Impatto tecnologico/formulativo delle caratteristiche fisiche di un API

Anastasia Foppoli
Università degli Studi di Milano

Milano, 23 aprile 2015

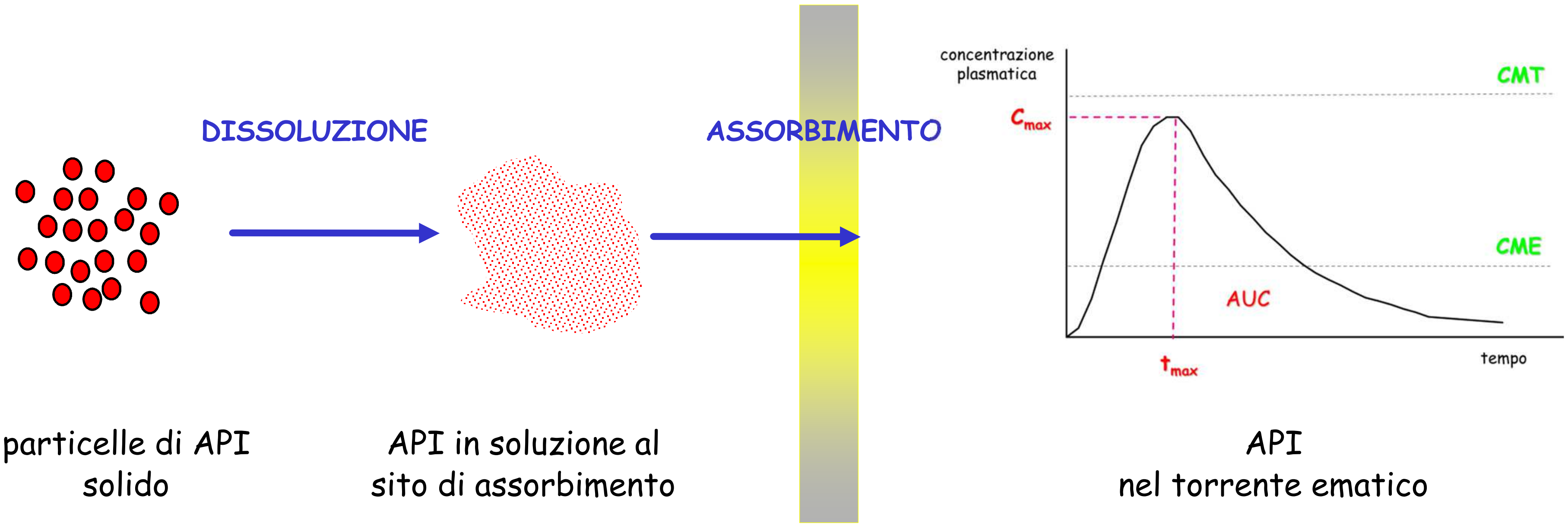
Il successo di un trattamento farmacologico non dipende esclusivamente dalla presenza del principio attivo ma anche da una sua corretta formulazione dal punto di vista tecnico e biofarmaceutico.

presentazione di alcuni esempi di impatto biofarmaceutico e tecnologico/formulativo delle caratteristiche fisiche dell'API

- ✓ granulometria /morfologia particellare (habitus)
  - area superficiale specifica
  - densita' apparente
  - ....
- ✓ forma cristallina [polimorfi e solvati]

presentazione di alcuni esempi di impatto biofarmaceutico

Processi che portano all'assorbimento di un principio attivo somministrato in forma solida per via extravascolare



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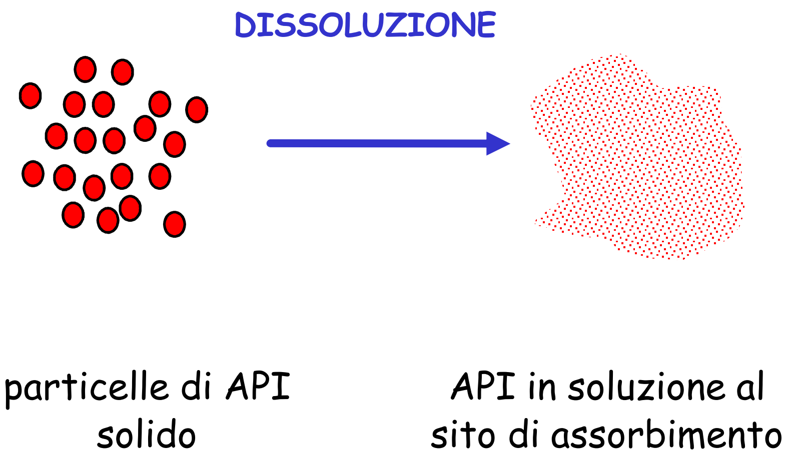

Processi che portano all'assorbimento di un principio attivo somministrato in forma solida per via extravascolare

Eq.Noyes-Whitney

$$dM/dt = DA\,(C_s - C_b)/h$$

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C_s = solubilità dell'API

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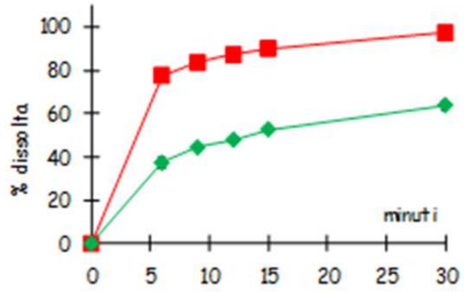
in vitro



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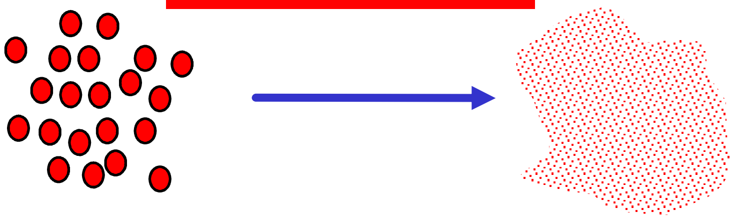
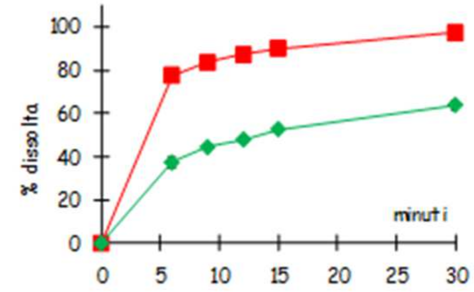
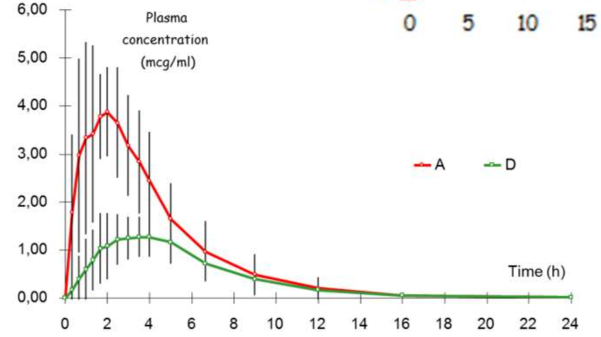
Processi che portano all'assorbimento di un principio attivo somministrato in forma solida per via extravascolare

