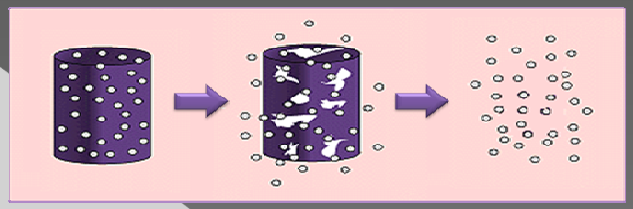
- *Teos*
- *Mtes*

HCl

H_2O
Sonic



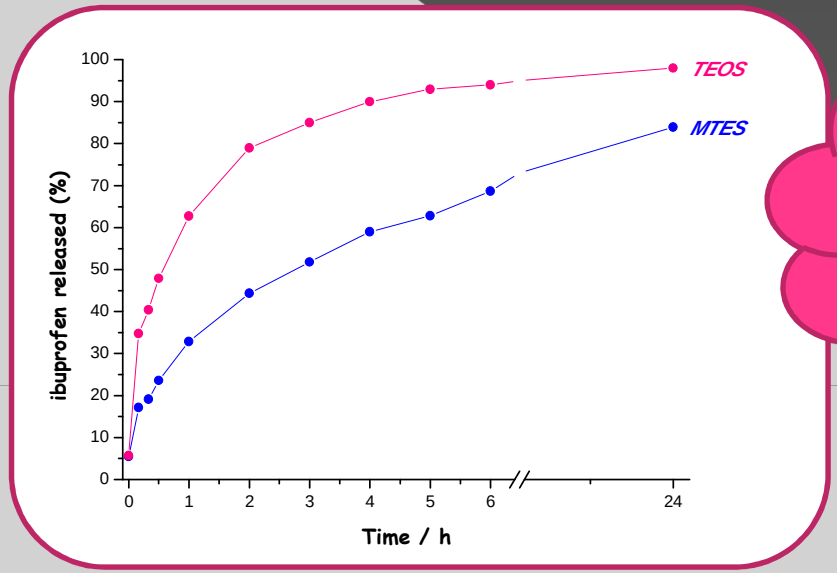
- *Aptes*



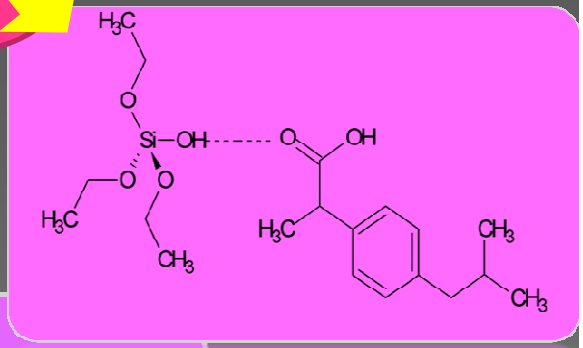
Matrix dissolution in the physiological solution

