

Stato solido di un API nello sviluppo di un Drug Delivery System

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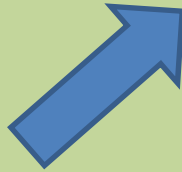
Università di Trieste

Dpt Ingegneria dei Materiali

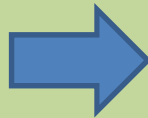
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**API SOLID STATE IN THE
DVPT OF A DDS**



**THE INITIAL SOLID STATE OF API CAN
INFLUENCE THE DDS PERFORMANCE**



**THE SOLID STATE OF API CAN CHANGE
ALONG THE PROCESS OF DDS PREPARATION**

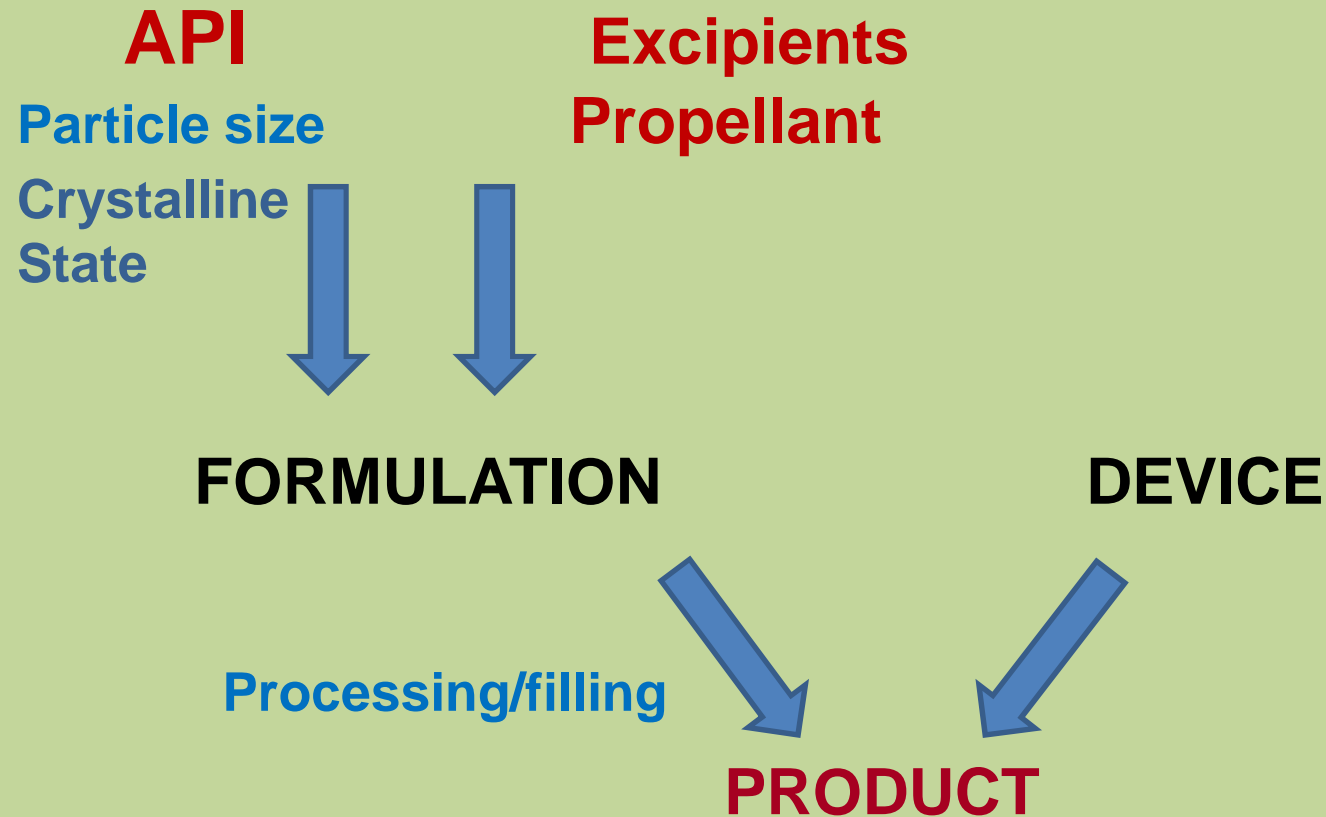


**THE SOLID STATE OF API CAN CHANGE
DURING THE DDS STORAGE**

API SOLID STATE IN THE DEVELOPMENT OF A DDS

- Development of a Powder Inhalatory System by SCF, MCA**
- Development of Composite Drug/Carrier Particles for Oral Improved Absorption by MCA**
- Development of Drug/Polymer Composites by HME**
- SCF Super Critical Fluid**
- MCA Mechano-chemical Activation (High Energy Cogrounding)**
- HME Hot Melt Extrusion**

DRUG DELIVERY TO THE LUNGS



- nebulisers (atomized drug aqueous solution; scarce portability))
- p MDIs pressurized metered dose inhalers (propellant criticality)
- DPIs Dry Powder Inhalers (no propellant)

Drug particulate properties for pulmonary drug delivery (DPI)

Particle characteristics

- solid state (crystallinity, impurities, solubility.....)
- particle size and distribution, shape, porosity
- surface chemistry & energy
- coformulation,blending

Influence on formulation

- physicochemical stability, bioavailability, toxicity
- aerosolisation, deposition profile, bioavailability
- powder handling, dose metering and uniformity,
- Stability
- dose uniformity