velocità di
DISSOLUZIONE



in vitro





in vivo

Eq.Noyes-Whitney

$$dM/dt = DA\,(C_s - C_b)/h$$

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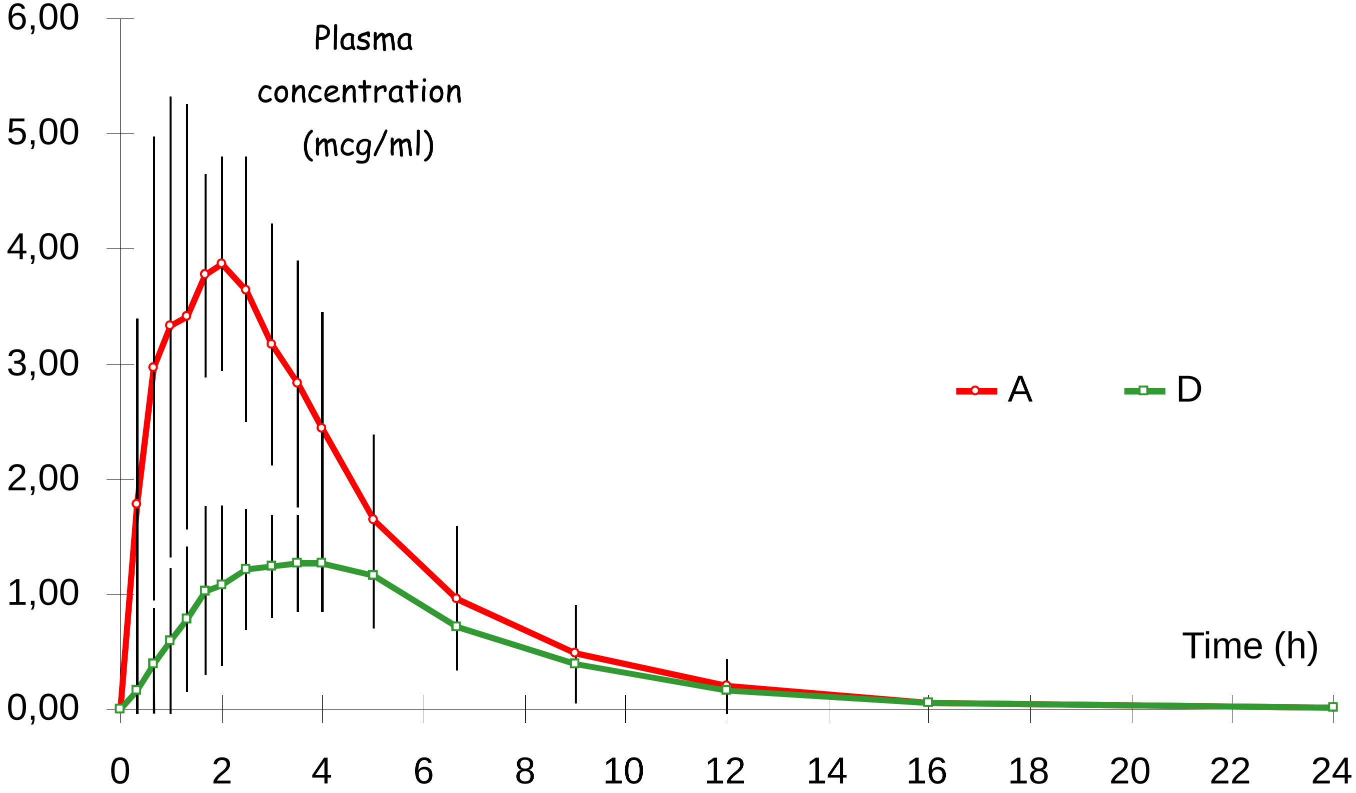
Nimesulide compresse: equivalenti non bioequivalenti



Plasma concentrations following oral administration of 2 tablet preparations *(mean conc ±sd, n=18)*

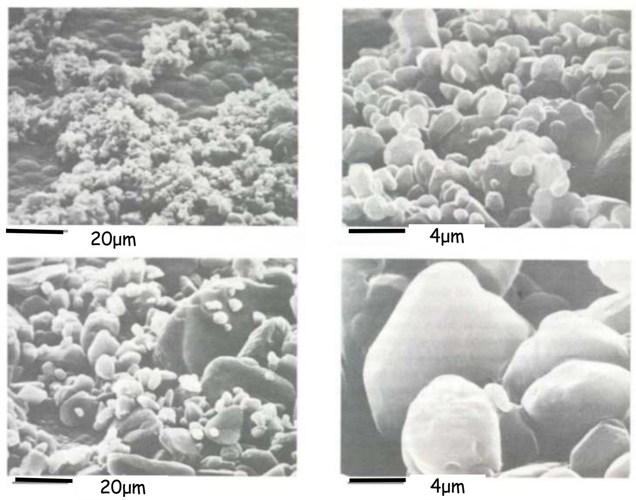
Adattato da:V. Hutt et al. Clin. Drug Invest. 21,361 (2001)

Granulometria & Biodisponibilità

Megestrolo Acetato sospensione

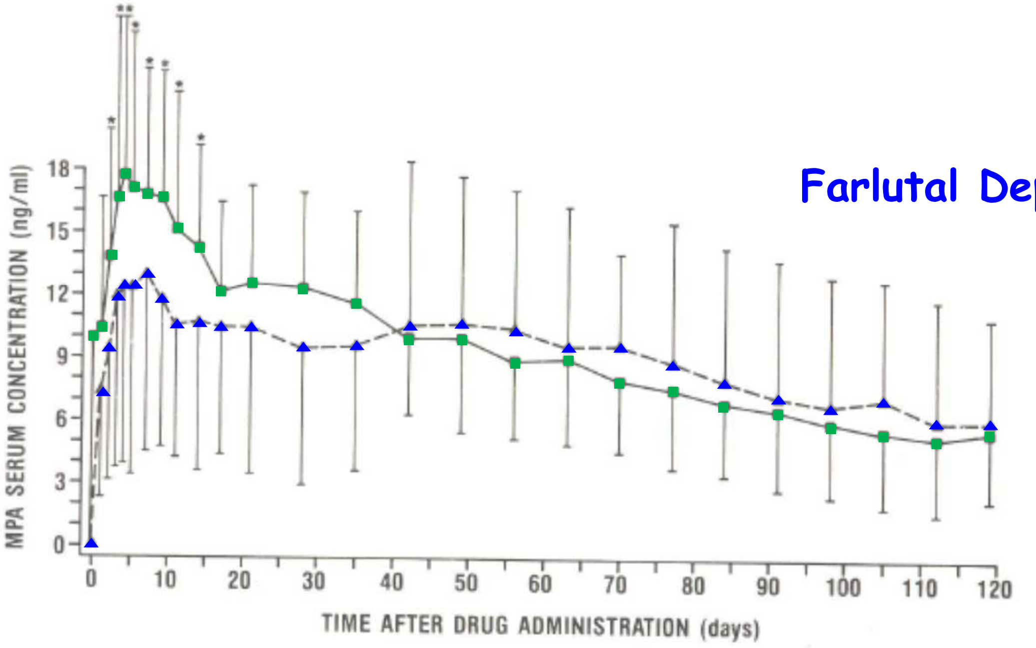
Depo-Provera®

Farlutal Depot ®



Adattato da: Comparative bioavailability of two medroxyprogesterone acetate suspensions.
Antal E.J. et al., Int. J. Pharm. 54, 33-39 (1989)

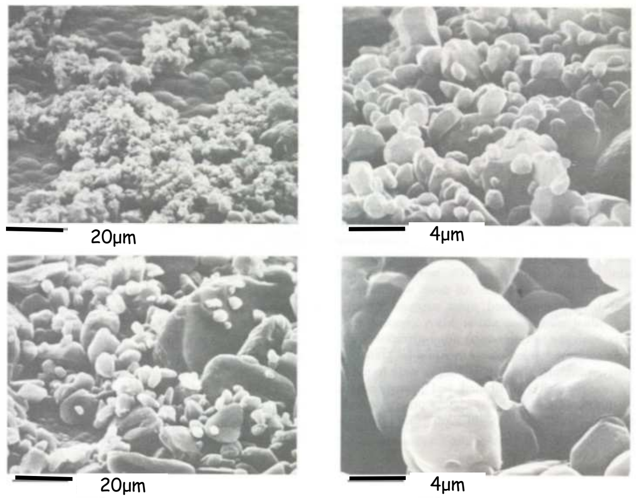
Megestrolo Acetato sospensione



Serum MPA concentrations following intramuscular administration of two MPA suspensions: Depo-Provera (n=20) ; Δ Farlutal Depot (n=18)

Depo-Provera®

Farlutal Depot ®



Somministrazione i.m.

C_{max} ed $AUC_{0\text{-}14g}$ > per Depo-Provera

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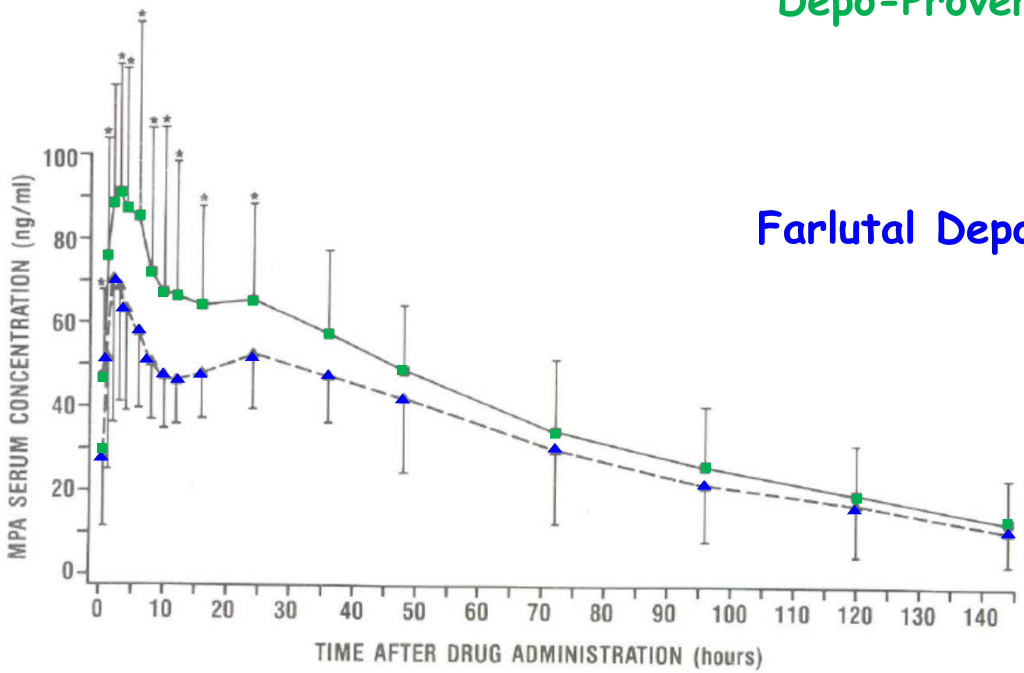
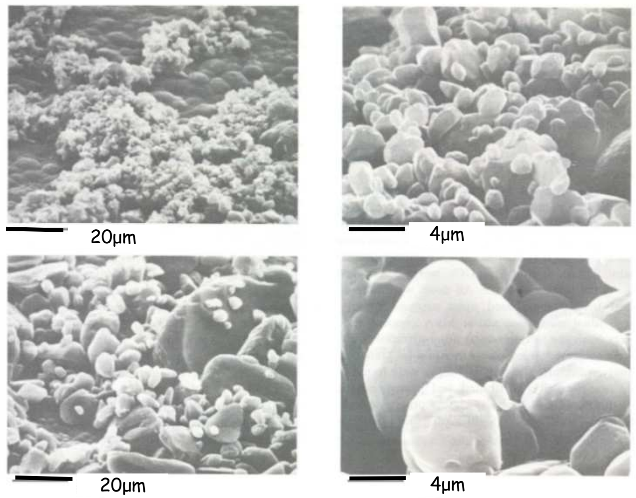