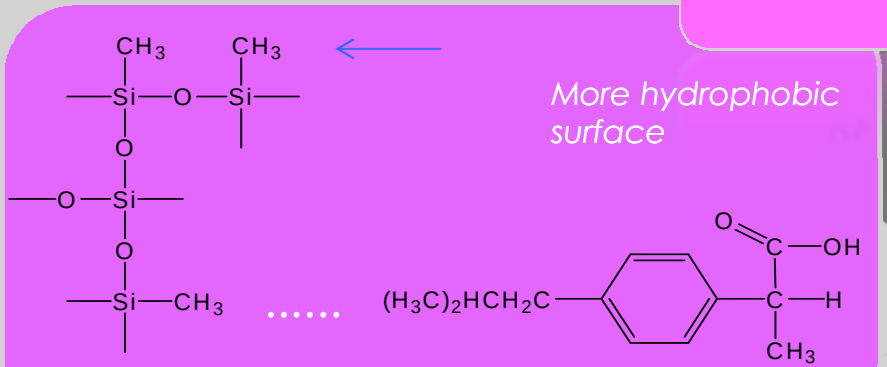
- *Aptes+Teos*

From TEOS to MTES for oral administration



Interaction between ibuprofen and the silanol groups on the silica surface

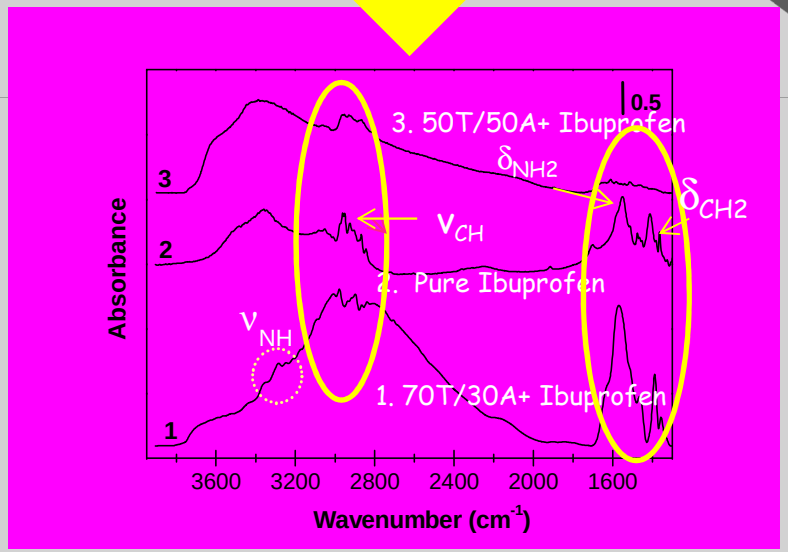




More hydrophobic surface

From TEOS to APTES for oral administration

No real interaction between the silica matrix and the drug itself



50T/50A

- *White*
- *Un-homogeneous*
- *Breakable*

60T/40A

- *White*
- *Monolithic*
- *Homogeneous*

70T/30A

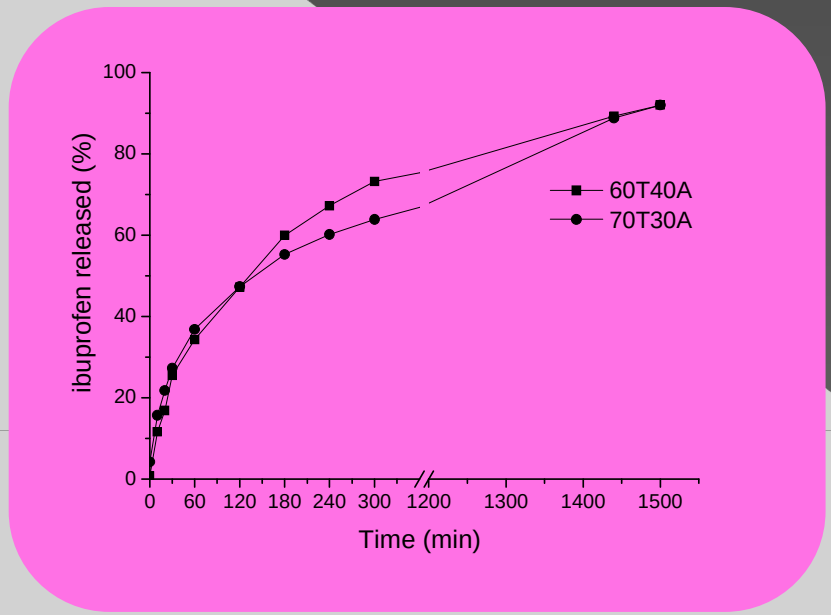
- *White*
- *Monolithic*
- *Homogeneous*

80T/20A

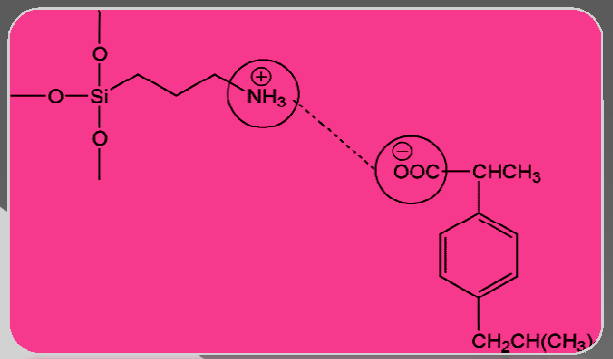
- *White*
- *Un-homogeneous*
- *Breakable*

Drug released

Comparison of the experimental release

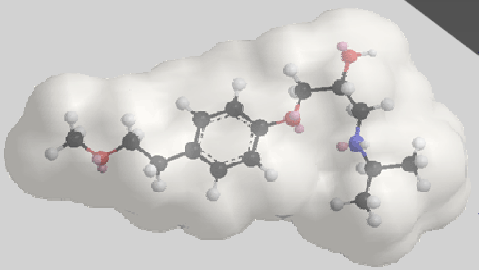


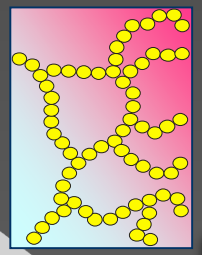
The presence of APTES in the gel composition has a significant effect in the ibuprofen release leading to a continuous and gradual delivery profile, very similar for the two matrices investigated (60T/40A; 70T/30A)