Dry Powder Inhalers

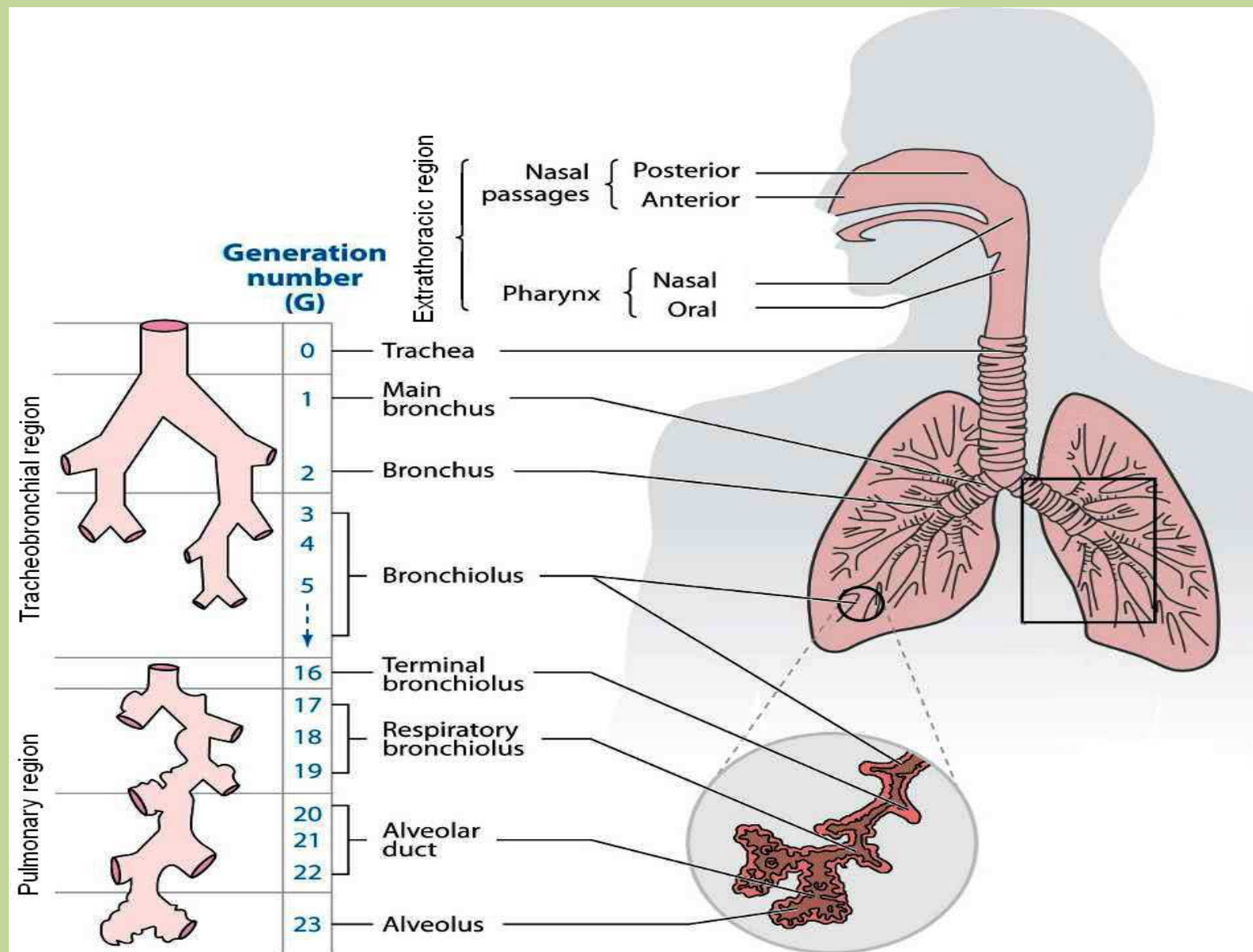
First generation	Drug Lactose (80-90%) Blends	Less than 20% Drug effectively delivered to lungs
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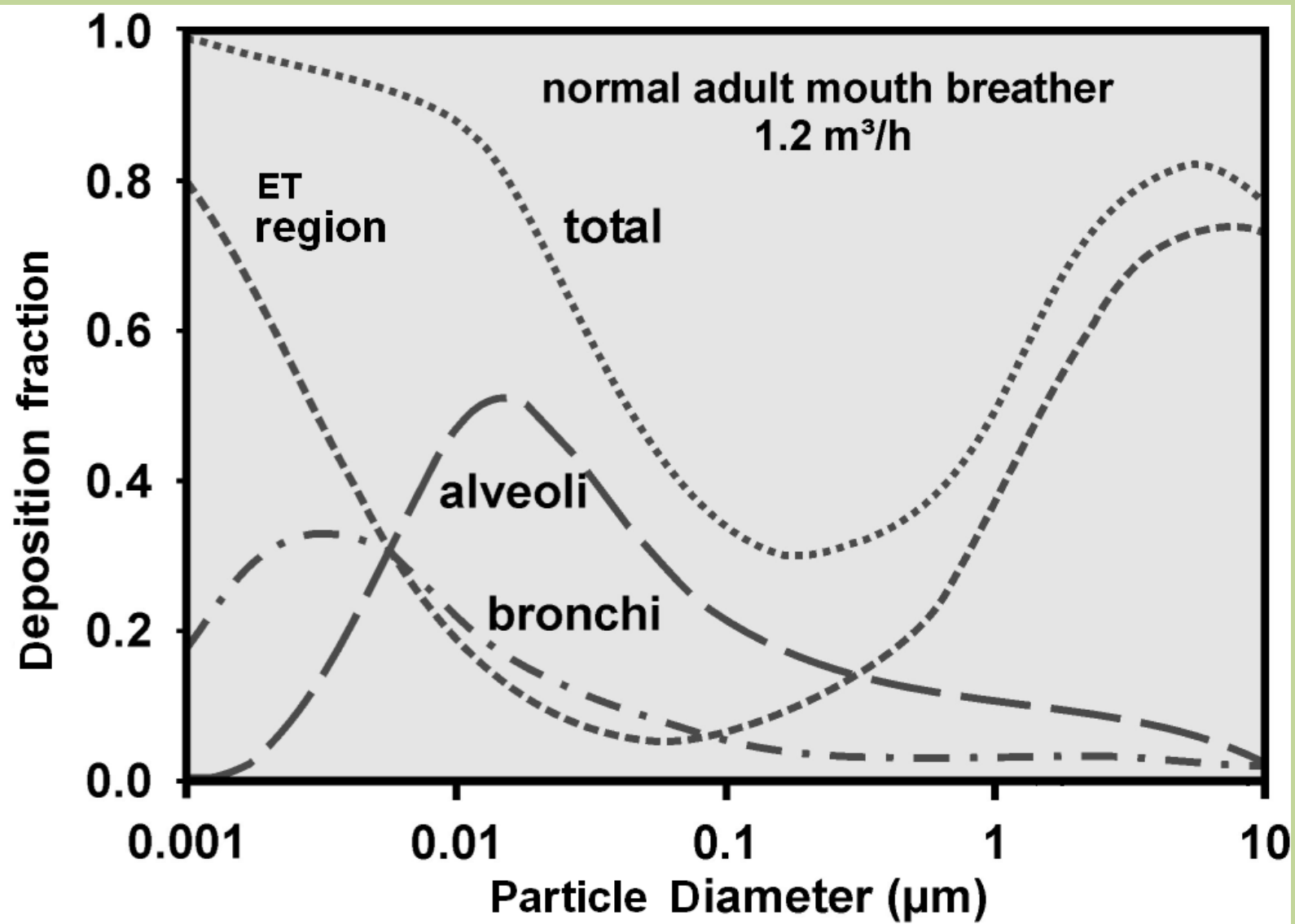
Second generation	Drug/carrier particle engineering	Up to 30-40% Drug Dose delivered to lungs
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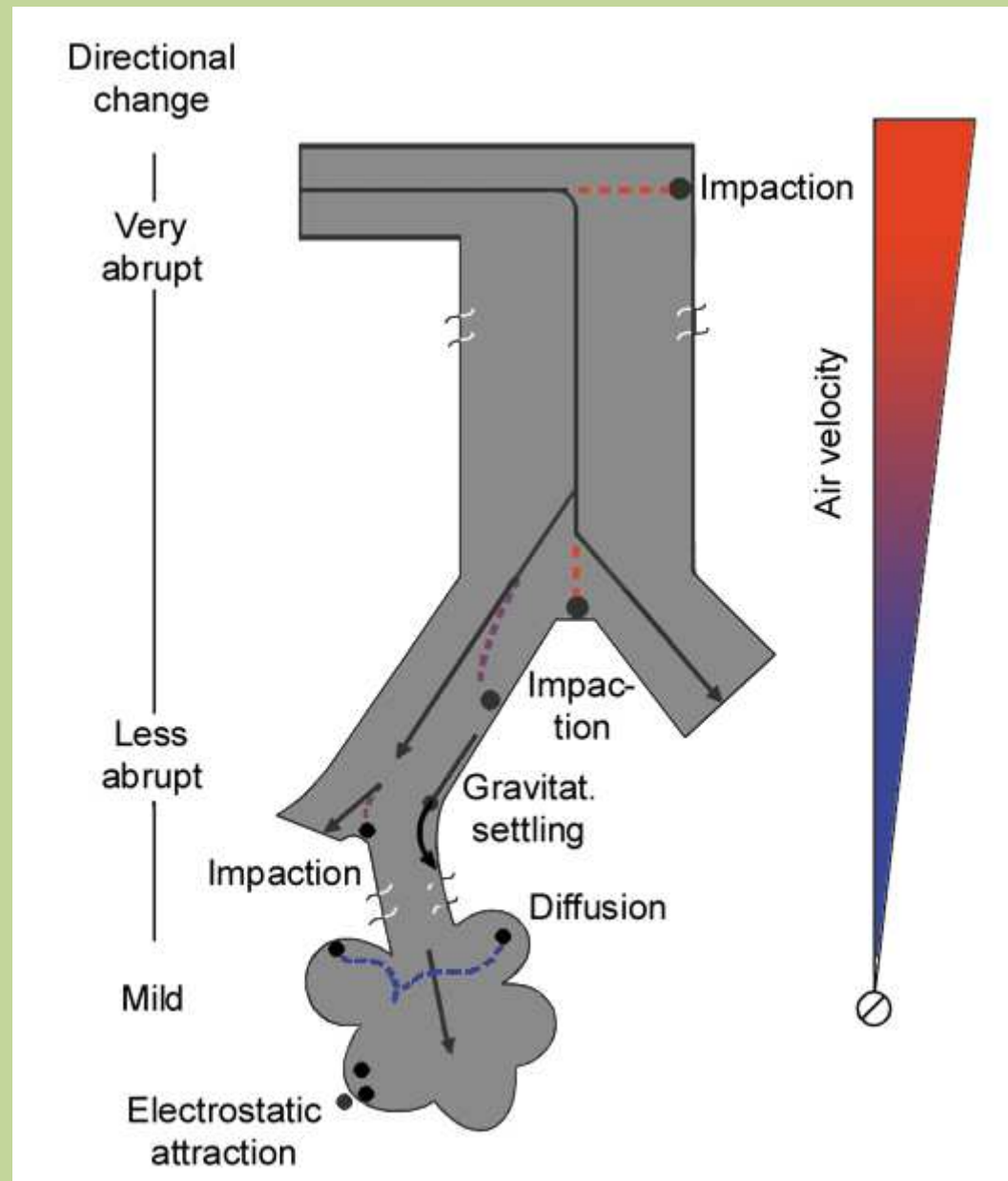


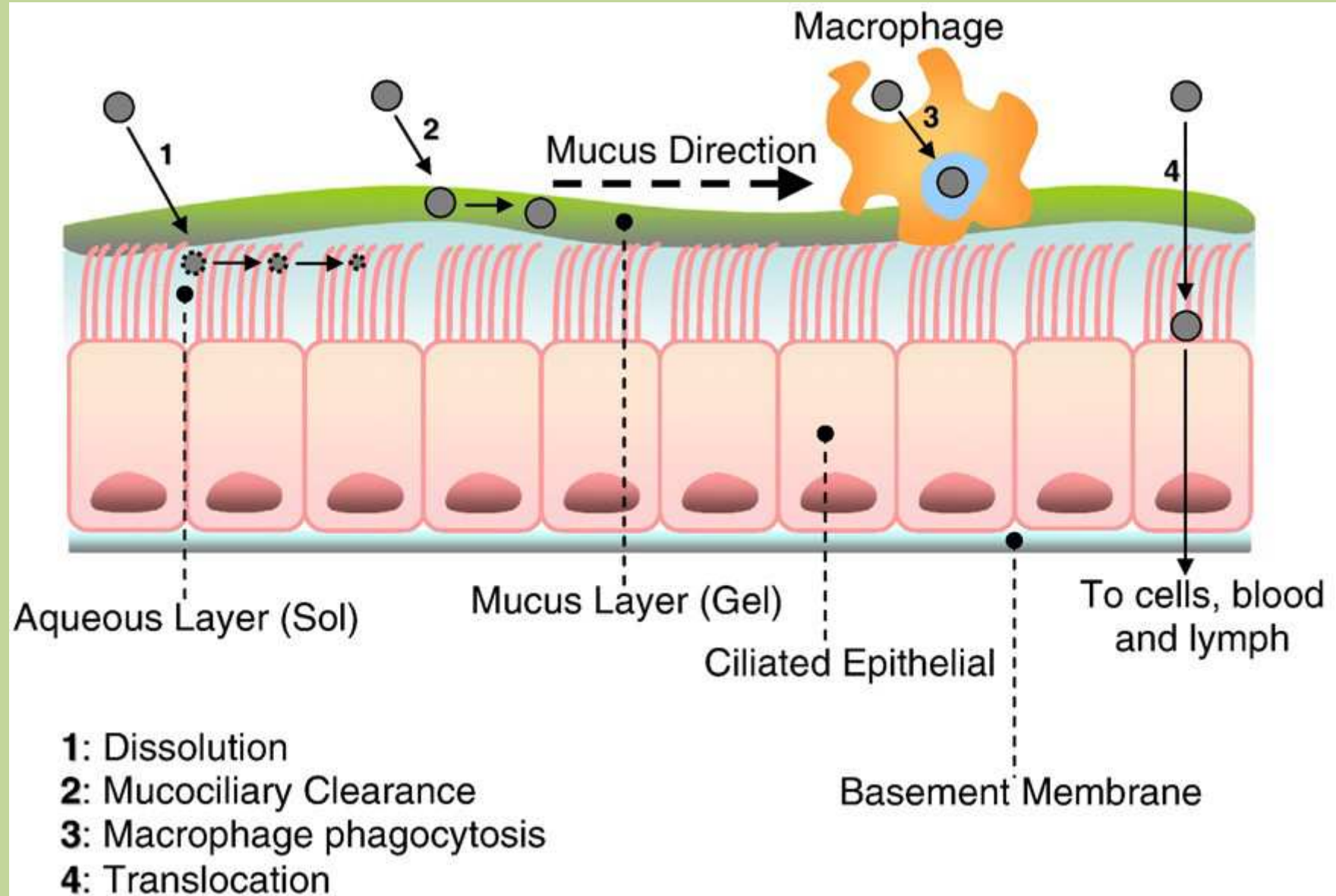
**drug , carrier surface are modified
to optimize detachment of drug particles**