Serum MPA concentrations following oral administration of two MPA suspensions:
Depo-Provera (n=20) ; Δ Farlutal Depot (n=16 crossover)

Depo-Provera®

Farlutal Depot ®



Somministrazione orale

C_{max} ed AUC > per Depo-Provera

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Associazione metformina/glibenclamide

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MET: solubile (>300mg/ml)
poco permeabile
dosaggio 500-1000mg *Glucophage®*

GLI: poco solubile (<0,01mg/ml)
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dosaggio 2.5-5mg *Micronase®*

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Valutazione comparativa dei profili farmacocinetici di MET e GLI ottenuti mediante somministrazione di :

$MET_{500mg}/GLI_{2.5\ mg}$ (2 cpr)

MET_{500mg} (2 cpr) + $GLI_{5\ mg}$ (1 cpr)

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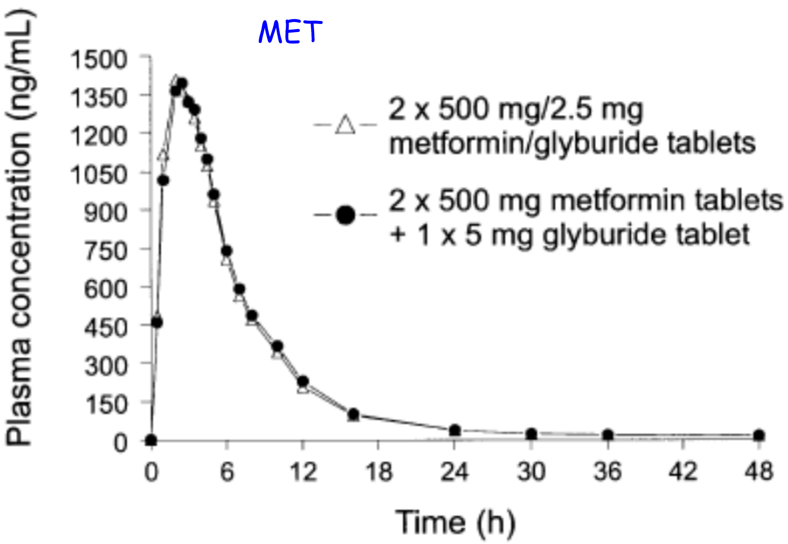
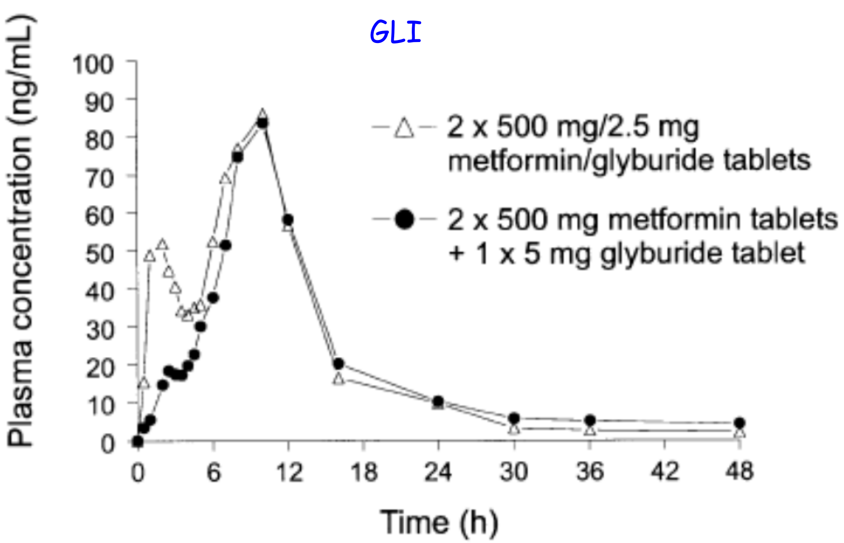
MET



GLI



MET: Glucovance BE Glucophage

GLI: comparabile BA, 2 picchi di conc. per il prodotto di associazione

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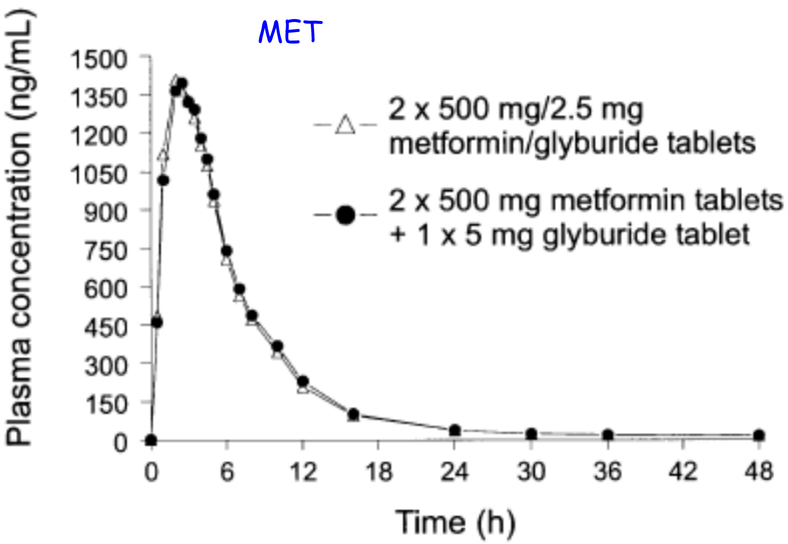

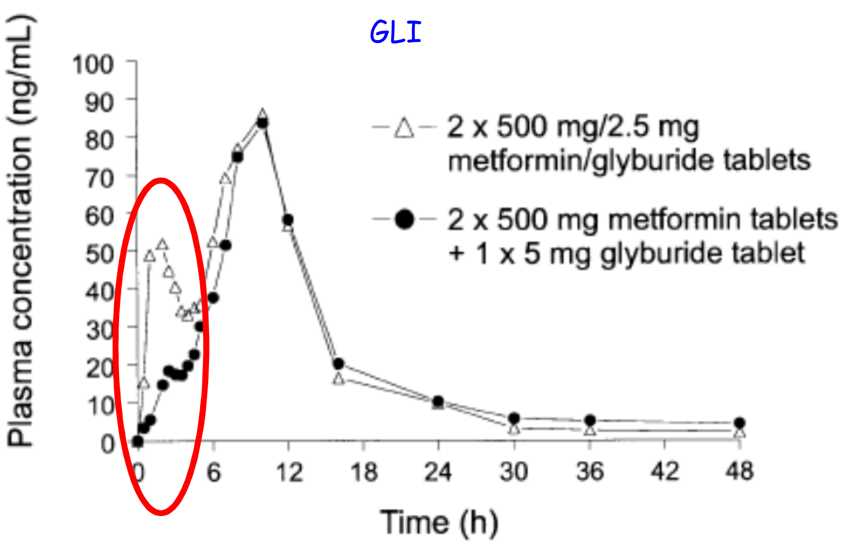

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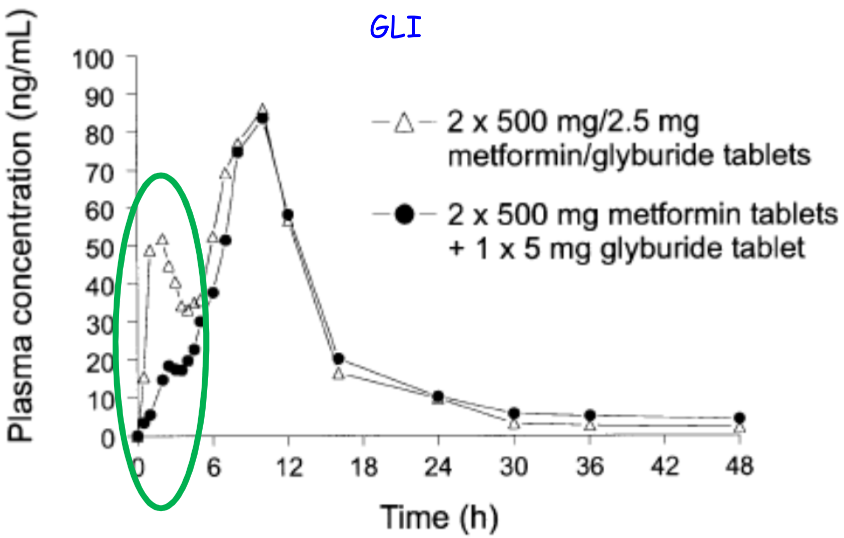
lower 2-hour PPGEs compared to separate glibenclamide and metformin tablets