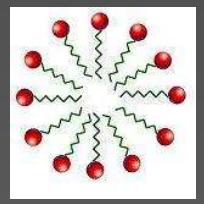
Interaction between the carboxy groups in the ibuprofen molecule and the amine groups on the silica surface

Controlled release of metoprolol tartrate from nanoporous silica matrices



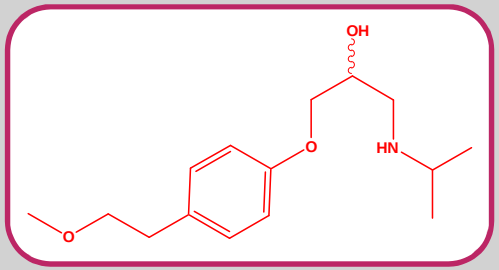


Synthesis



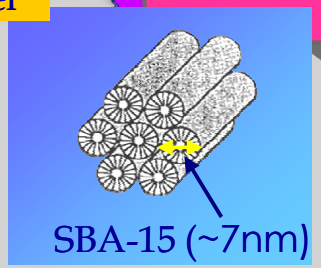
Sol – gel (one-step)

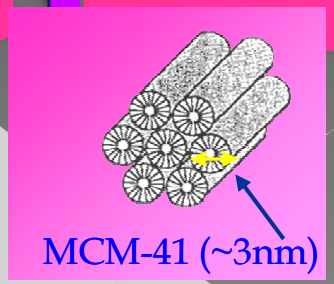
Structure-Directing Agents



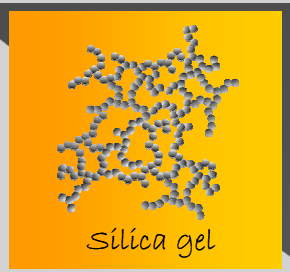
P-123

CTA-Br



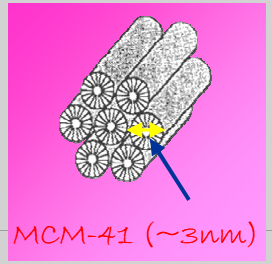


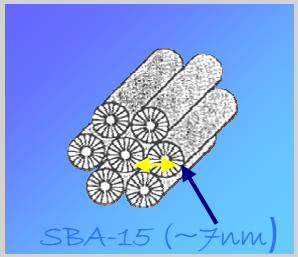
Synthesis



H_2O+TEOS Cat. → sonication → SOL → Metoprolol / water → gel ageing → Silica gel+MPT tablet