**DRUG SURFACE ENERGY
DRUG CRYSTALLINE STATE
DRUG PARTICLE SIZE**









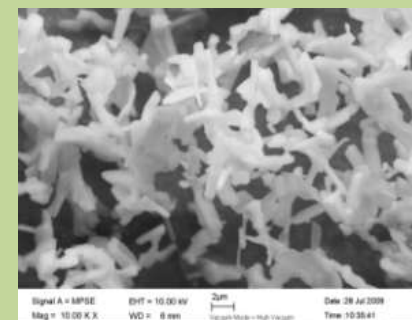
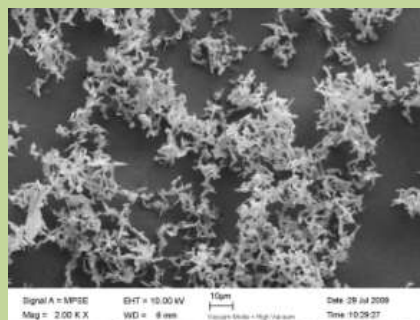
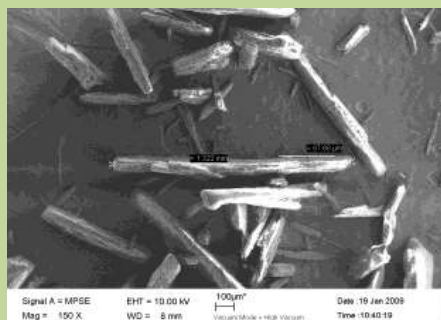
Drug particles deposited over lung alveoli must dissolve



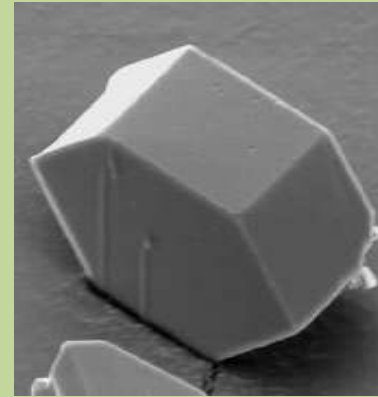
**In the lungs only 10-20 ml of aqueous fluid with bio-surfactants
over 100 m² of lung alveoli surface**



Drug API solid state characteristics (particle size, crystalline state & shape) even more critical than for other administration routes

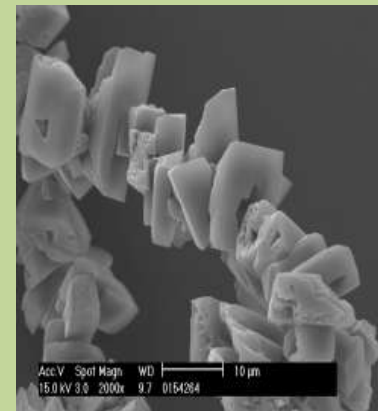
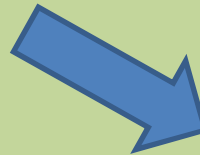
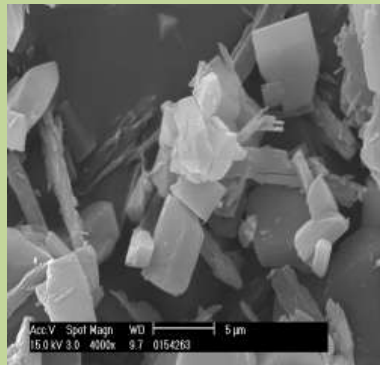


API DRUG A



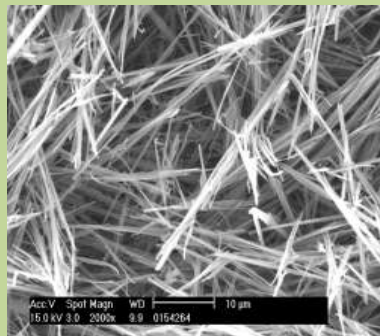
**API DRUG A
SCF PROCESSED**

API DRUG B



**API DRUG B
API DRUG C
COCRYSTALS
COMPOSITE
SCF PROCESSED
PARTICLES**

API DRUG C

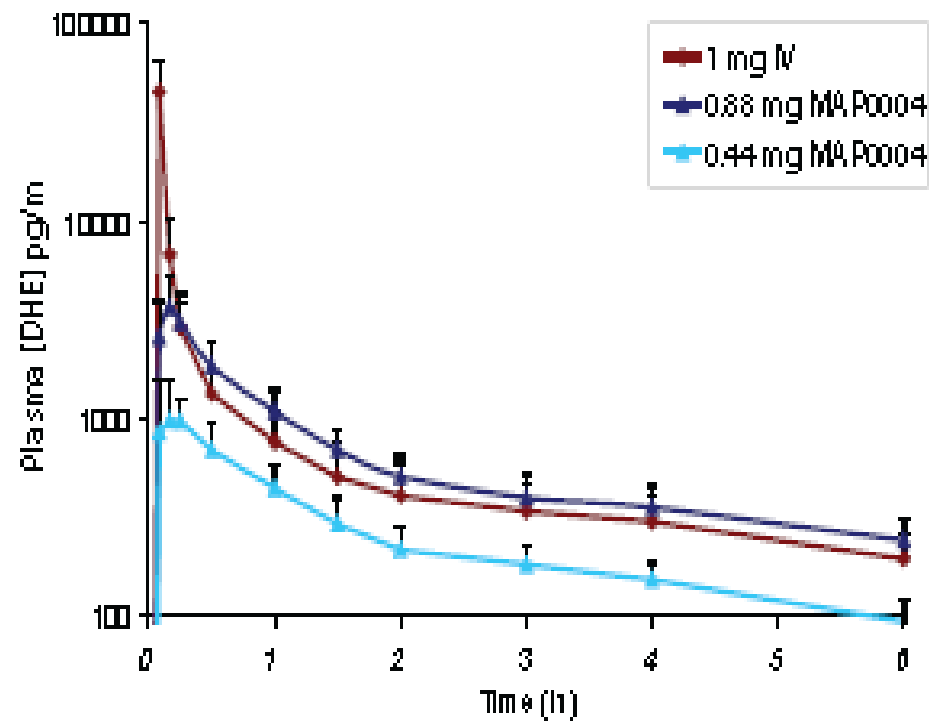


MDI migraine product with SCF processed drug particles

- **MAP Pharmaceuticals Inc with Tempo™ device**
- **‘Levadex’ – inhaled version of dihydroergotamine tartrate; SCF processed drug particles**
- **Benefits of Levadex - rapid onset, long lasting, broadly efficacious, convenient and consistent delivery, low incidence of side effects**

SCF PROCESSED DHE ANTI-MIGRAINE DRUG PARTICLES; HUMAN BIOAVAILABILITY AFTER INHALATION

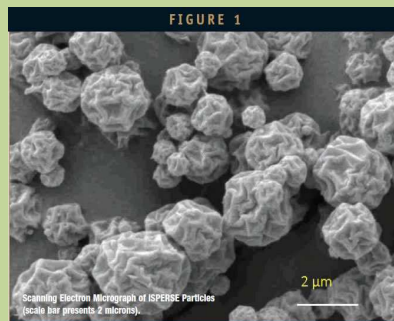
Figure 2. PK profiles of DHE in plasma, following IV and MA P0004 administration



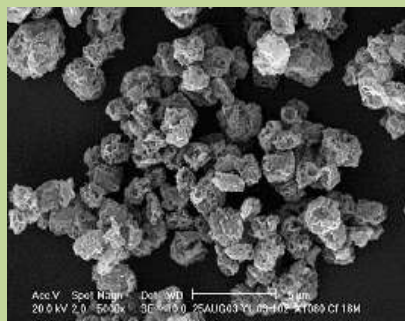
DRUG/CARRIER COMPOSITE PARTICLES

Drug - carrier composite particles can be prepared by different technologies:

- spray-drying
- super critical fluid SCF
- mechano-chemical fusion MCF



Spray-drying



SCF

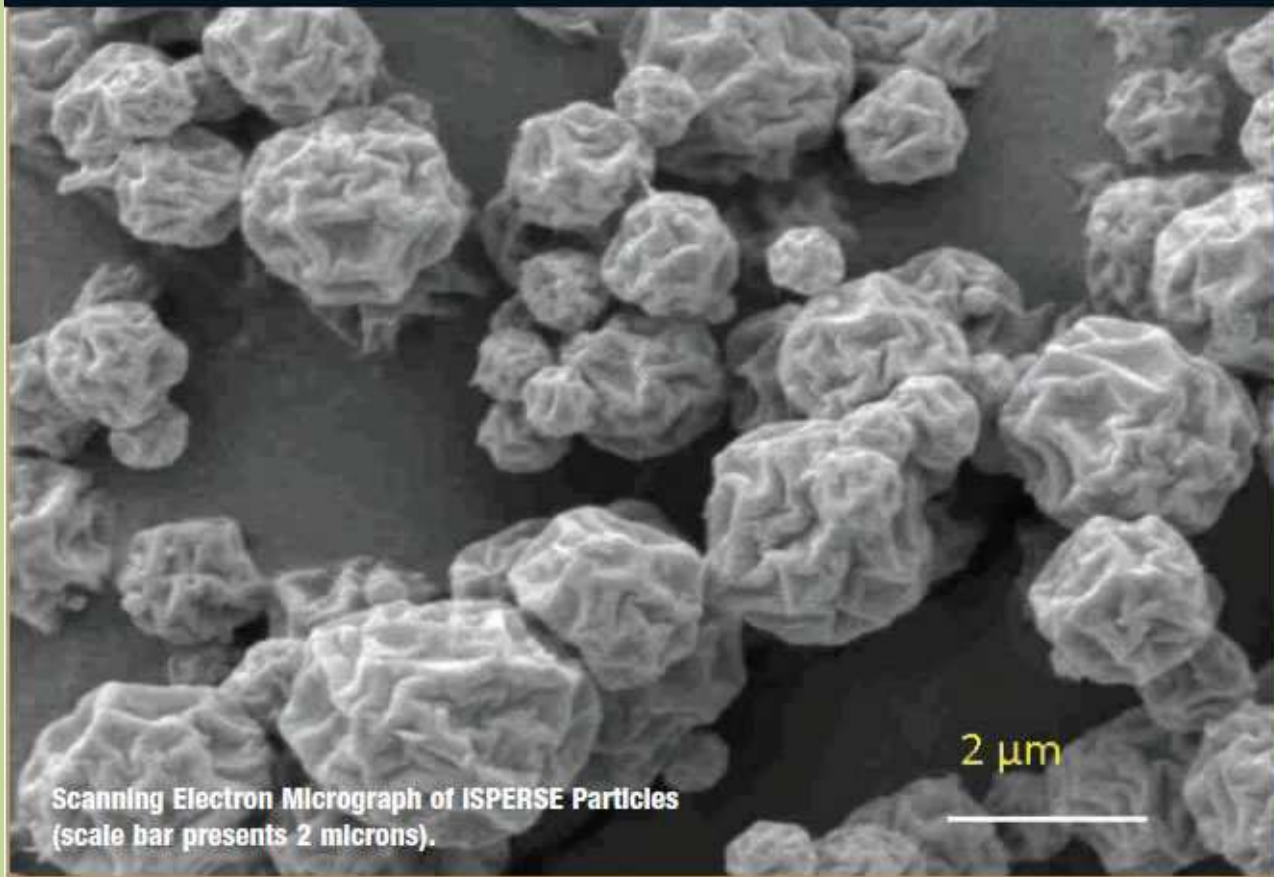


MCF

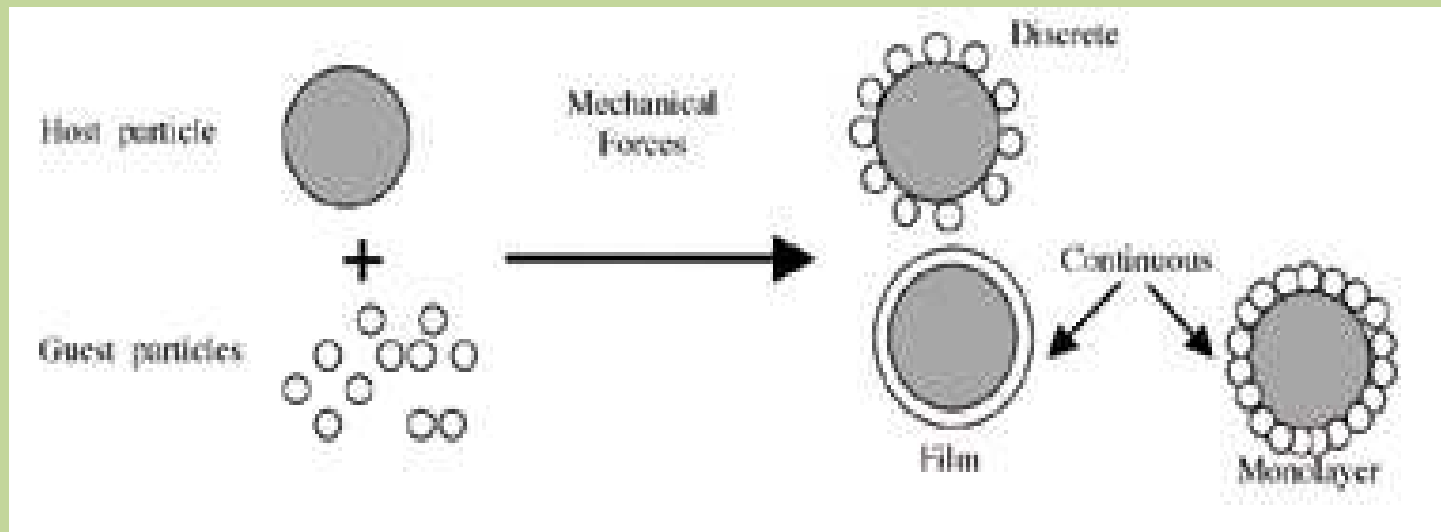
NEW DRUG /CARRIER COMPOSITE PARTICLES FOR INHALATION PULMATRIX®

drug/carrier composite prepared by spray-drying
(proprietary carrier selection / final density – high drug dose)

FIGURE 1



Mechano-fusion powder deposition/coating



Carrier



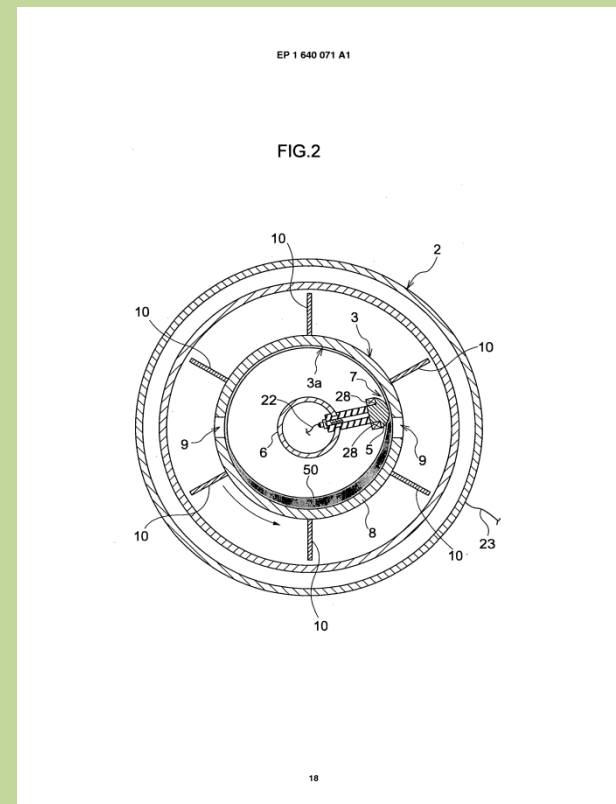
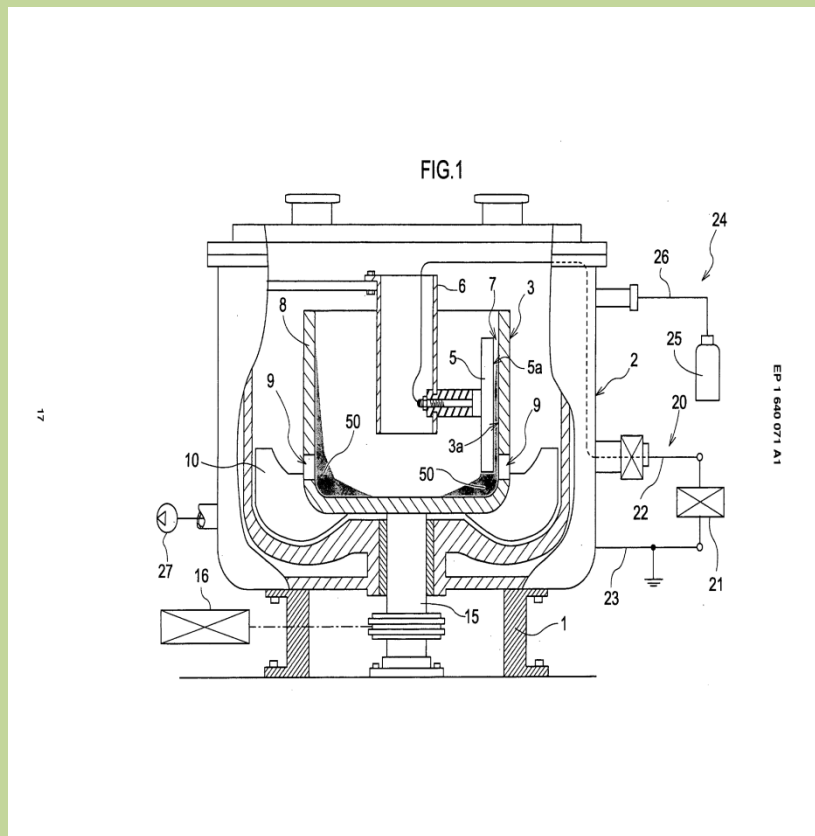
Composite