Da: Pharmacokinetic and pharmacodynamics of Glyburide/Metformin tablets (Glucovance) versus equivalent doses of Glyburide and Metformin in parients with type 2 diabetes.
S.R. Donahue et al., Clin. Pharmacokinetic., 41(5), 1301 (2002)

Associazione metformina/glibenclamide

Glucovance®: $MET_{500mg}/GLI_{2.5mg}$

… the glyburide used in GLUCOVANCE has a particle size distribution of

25% undersize volume not more than 6 μm,

50% undersize value not more than 7 to 10 μm, and

75% undersize value not more than 21 μm…..

Glucovance prescribing information. Bristol-Meyers Squibb Company 2001, Princeton (NJ)

Associazione metformina/glibenclamide

	particle size (um)			surface area
Glyburide reference	D25	D50	D75	m^2/g
F1	15	33	62	0.5
F2	28	58	88	ND
F3	10	25	52	ND
F4	6	11	19	ND
commercial non-micronized GLY	13	29	56	0.5

Formulazioni di MET/GLI 500/2.5
con GLI a diverso particle size

Adattato da: Development of a Glyburide-Metformin fixed combination tablet with optimized Glyburide particle size. Timmins P. at al., Drug Development Research 66, 25-35 (2006)

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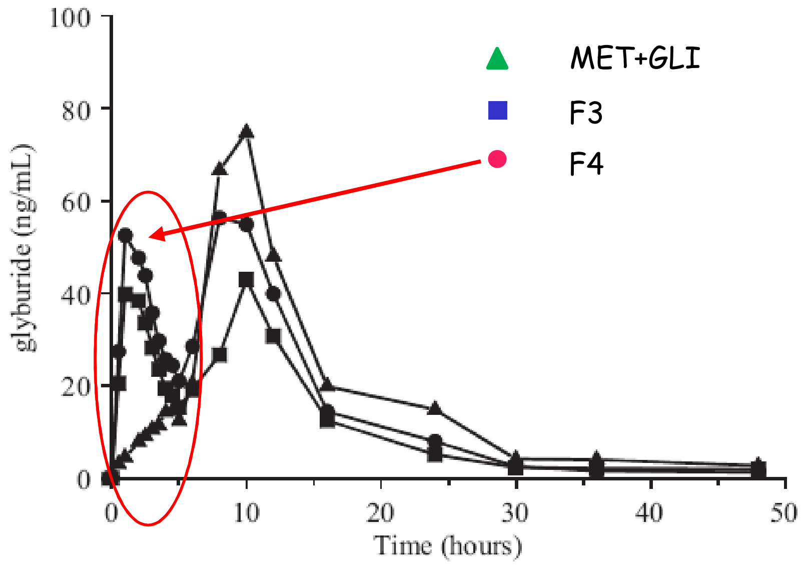


Plasma concentration time curves for glyburide from different glyburide-metformin tablets formulations

Adattato da: Development of a Glyburide-Metformin fixed combination tablet with optimized Glyburide particle size. Timmins P. at al., Drug Development Research 66, 25-35 (2006)

Esempi di documentata bioinequivalenza tra preparazioni contenenti il principio attivo in una diversa forma fisica (amorfi, polimorfi solvati)

Novobiocina (1960)

CAF palmitato (1967, 1980)

Ampicillina (1968, 1981)

Clortetraciclina (1974)

Amobarbital (1981)

6- mercaptopurina (1981)

Fenilbutazione (1984)

Indometacina (1987)

Cimetidina (1987)

Carbamazepina (1992, 2000, 2003)

Ossitetraciclina cloridrato (1999)

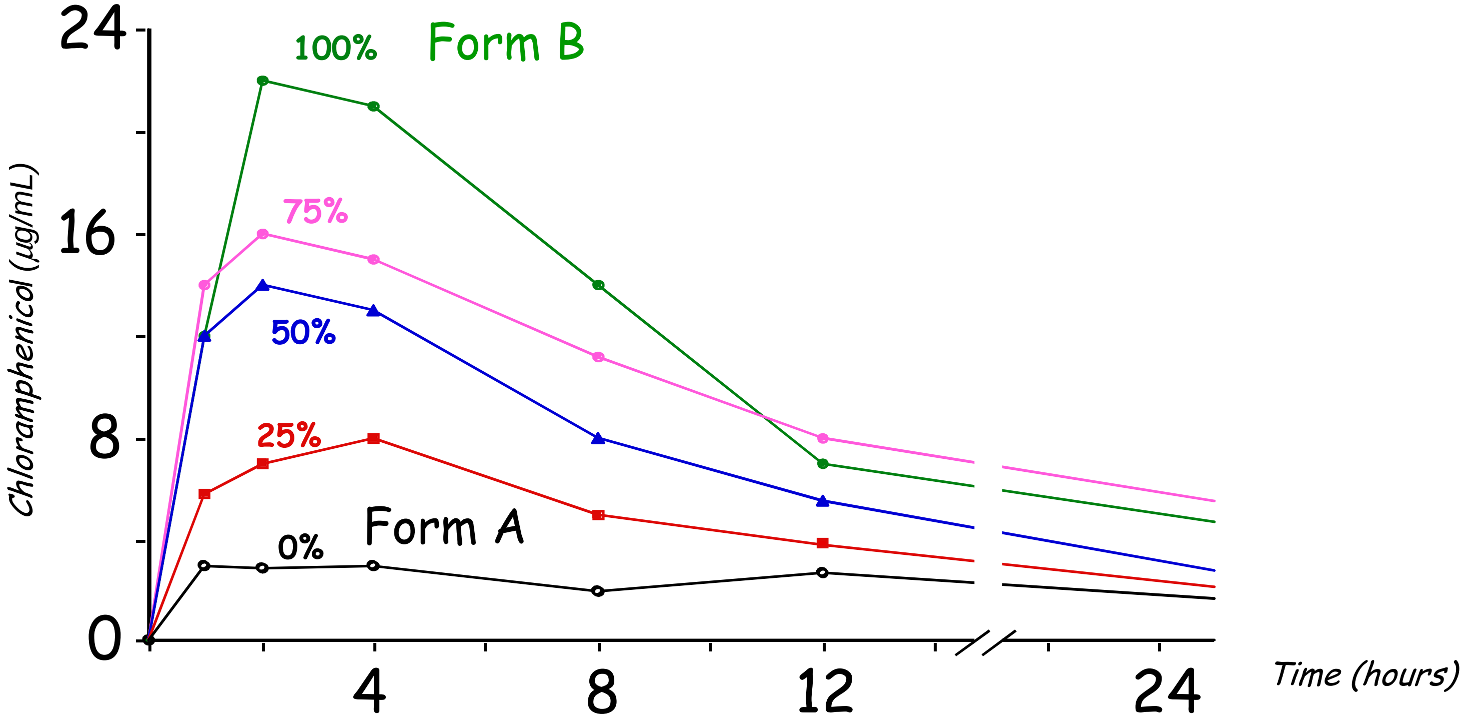
Celecoxib (2006)

…….