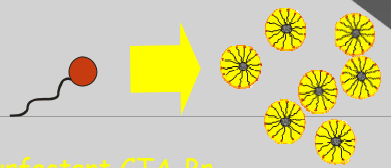
1 step: MCM-41 / SBA-15 synthesis





Surfactant CTA-Br

Surfactant P123

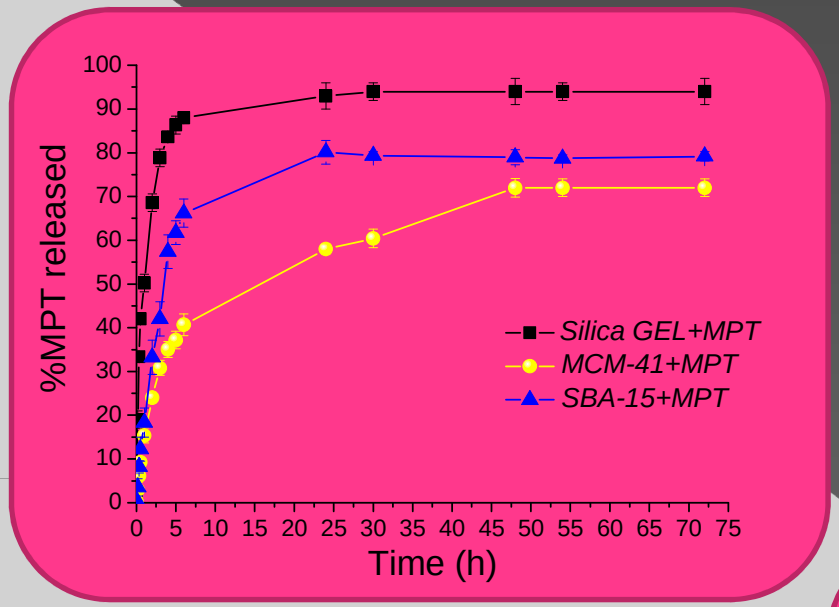


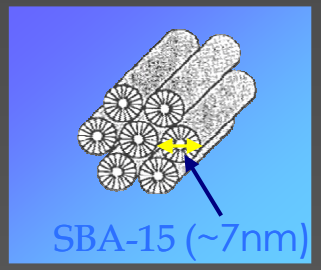
TEOS → Calcination → MCM-41 / SBA-15

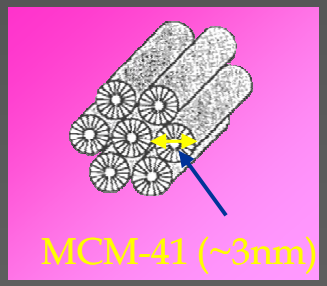
2 step: [MCM-41+MPT: drug introduction / SBA-15]

MCM-41 → Wetness impregnation → EtOH → Solvent evaporation → Metoprolol tartrate → MCM-41+MPT powder → Pressature → MCM-41+MPT tablet

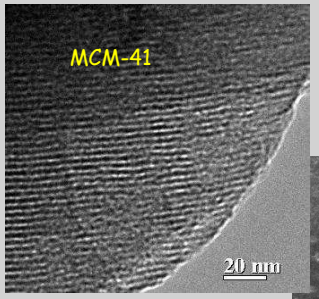
MCM-41/ SBA-15

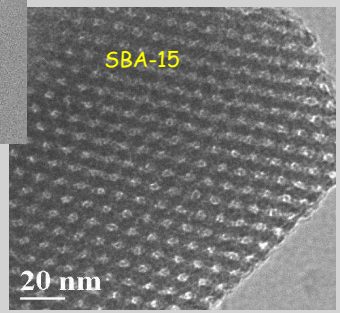

%MPT released
Time (h)
Silica GEL+MPT
MCM-41+MPT
SBA-15+MPT

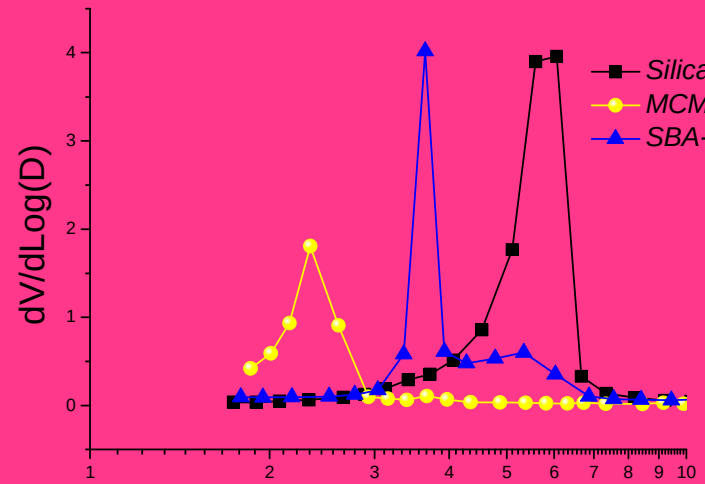

SBA-15 (~7nm)


MCM-41 (~3nm)