Drug

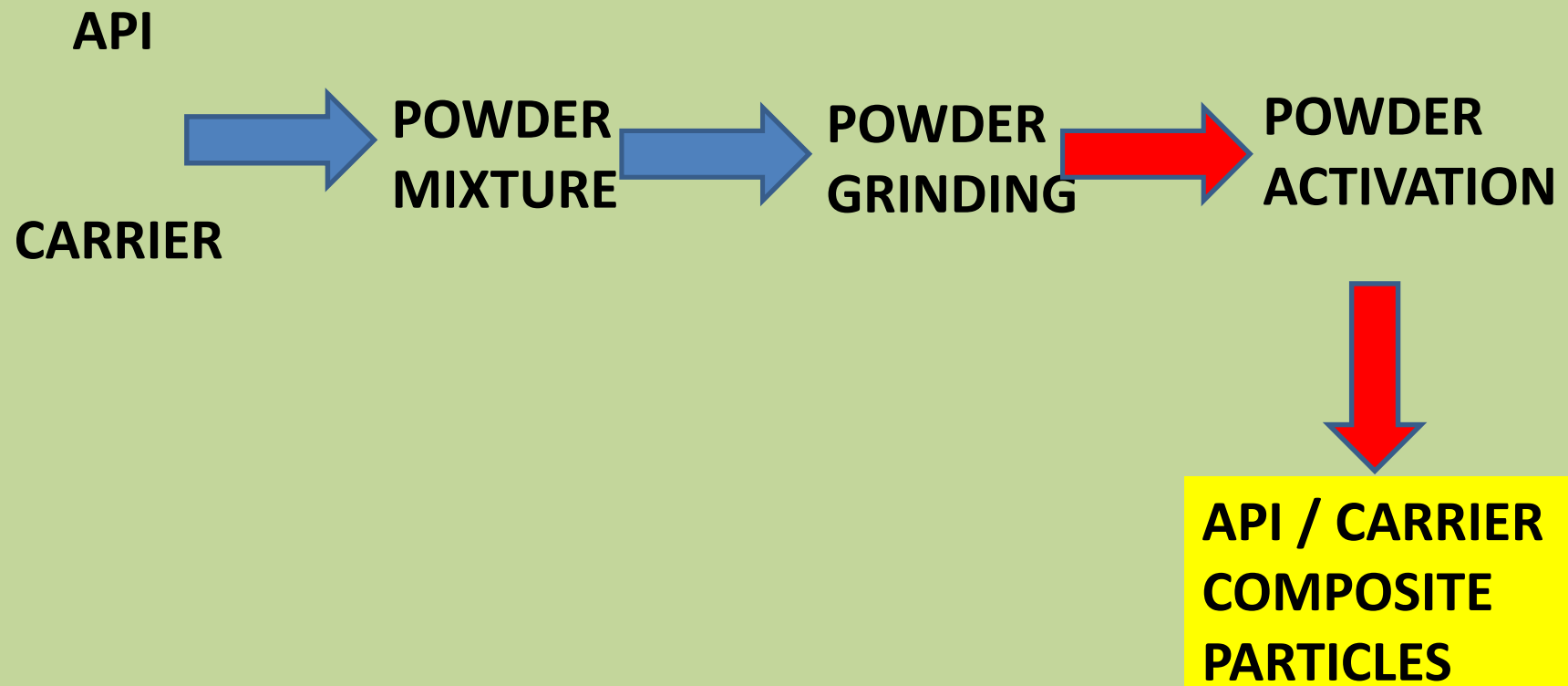


Mechano-fusion reactor

Mechano-fusion reactor



MECHANO-CHEMICAL ACTIVATION BY HIGH ENERGY COGRINDING

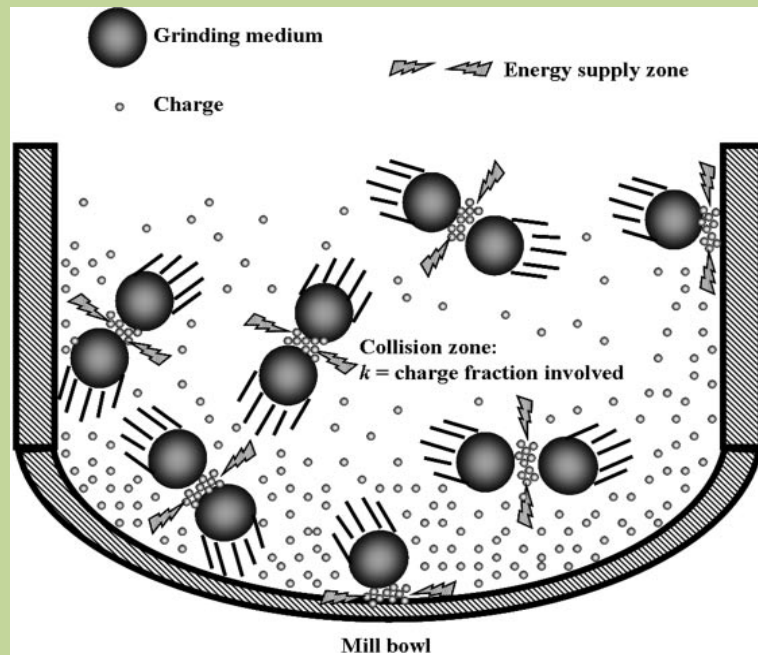


MECHANO-CHEMICAL ACTIVATION BY HIGH ENERGY COGRINDING

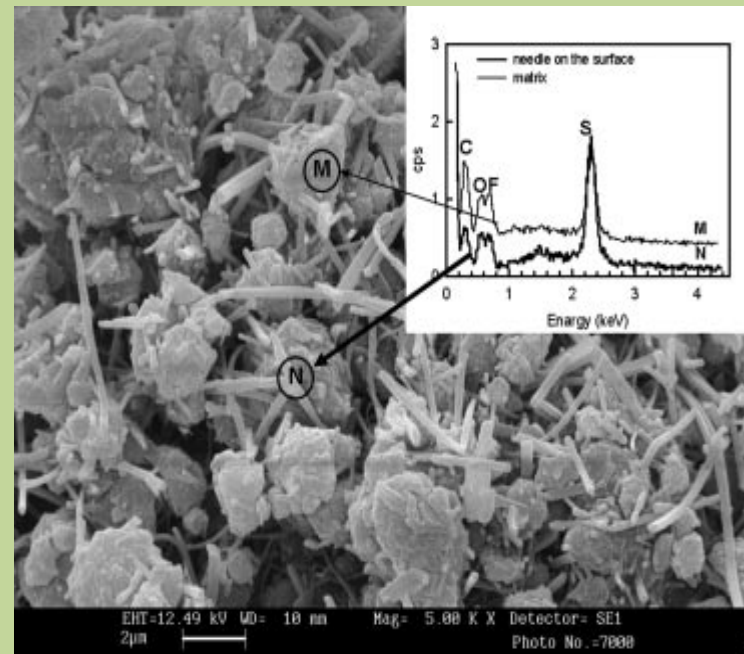


MECHANO-CHEMICAL ACTIVATION MCA

drug inclusion into polymer carrier by high energy cogrinding



High Energy planetary ball mill



SEM & EDS analysis of composite
drug/carrier particles
(EDS energy dispersive spectrometer)