Cloramfenicolo palmitato sospensione orale

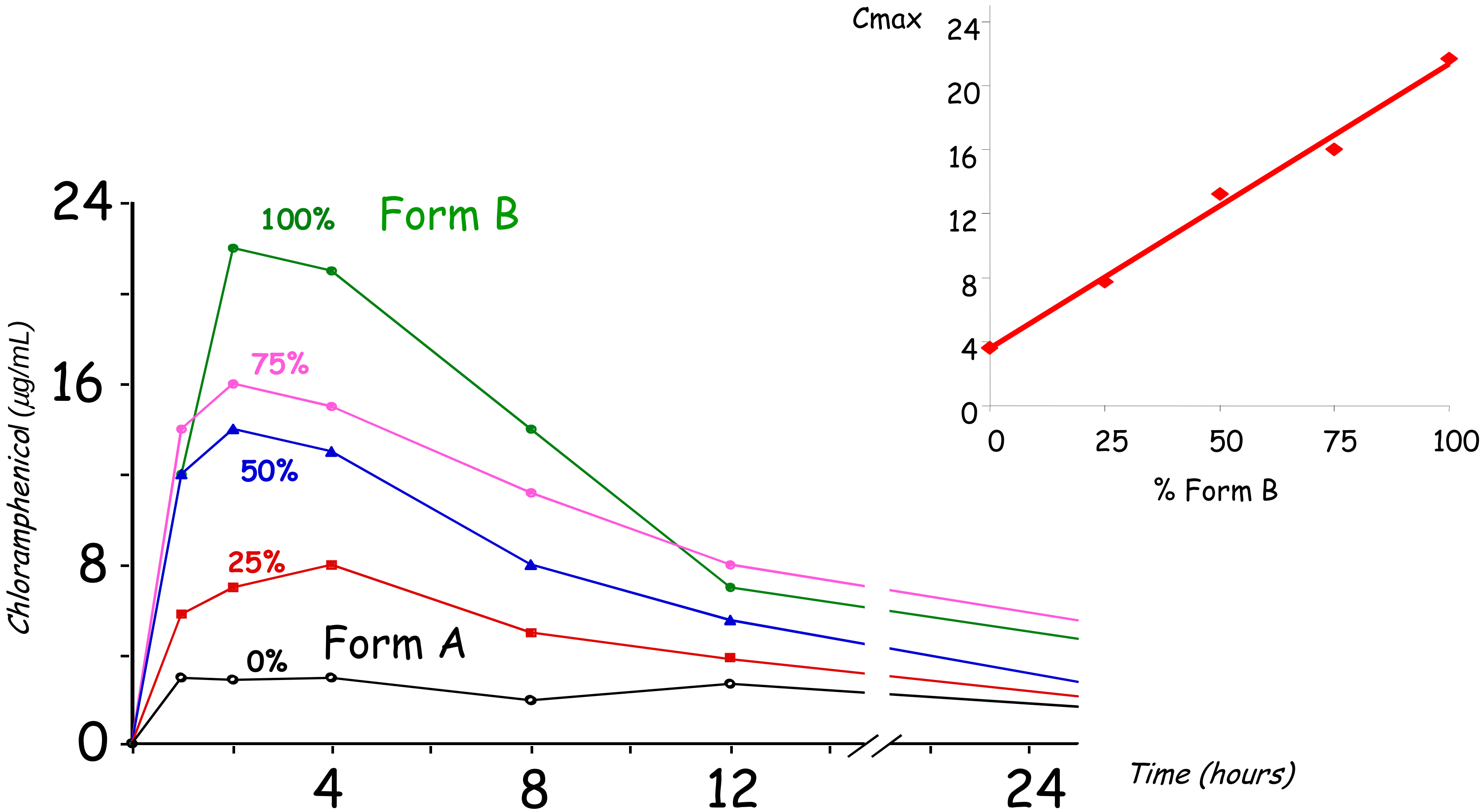
Forma A, stabile

Forma B, metastabile



Redrawn from: A. Aguiar et al. J. Pharm. Sci., 56 (7), 847-853 (1967)

Cloramfenicolo palmitato sospensione orale



Redrawn from: A. Aguiar et al. J. Pharm. Sci., 56 (7), 847-853 (1967)

Carbamazepina

casi documentati di bioinequivalenza tra medicinali generici e originatore

The bioinequivalence of carbamazepine tablets with a history of clinical failures. M.C. Meyer et al., Pharm. Res., 9(12), 1612-1616, (1992)

discordanza tra i dati in vivo su preparati contenenti forma anidra ed idrata....

Pharmacokinetics and dissolution of two crystalline forms of carbamazepine. P.Kahela et al., Int. J. Pharm., 14, 103-112, (1983)

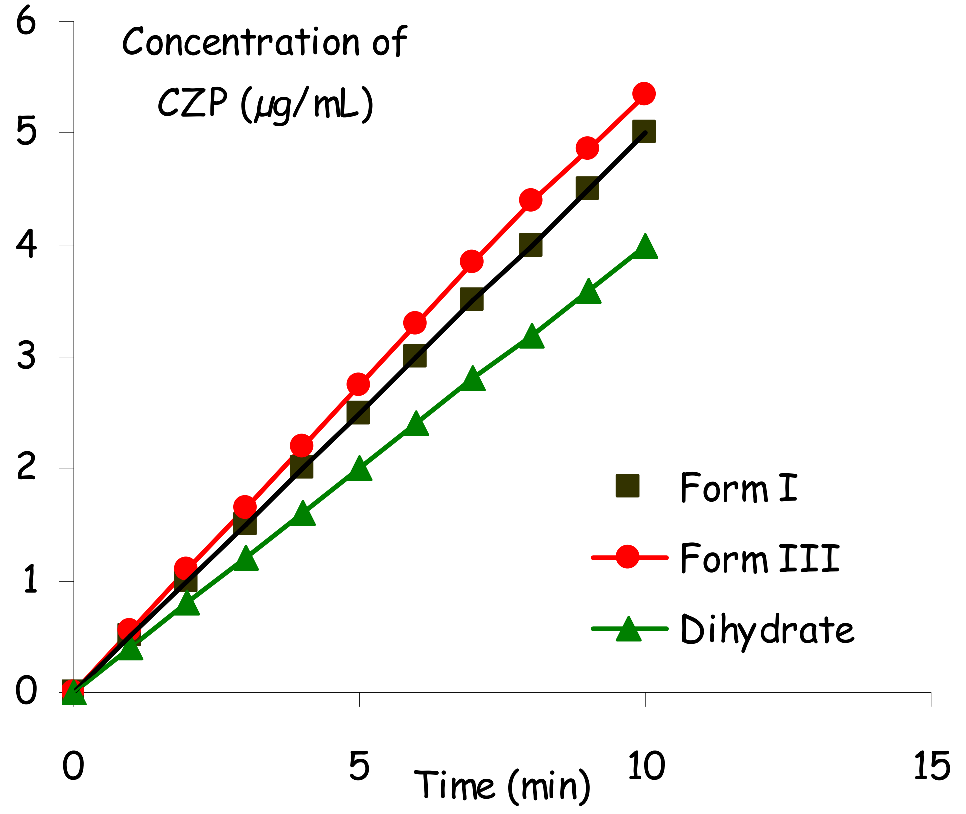
... forse imputabile alla possibilità di conversione della forma anidra in idrata....

Kinetics of transition of anhydrous carbamazepine to carbamazepine dihydrate in aqueous suspensions. W.W. Ling Young et al., J. Pharm. Sci., 80(5), 496-500, (1991)

Studio mirato in vitro e in vivo sul comportamento di forme cristalline diverse

Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. Y. Kobayashi et al., Int. J. Pharm., 193, 137-146, (2000)

Carbamazepina forme cristalline



	IDR [mg $cm^{-2}min^{-1}$]	Cs app [mg mL^{-1}]
forma I	61.8	460.2
forma III	67.4	501.9
diidrato	41.8	311.1