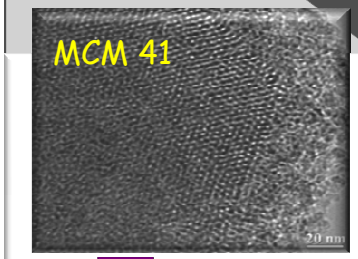

Silica gel


MCM-41
20 nm

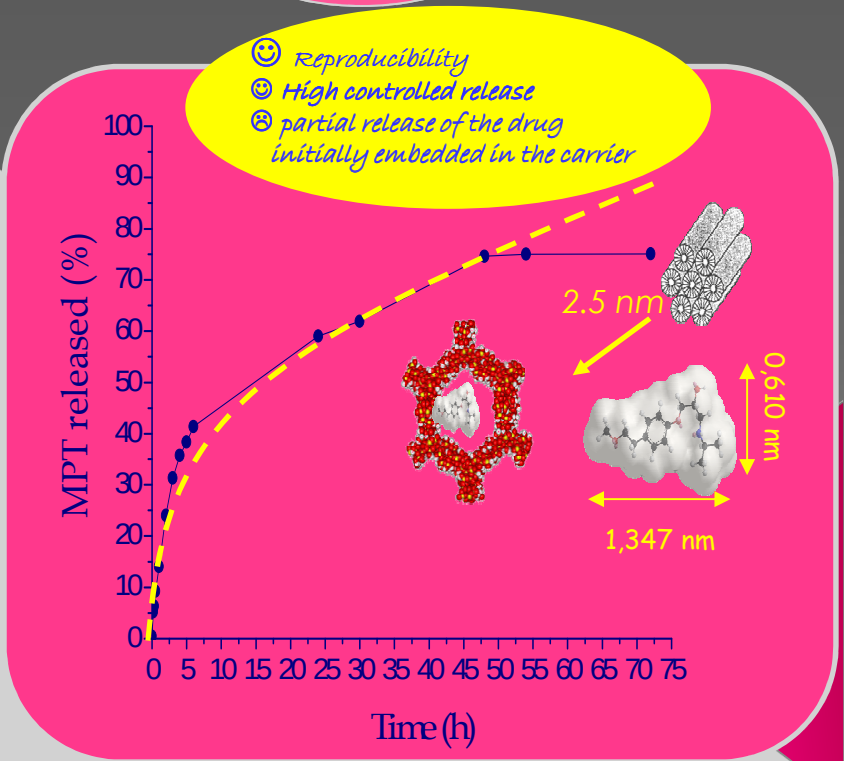

SBA-15
20 nm


dV/dLog(D)
Pore diameter (nm)
Silica GEL+MPT
MCM-41+MPT
SBA-15+MPT

MCM-41 DRUG RELEASE



Close correlation between the drug release kinetic and the textural properties of the carriers



Structure -directing agent for the synthesis of TiO2- based Drug Delivery Systems

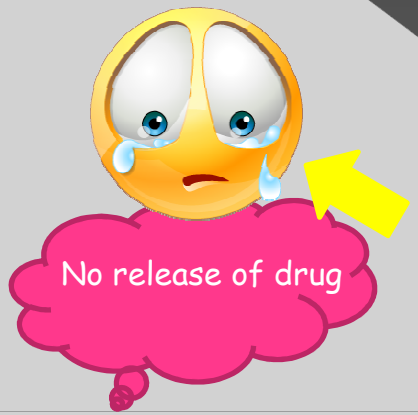
Synthesis

Sol – gel (one-step)

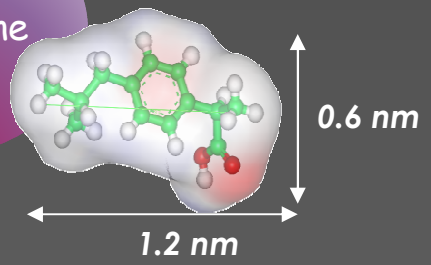
Structure-Directing Agents

P-123

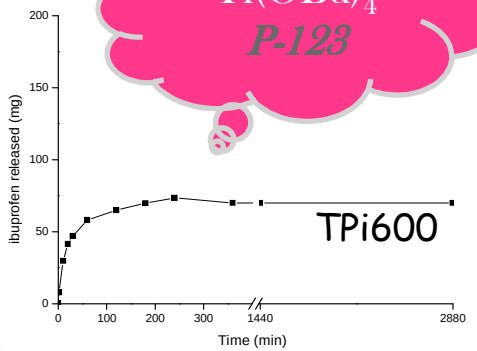
CTA-Br



Ibuprofene



$Ti(OBu)_4$ *P-123*

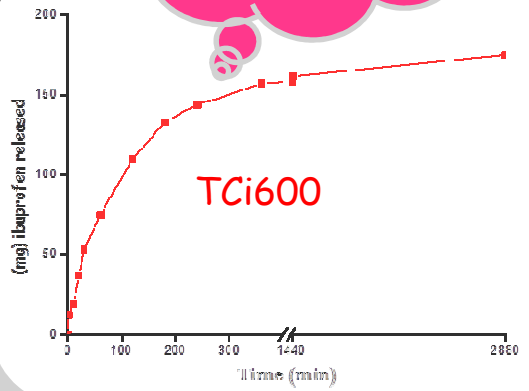


Only 30% of the drug is released .

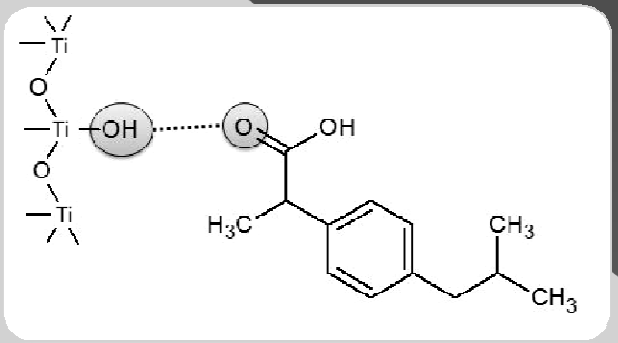
The release is almost complete.