PLANETARY BALL MILL



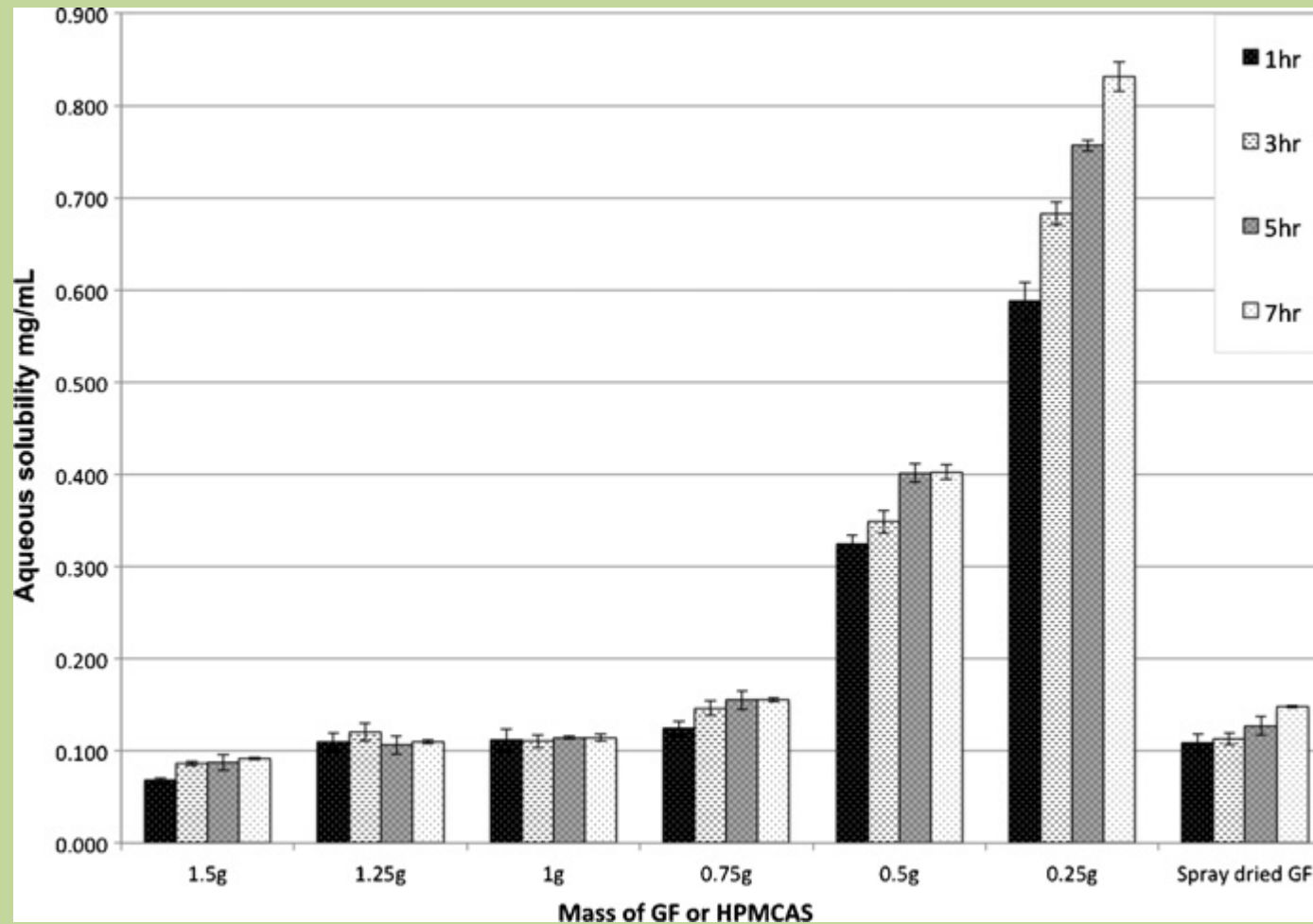
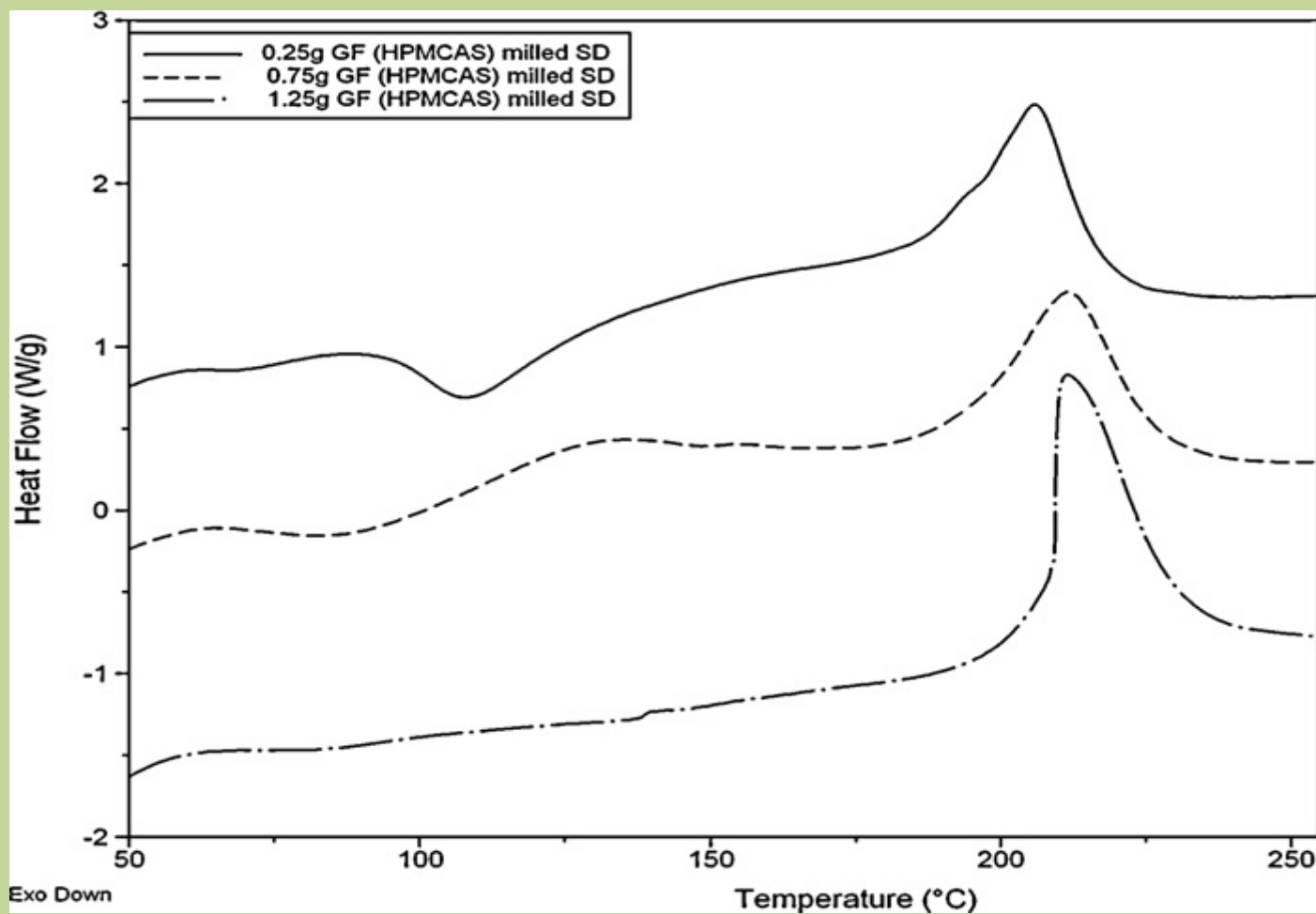
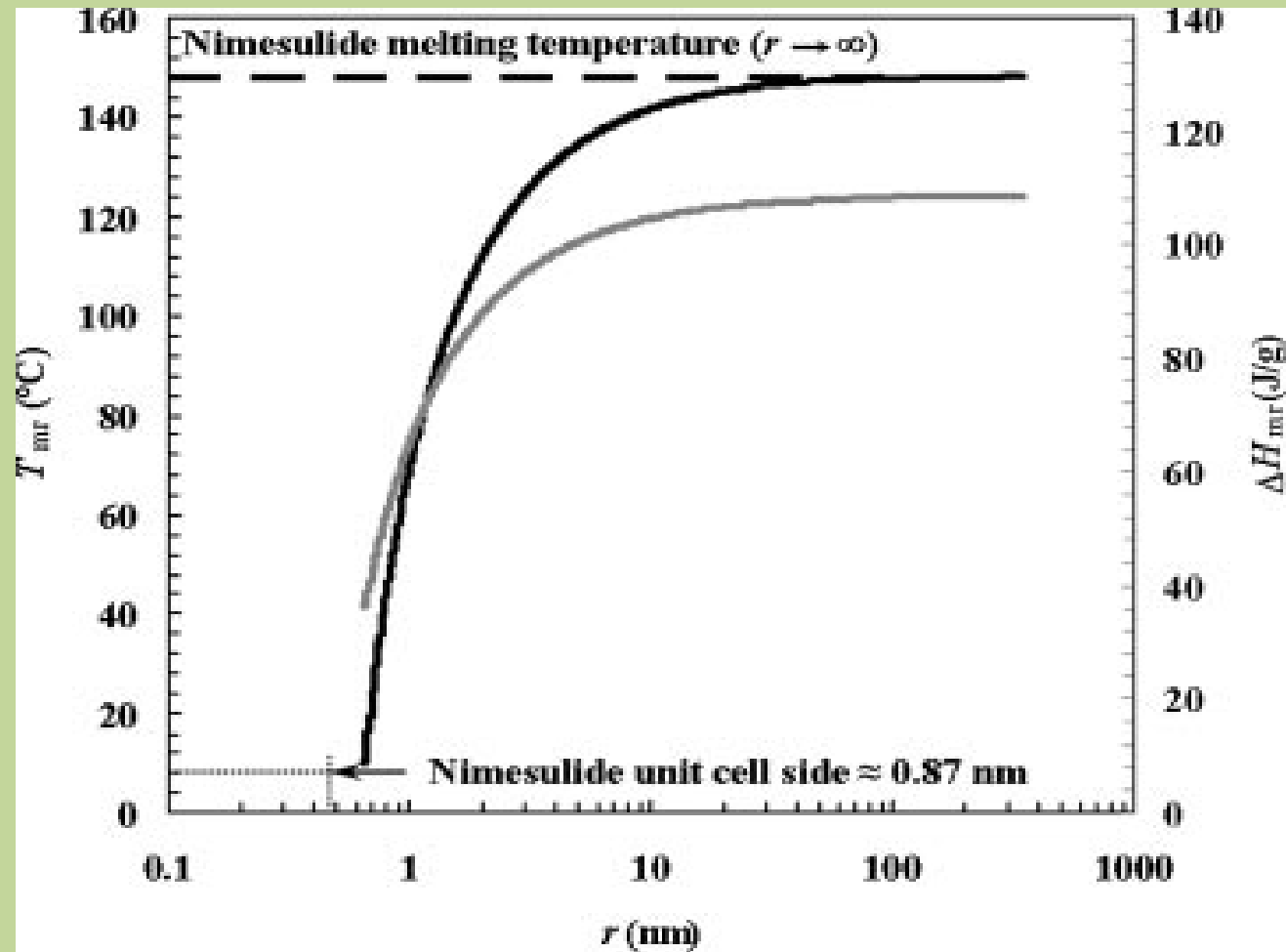


Fig. 3. Saturation solubility (pH 6.8) of GF from GF/HPMCAS **ball milled** composites containing 50 wt% GF and milled using different ratios powder mass/ball mass in and from **spray dried** solid dispersions.