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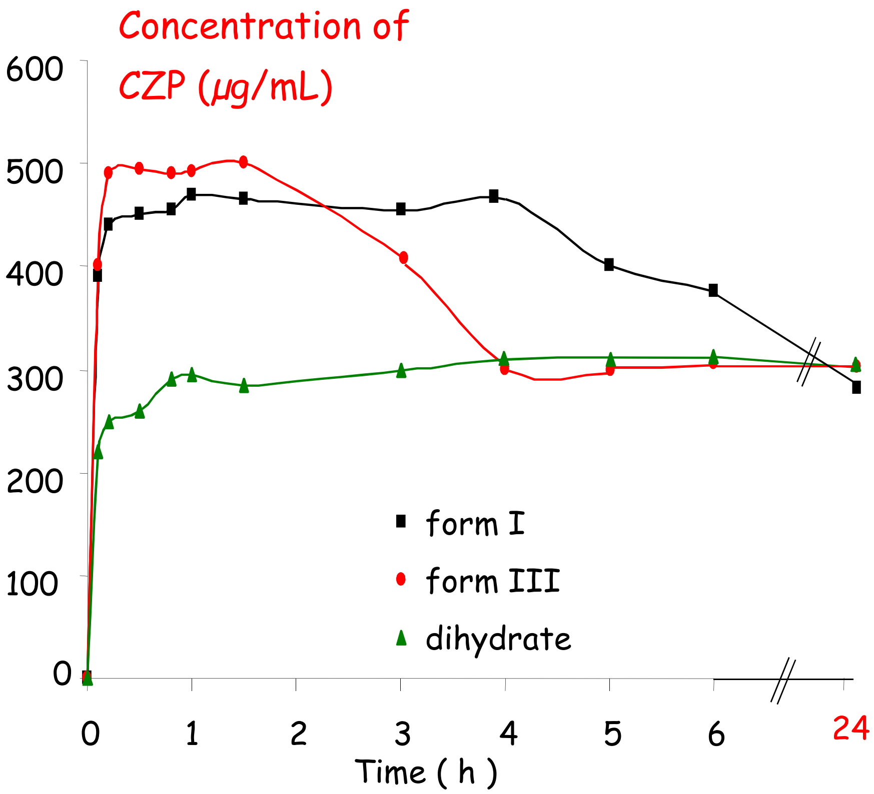
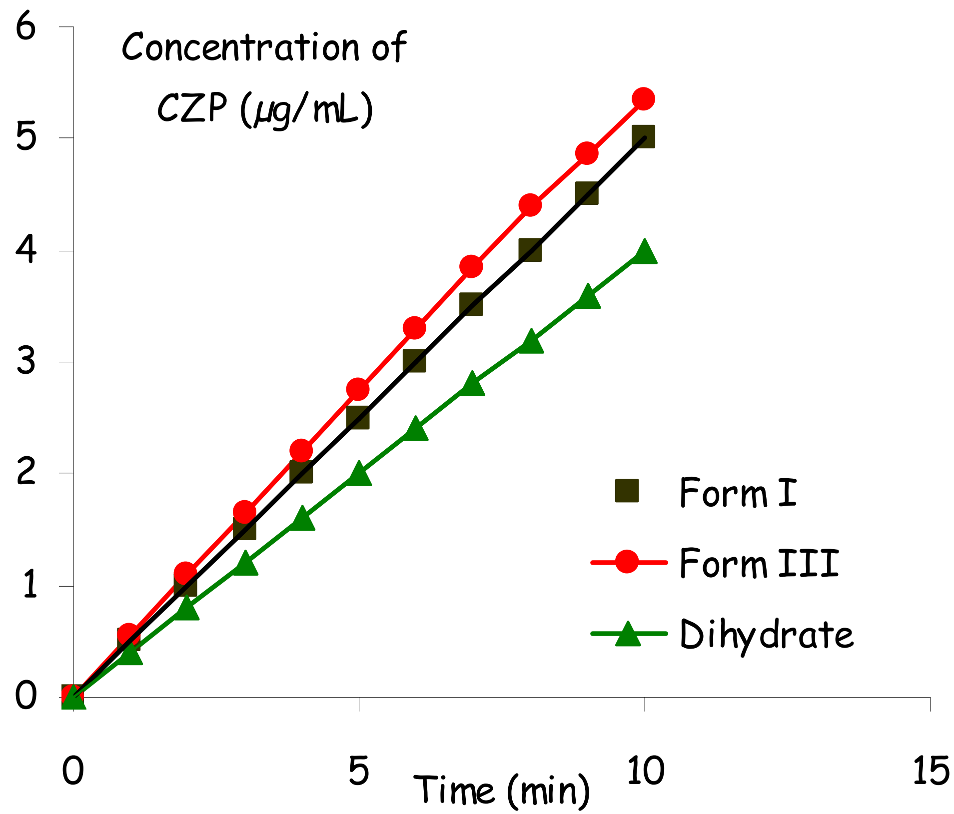
Carbamazepina forme cristalline





le due forme anidre convertono in quella idrata con diversa velocità

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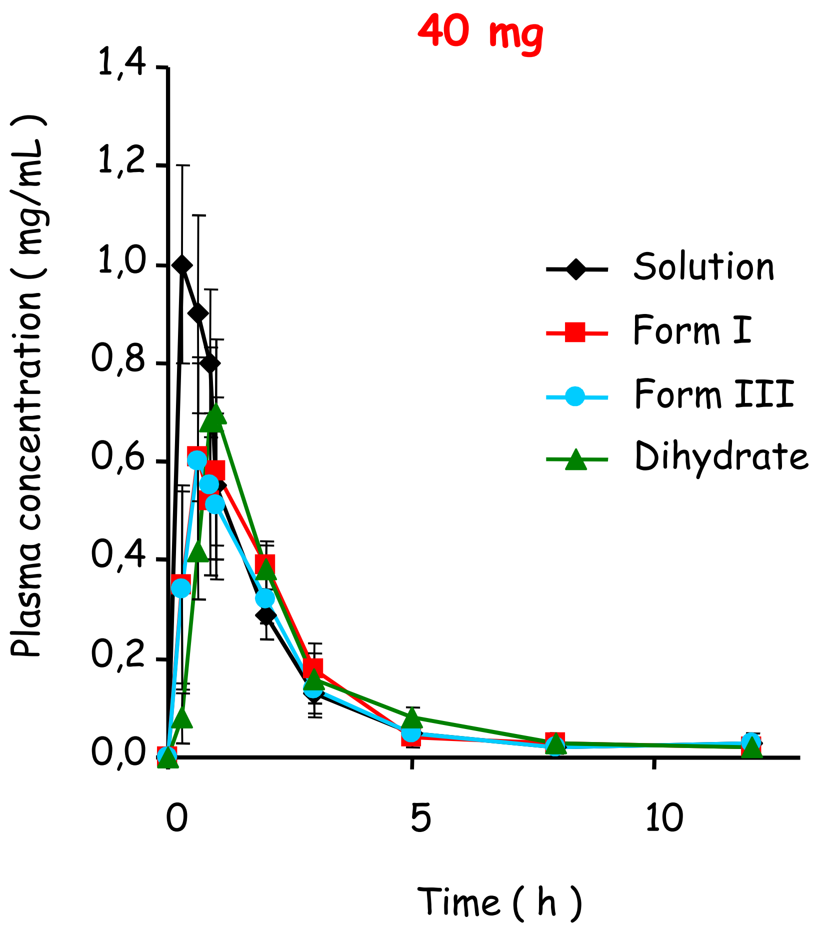

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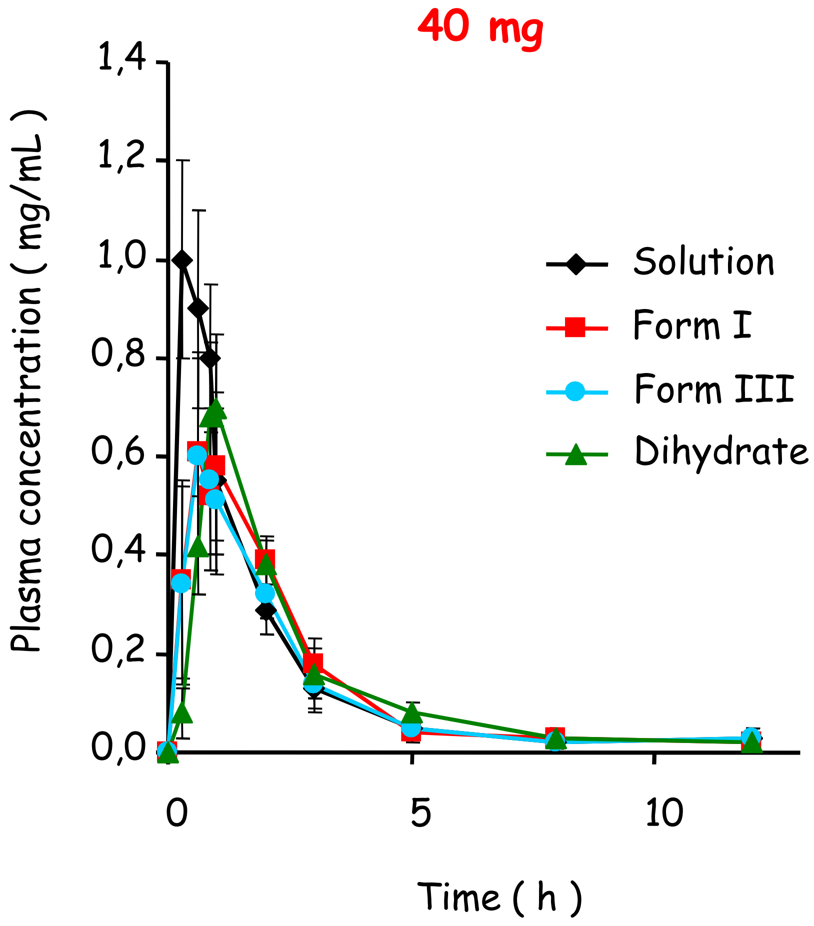