The release is more-controlled

$Ti(OBu)_4$ *CTA-Br*

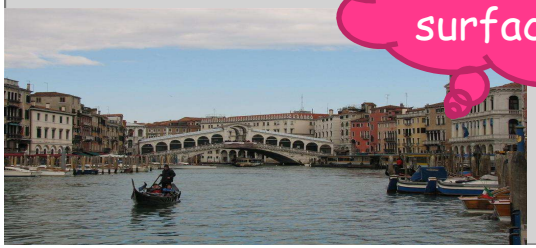


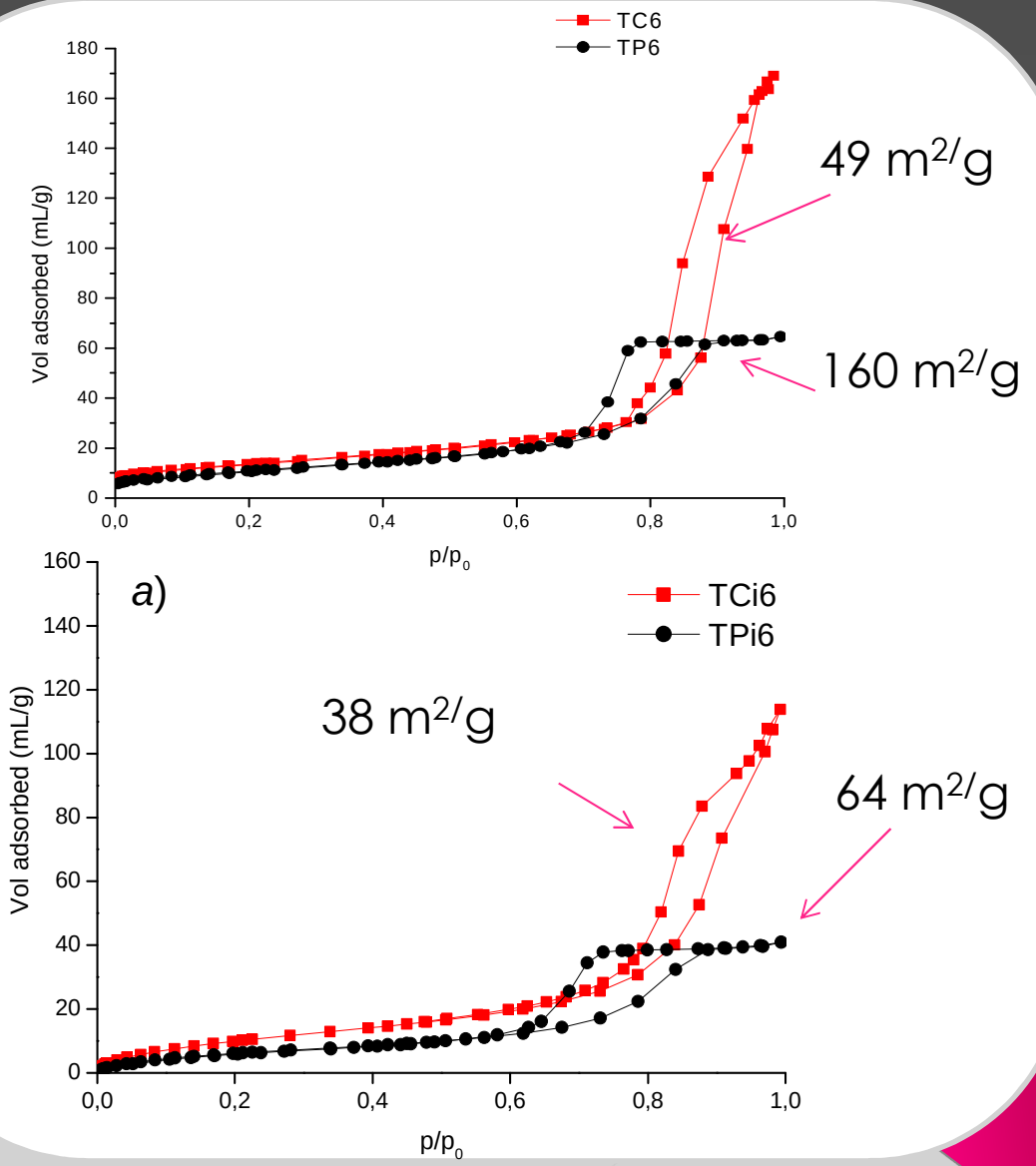
Effect of the template agent



Sample	BET surface area (m^2/g)
TC6	49
TCi6	38
TP6	160
TPi6	64

Very strong decrease of surface area

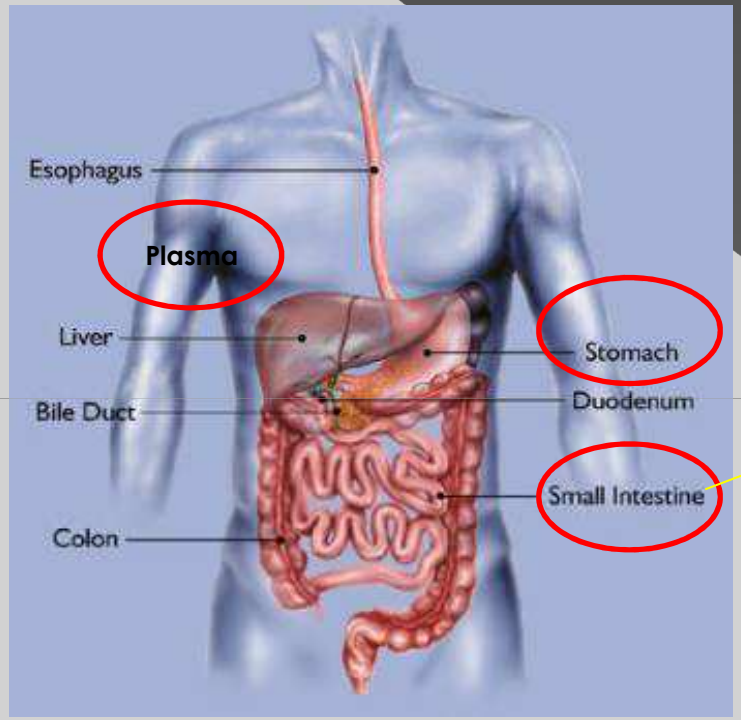


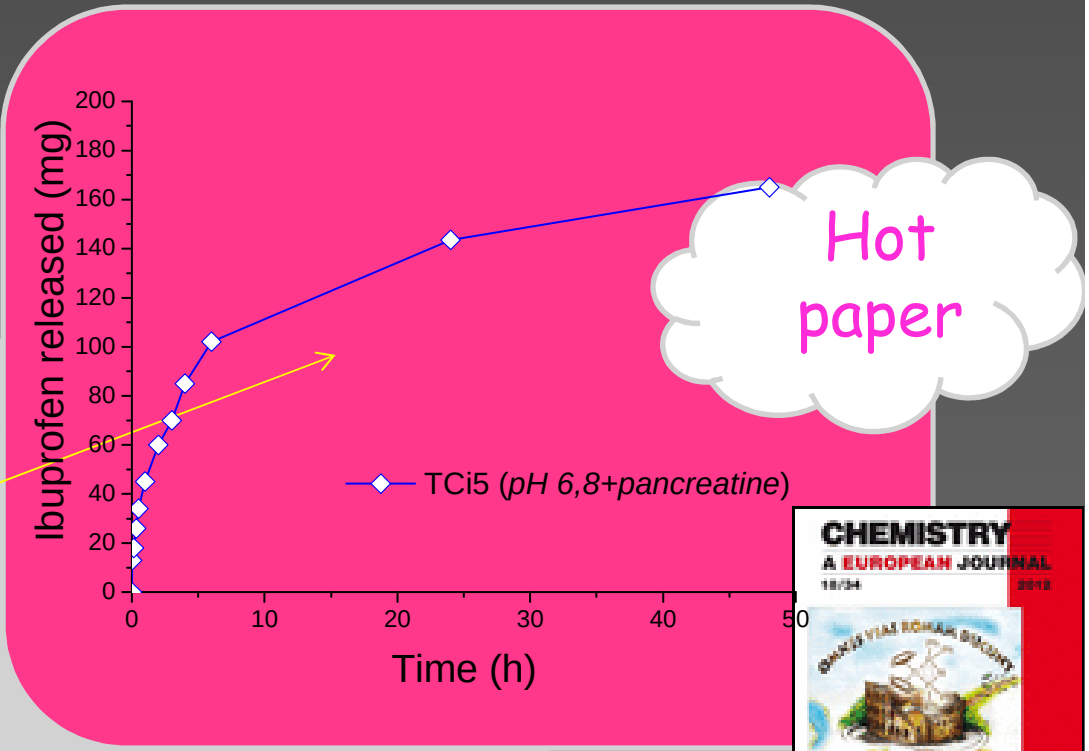


Effect of drug amount

The drug that is on the surface is the first to be released without much control over the rate of desorption; on the contrary, the rate of desorption of the drug that is contained within the porous structure is controlled by both the shape and the size of the pores in the support, thus resulting in a more gradual release