DSC OF BALL MILLED DRUG/POLYMER AT DIFFERENT RATIOS POWDER MASS/BALL MASS





**DRUG MELTING TEMPERATURE IS
INVERSELY PROPORTIONAL TO CRYSTAL SIZE**

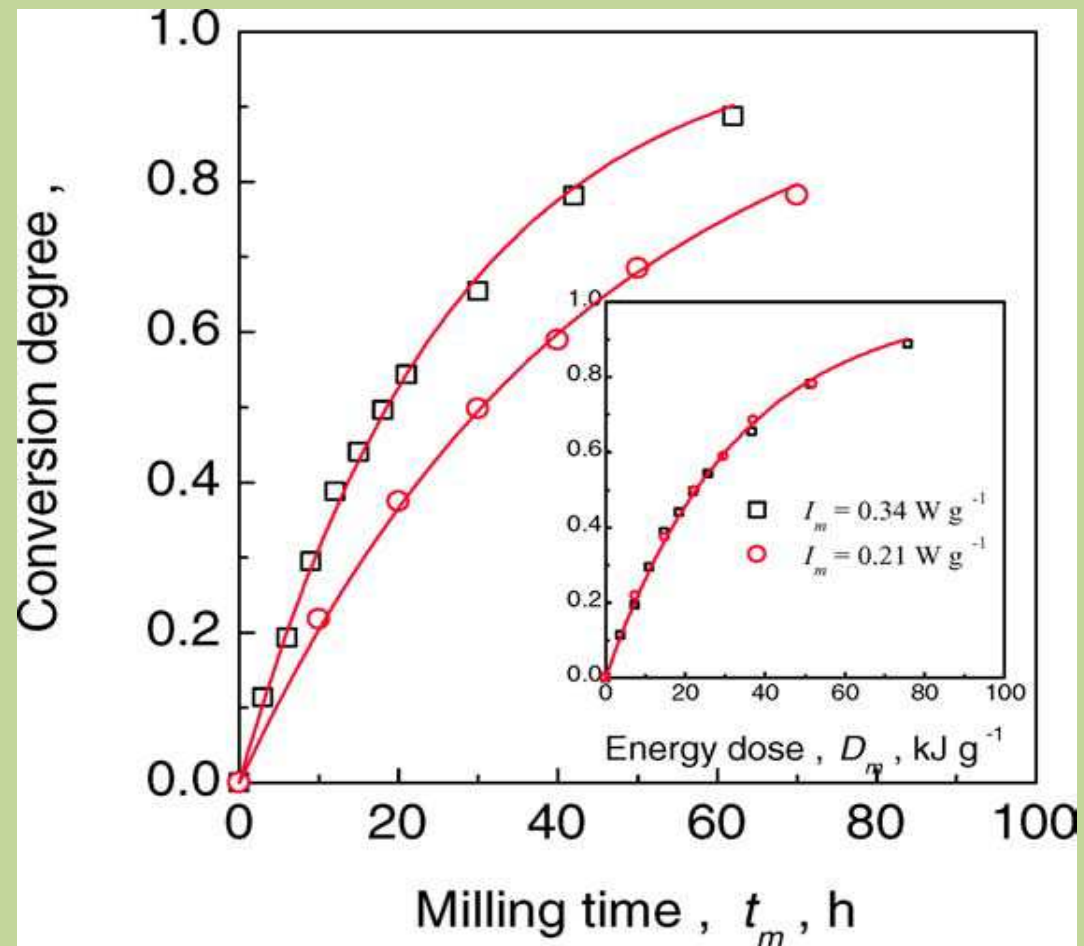
MECHANO-CHEMICAL ACTIVATION MCA

drug inclusion into polymer carrier by high energy cogrinding

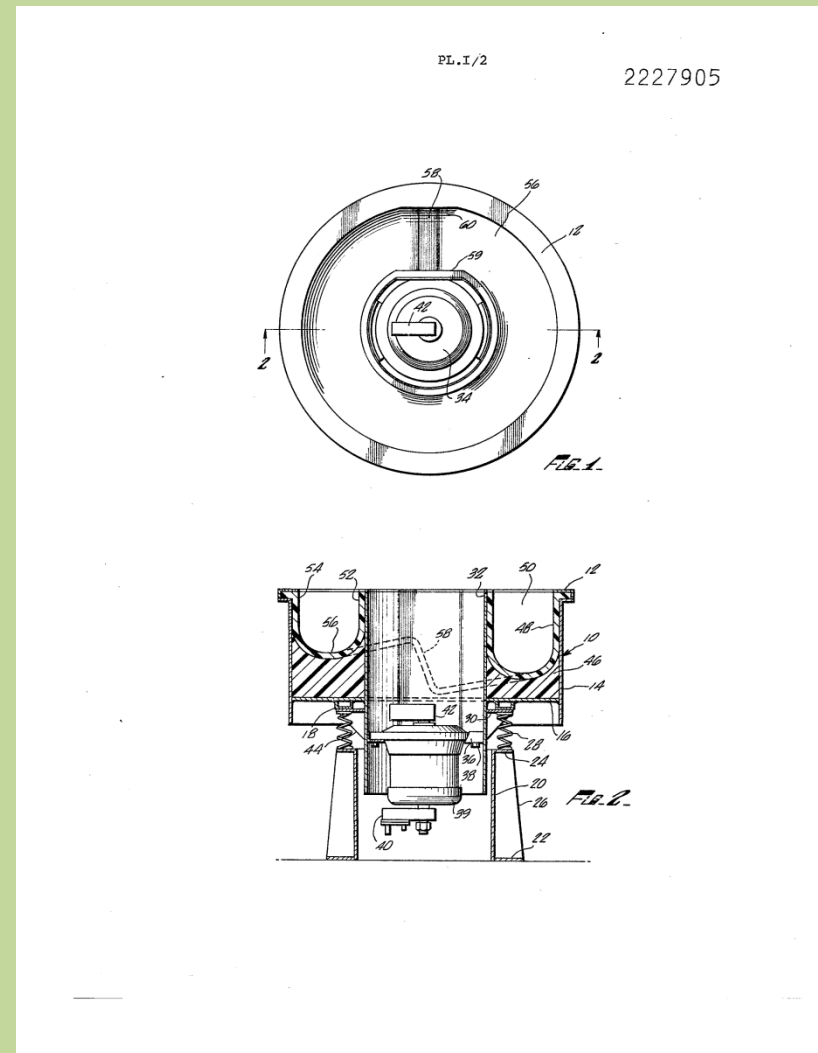
Amorphization
Degree of drug
Original
Crystallinity

$$I_m = E / m$$

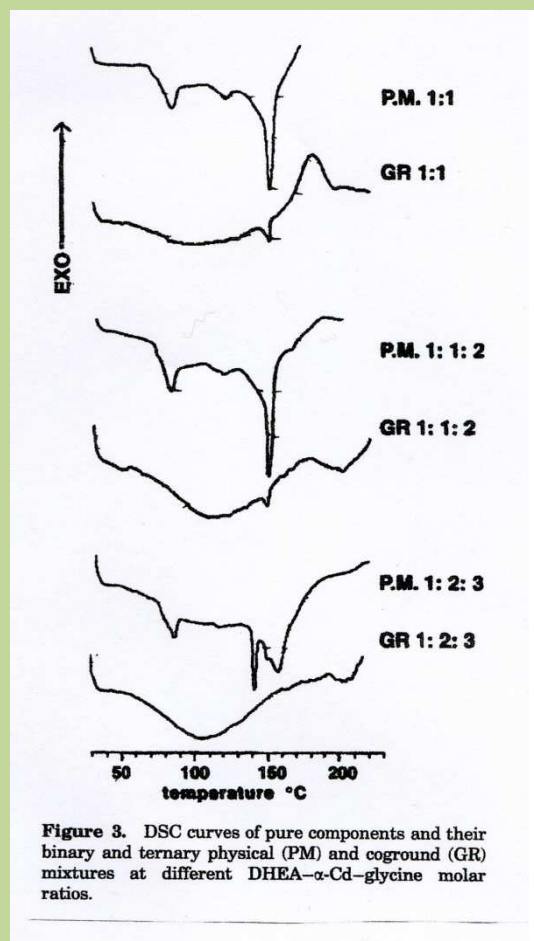
Intensity milling I_m is the total
energy transferred per unit mass



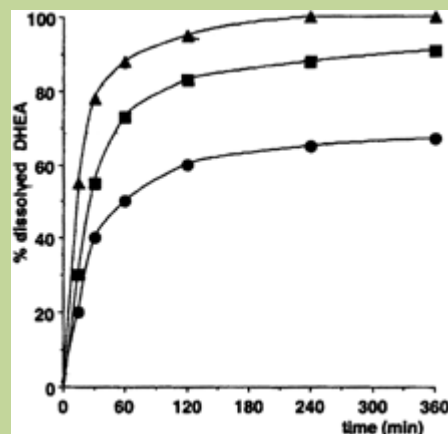
HIGH ENERGY VIBRATION MILLS



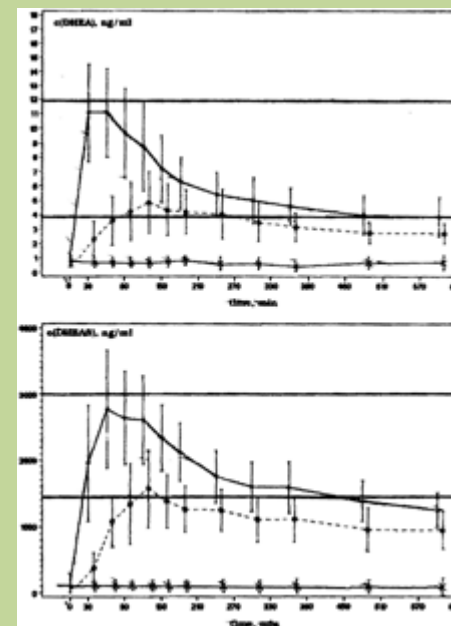
Enhancement of dehydroepiandrosterone solubility and bioavailability by ternary MCA (High Energy vibration mill) with α -cyclodextrin and glycine



DHEA DSC



DHEA dissolution rate



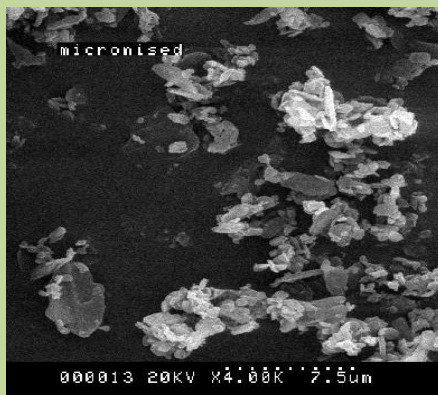
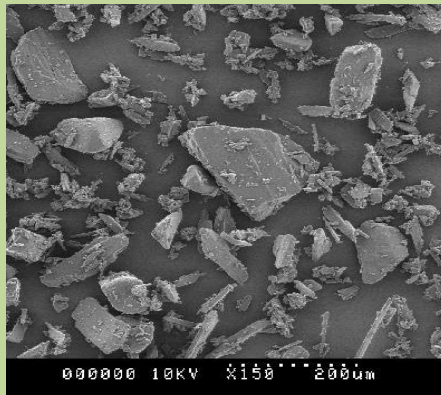
DHEA Plasma levels