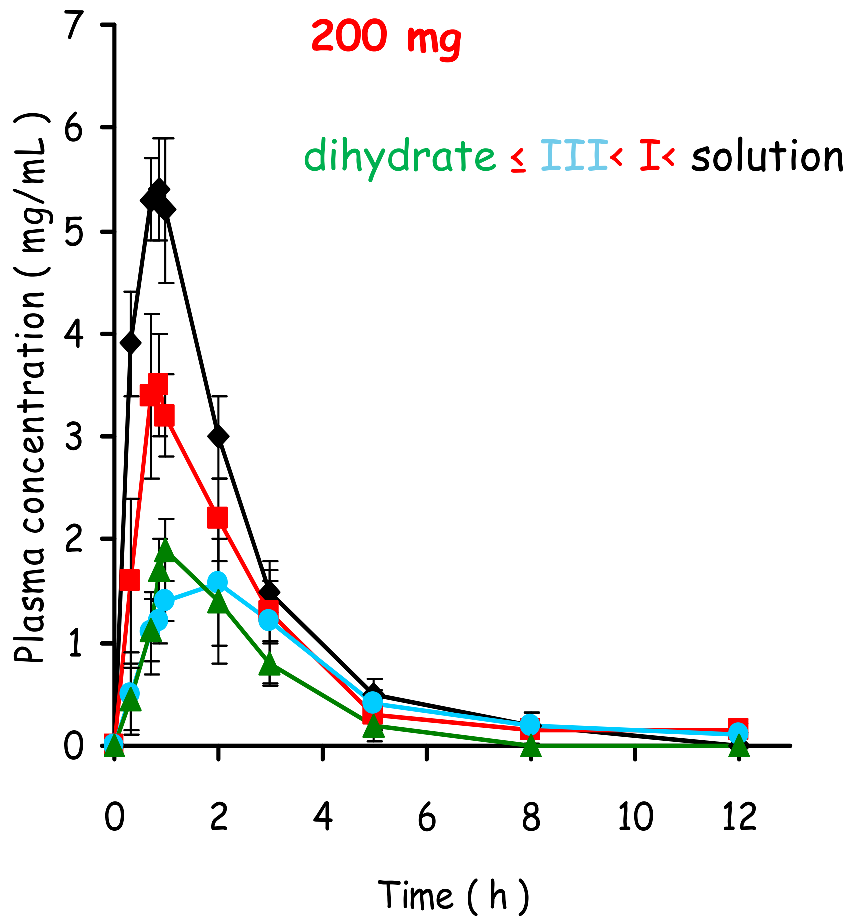

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presentazione di alcuni esempi di impatto tecnologico/produttivo

Caratteristiche fisiche API

PROCESSABILITA'

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- ✓ granulometria /morfologia particellare
- ✓ forma cristallina

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PROCESSABILITA'

Scorrevolezza	*mescolazione, ripartizione polveri*
Impaccamento/Volume apparente	*filtrazione, ripartizione polveri, stoccaggio*
Capacita' di compattazione	*produzione di compresse*
Velocità di sedimentazione	*allestimento di sospensioni (stabilità fisica)*
Solubilità apparente	*dissoluzione*
…………..	……………….

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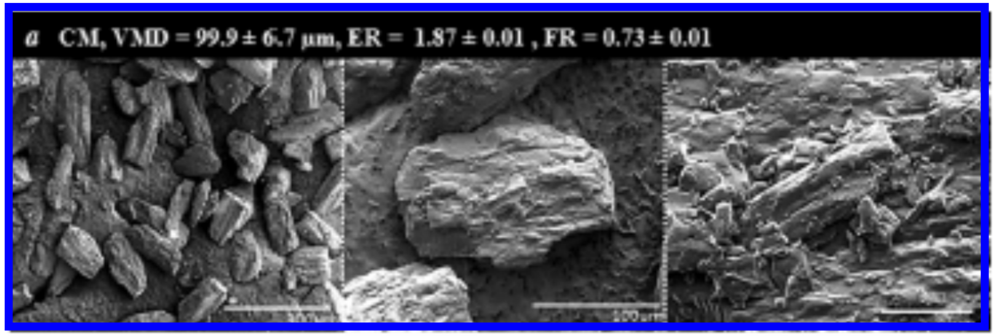
…………….	………………..

mannitolo a diversa granulometria per DPI

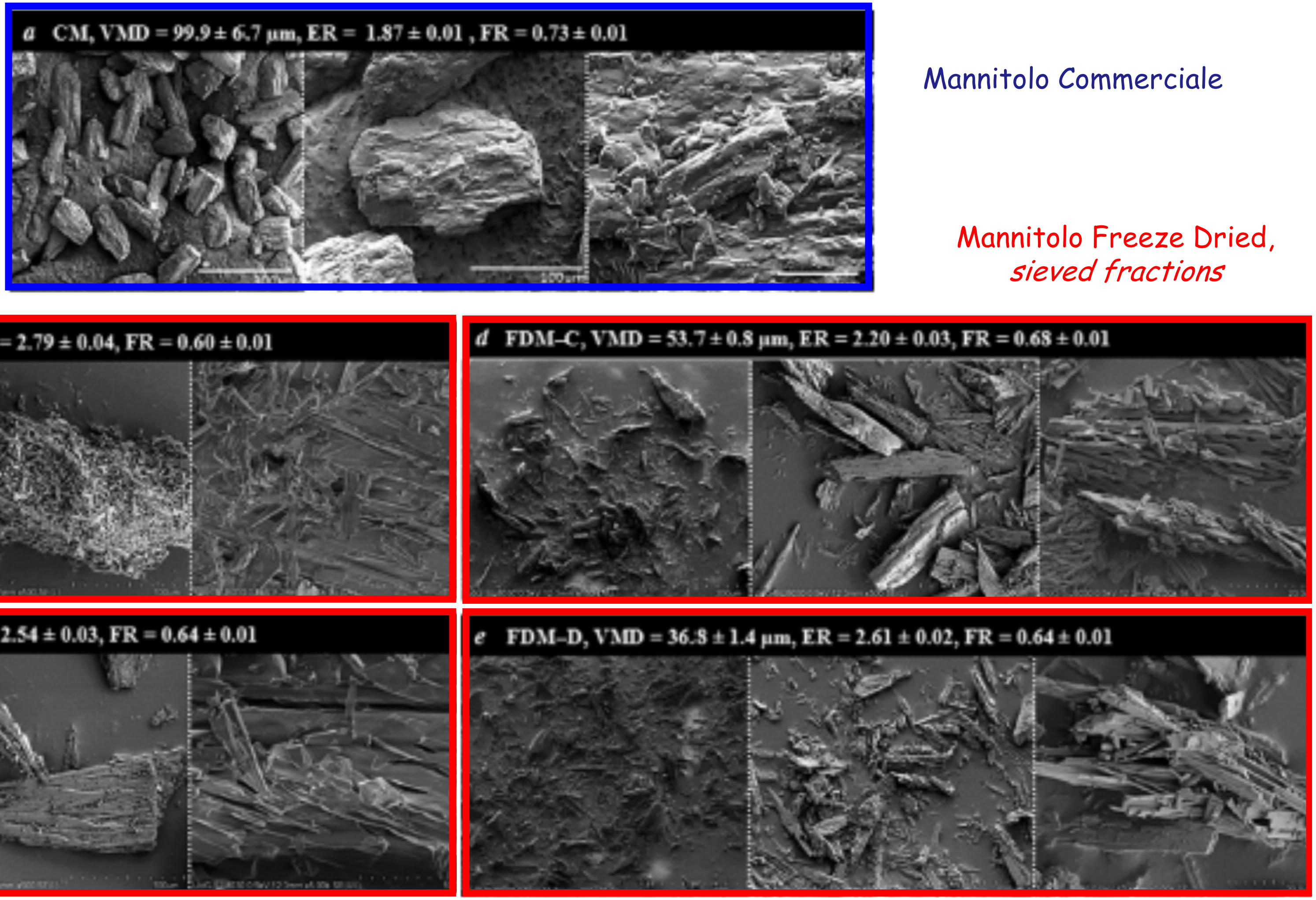


Mannitolo Commerciale

mannitolo a diversa granulometria per DPI

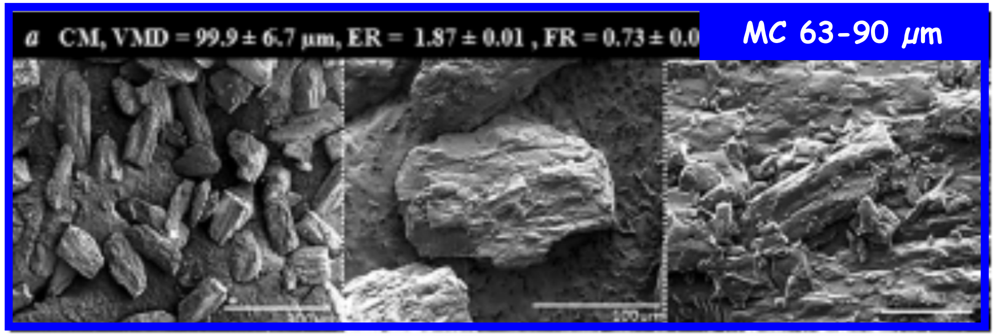
Mannitolo Commerciale

Mannitolo Freeze Dried, *sieved fractions*



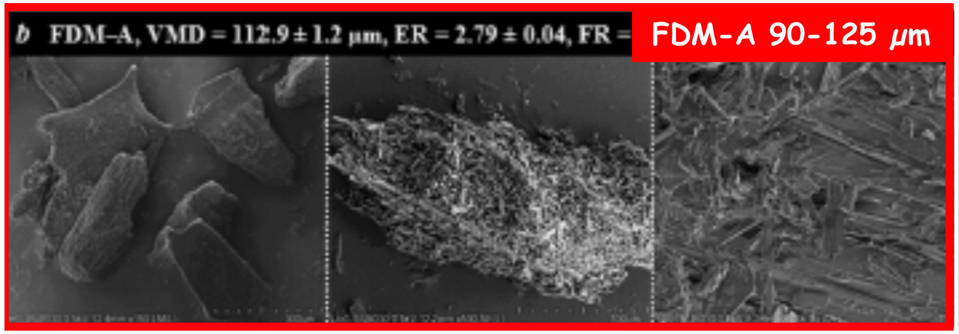
Dry powder inhalers: physicochemical and aerosolization properties of several size-fractions of a promising alternative carrier, freeze-dried mannitol. W. Kaialy et al., Eur. J. Pharm. Sci.,68(5), 56-67 (2015)