DELIVERY BEHAVIOUR ALONG THE GASTROINTESTINAL TRACT

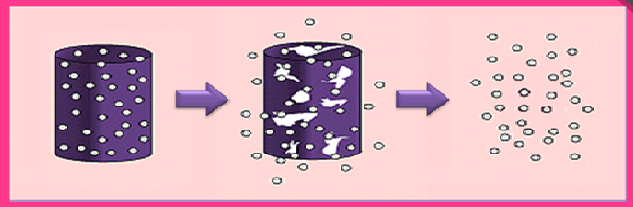




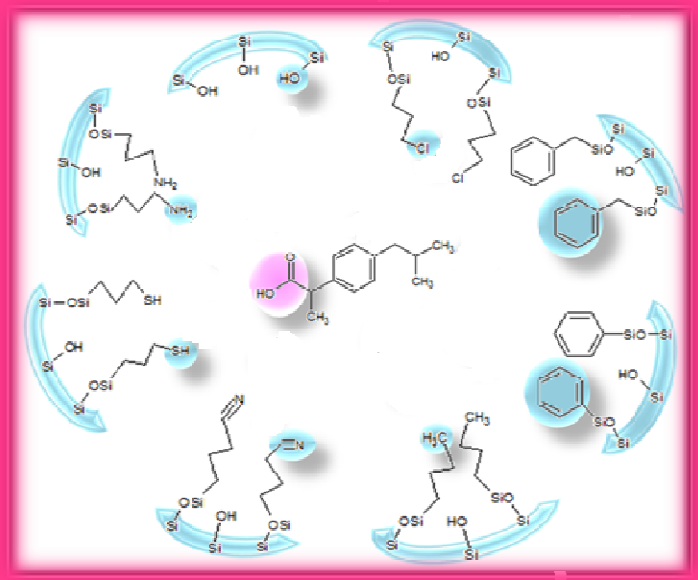
TiO_2 –DDSs not only act very well in a medium that simulates the intestinal environment (pH 6.8 with pancreatin), but seem to have an improved performance in this medium to some extent (with a more-gradual and controlled release)

Conclusions

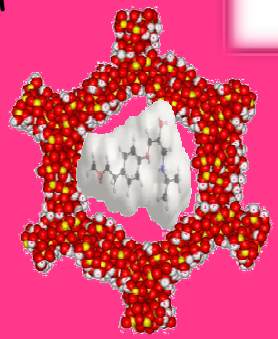
Matrix erosion

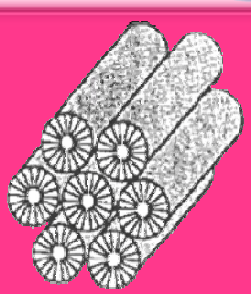


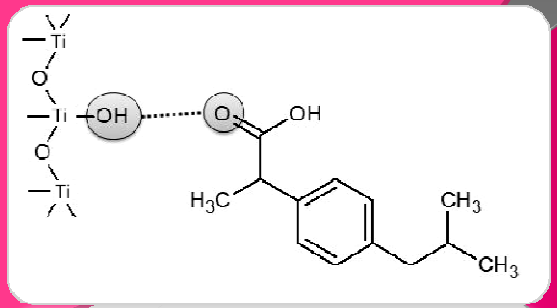
Interaction between matrix and drug molecules

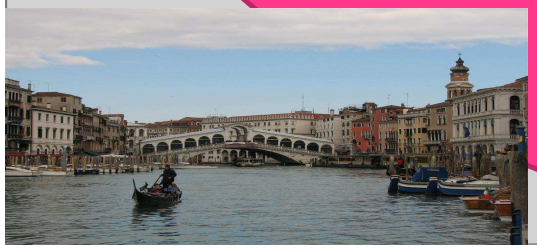


Diffusion through the matrix









Acknowledgement

Dr. Elena Ghedini,
Dr. Valentina Nichele,
Dr. Federica Menegazzo
Dr. Valentina Trevisan
Prof. Francesco Pinna
Sig. Tania Fantinel
Dip. Molecular Sciences
and Nanosystems Ca' Foscary University

Prof. Giuseppe Cruciani
Department of Physics and Earth Sciences,
University of Ferrara

Dr. Giuseppina Cerrato ,
Dr. Valentina Aina
Dr. Valentina Crocellà
Dip. Chimica & NIS Centre of Excellence
University of Turin