Reproducibility of mechano-chemical activation

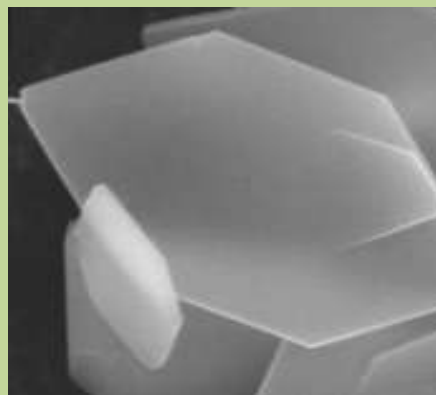


CRITICAL RELEVANCE OF DRUG API PHYSICO-CHEMICAL CHARACTERISTICS

particle size



crystalline state

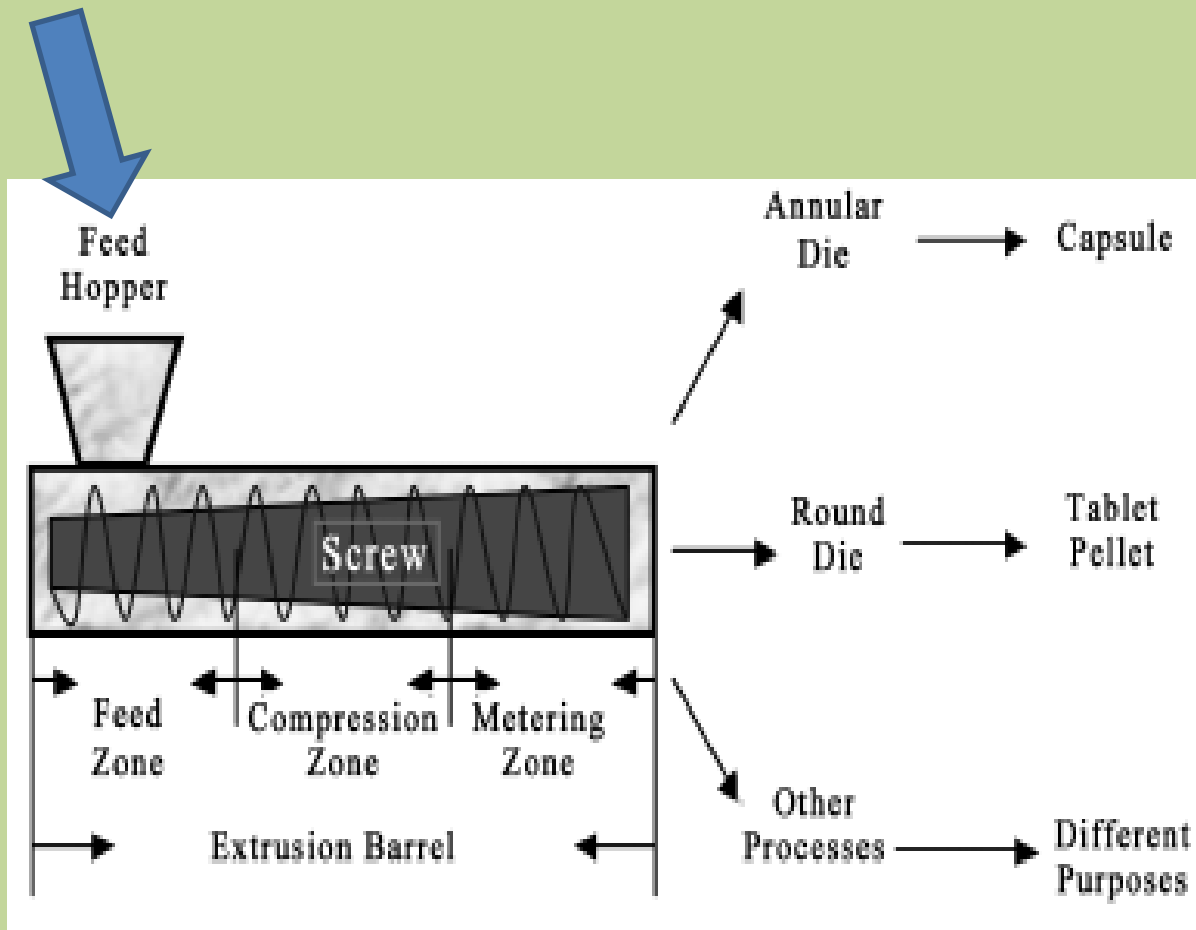


Different particle sizes or crystalline structures can lead to different activation times

HOT MELT EXTRUSION HME

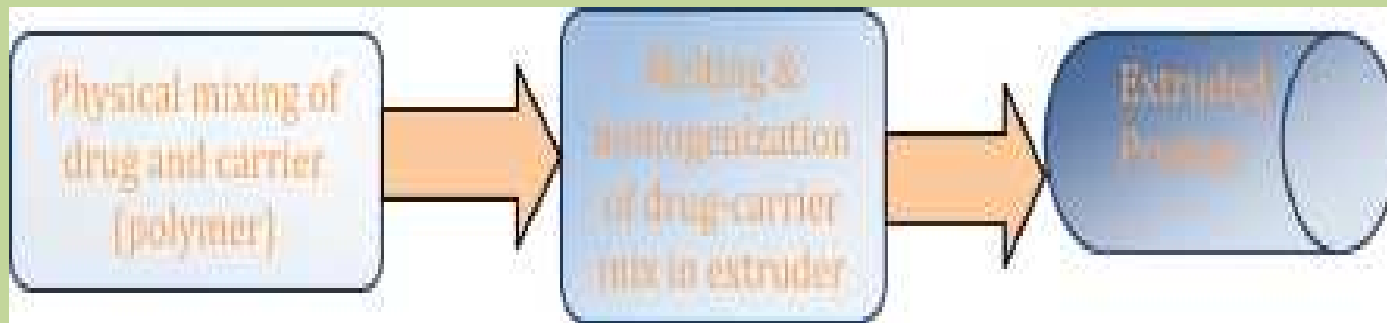
HOT MELT EXTRUSION

API
POLYMER POWDERS

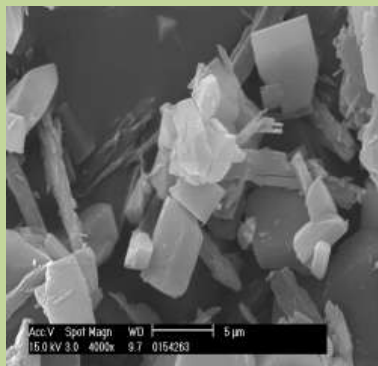


**INJECTION
MOLDING**

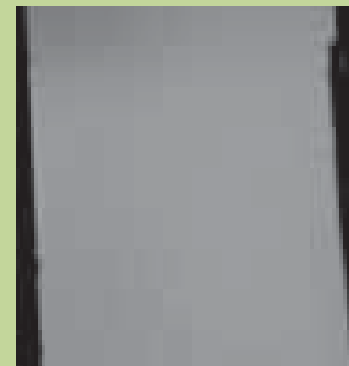
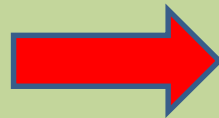
FILMS



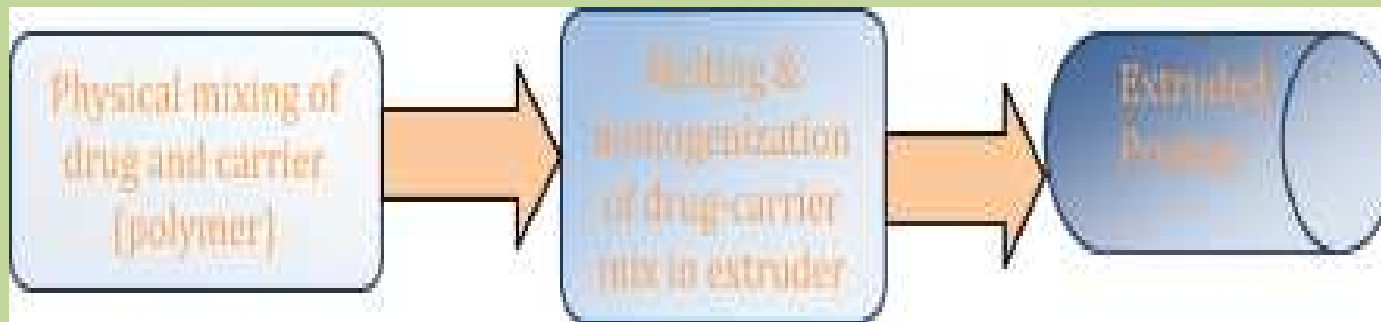
THE CRYSTALLINE API IS MELTED (DISSOLVED) IN THE POLYMER



**API POWDER
CRYSTALLINE**



**API MOLECULARLY DISPERSED
IN THE POLYMERIC FILM**



THE CRYSTALLINE API IS DISPERSED MOLECULARLY IN THE POLYMER

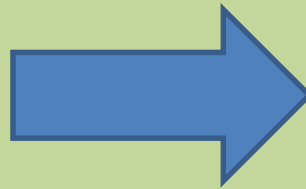
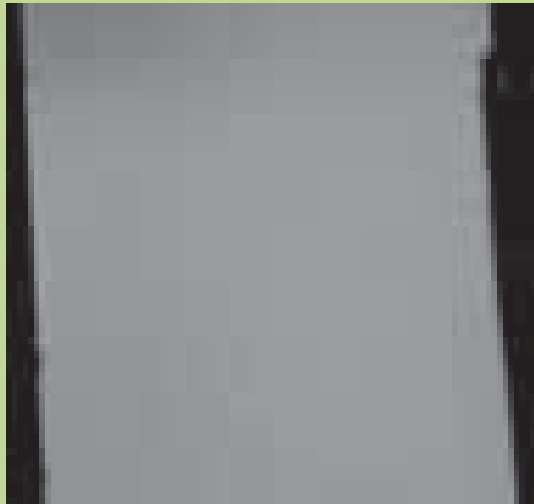


LOW GLASS TRANSITION TEMPERATURE POLYMER CAN LEAD TO API PHYSICAL CHANGE (RECRYSTALLIZATION) DURING STORAGE

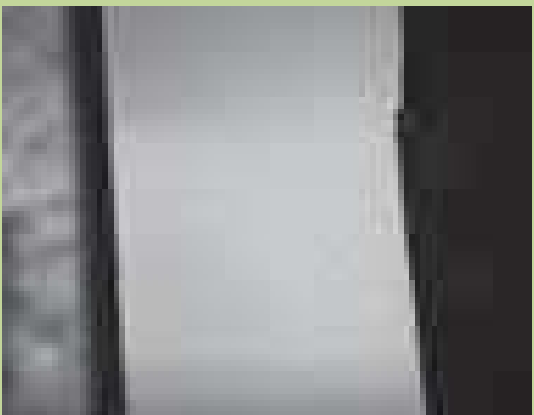


RELEVANCE OF PHYSICO-CHEMICAL PROPERTIES OF POLYMER CARRIER

API RECRYSTALLIZATION IN HME FILMS DURING STORAGE



6 MONTHS 30°



CONCLUSIONS

API SOLID STATE IS CRITICAL IN THE PERFORMANCE OF ADVANCED POWDER DELIVERY SYSTEMS, E.G. INHALATORY

API SOLID STATE CAN BE CHANGED BY DDS PREPARATION PROCESS, E.G BY MECHANO-CHEMICAL ACTIVATION

API SOLID STATE CAN CHANGE DURING DDS STORAGE

**API IN SOLID STATE PROCESSES,
E.G. MECHANOCHEMICAL ACTIVATION**



API SOLID STATE EVEN MORE CRITICAL