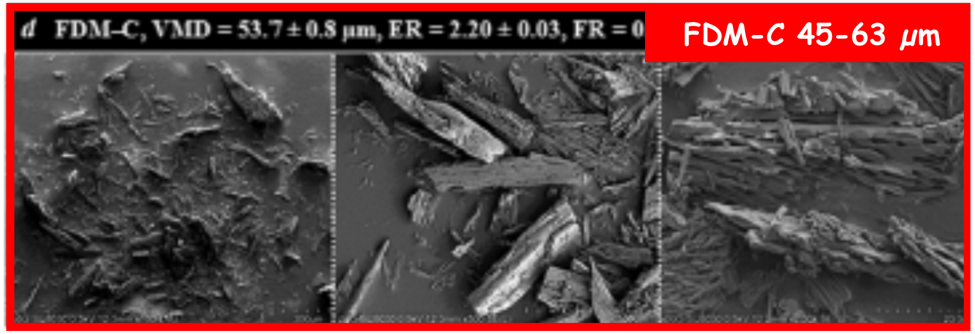
mannitolo a diversa granulometria per DPI

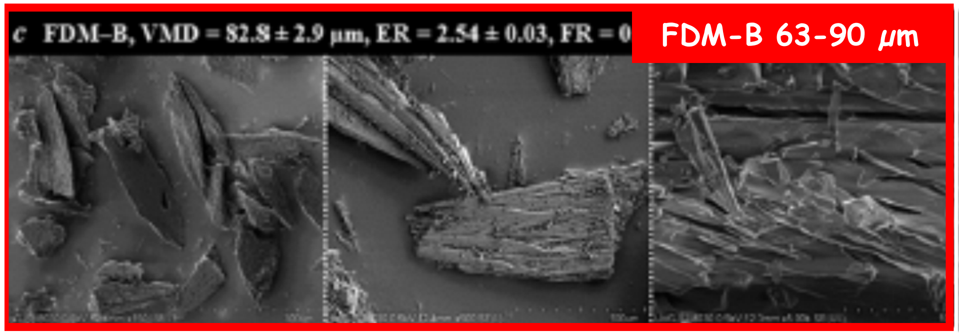


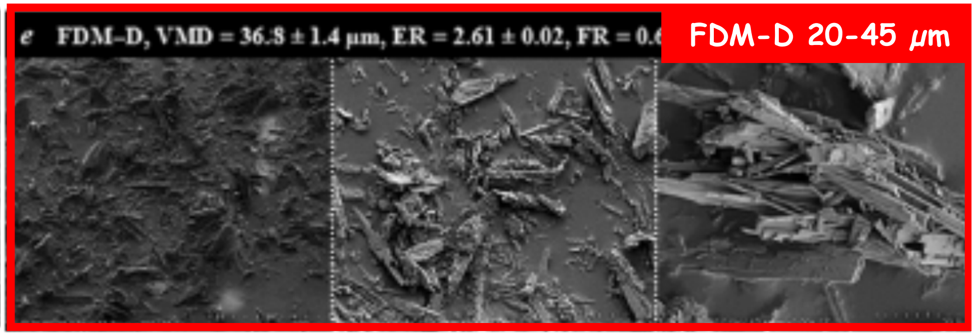
Mannitolo Commerciale

Mannitolo Freeze Dried
particle size: *A>B>C>D*









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Particle size

Physicochemical property	CM	Freeze-dried mannitol product			
		FDM-A	FDM-B	FDM-C	FDM-D
$D_{10\%}$ (µm)	54.9 ± 10.5	46.0 ± 3.6	27.1 ± 3.9	14.2 ± 0.2	10.4 ± 0.9
$D_{50\%}$ (µm)	99.9 ± 6.2	119.7 ± 1.4	82.9 ± 3.1	48.5 ± 0.3	33.5 ± 1.3
$D_{90\%}$ (µm)	145.8 ± 3.4	160.0 ± 0.8	136.7 ± 4.4	100.6 ± 2.6	67.7 ± 2.1
VMD (µm)	94.8 ± 4.6	113.0 ± 1.2	82.8 ± 2.9	53.7 ± 0.8	36.8 ± 1.5
$FPM_{<5µm}$ (%)	1.2 ± 1.1	1.4 ± 0.1	1.9 ± 0.3	3.3 ± 0.0	4.8 ± 0.5
Span	0.9 ± 0.1	1.0 ± 0.0	1.3 ± 0.1	1.8 ± 0.0	1.7 ± 0.1

Particle size

	CM	Freeze-dried mannitol product			
Physicochemical property		FDM-A	FDM-B	FDM-C	FDM-D
$D_{10\%}$ (µm)	54.9 ± 10.5	46.0 ± 3.6	27.1 ± 3.9	14.2 ± 0.2	10.4 ± 0.9
$D_{50\%}$ (µm)	99.9 ± 6.2	119.7 ± 1.4	82.9 ± 3.1	48.5 ± 0.3	33.5 ± 1.3
$D_{90\%}$ (µm)	145.8 ± 3.4	160.0 ± 0.8	136.7 ± 4.4	100.6 ± 2.6	67.7 ± 2.1
VMD (µm)	94.8 ± 4.6	113.0 ± 1.2	82.8 ± 2.9	53.7 ± 0.8	36.8 ± 1.5
$FPM_{<5\mu m}$ (%)	1.2 ± 1.1	1.4 ± 0.1	1.9 ± 0.3	3.3 ± 0.0	4.8 ± 0.5
Span	0.9 ± 0.1	1.0 ± 0.0	1.3 ± 0.1	1.8 ± 0.0	1.7 ± 0.1

Particle size

Physicochemical property	CM	Freeze-dried mannitol product			
		FDM-A	FDM-B	FDM-C	FDM-D
$D_{10\%}$ (µm)	54.9 ± 10.5	46.0 ± 3.6	27.1 ± 3.9	14.2 ± 0.2	10.4 ± 0.9
$D_{50\%}$ (µm)	99.9 ± 6.2	119.7 ± 1.4	82.9 ± 3.1	48.5 ± 0.3	33.5 ± 1.3
$D_{90\%}$ (µm)	145.8 ± 3.4	160.0 ± 0.8	136.7 ± 4.4	100.6 ± 2.6	67.7 ± 2.1
VMD (µm)	94.8 ± 4.6	113.0 ± 1.2	82.8 ± 2.9	53.7 ± 0.8	36.8 ± 1.5
$FPM_{<5µm}$ (%)	1.2 ± 1.1	1.4 ± 0.1	1.9 ± 0.3	3.3 ± 0.0	4.8 ± 0.5
Span	0.9 ± 0.1	1.0 ± 0.0	1.3 ± 0.1	1.8 ± 0.0	1.7 ± 0.1

Bulk properties

Physicochemical property	CM	Freeze-dried mannitol product			
		FDM-A	FDM-B	FDM-C	FDM-D
Bulk density (g/cm^3)	0.54 ± 0.01	0.24 ± 0.01	0.19 ± 0.01	0.08 ± 0.00	0.09 ± 0.00
Tap density (g/cm^3)	0.63 ± 0.01	0.31 ± 0.02	0.26 ± 0.01	0.11 ± 0.00	0.12 ± 0.00
Porosity (%)	63.9 ± 0.9	84.3 ± 0.5	86.9 ± 0.8	94.6 ± 0.5	93.7 ± 0.4
CI (%)	17.7 ± 1.7	17.7 ± 1.4	24.5 ± 3.4	26.0 ± 0.8	27.5 ± 1.7
Flow	good	good	poor	poor	poor

Particle size

Physicochemical property	CM	Freeze-dried mannitol product			
		FDM-A	FDM-B	FDM-C	FDM-D
$D_{10\%}$ (µm)	54.9 ± 10.5	46.0 ± 3.6	27.1 ± 3.9	14.2 ± 0.2	10.4 ± 0.9
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VMD (µm)	94.8 ± 4.6	113.0 ± 1.2	82.8 ± 2.9	53.7 ± 0.8	36.8 ± 1.5
$FPM_{<5\mu m}$ (%)	1.2 ± 1.1	1.4 ± 0.1	1.9 ± 0.3	3.3 ± 0.0	4.8 ± 0.5
Span	0.9 ± 0.1	1.0 ± 0.0	1.3 ± 0.1	1.8 ± 0.0	1.7 ± 0.1

Bulk properties

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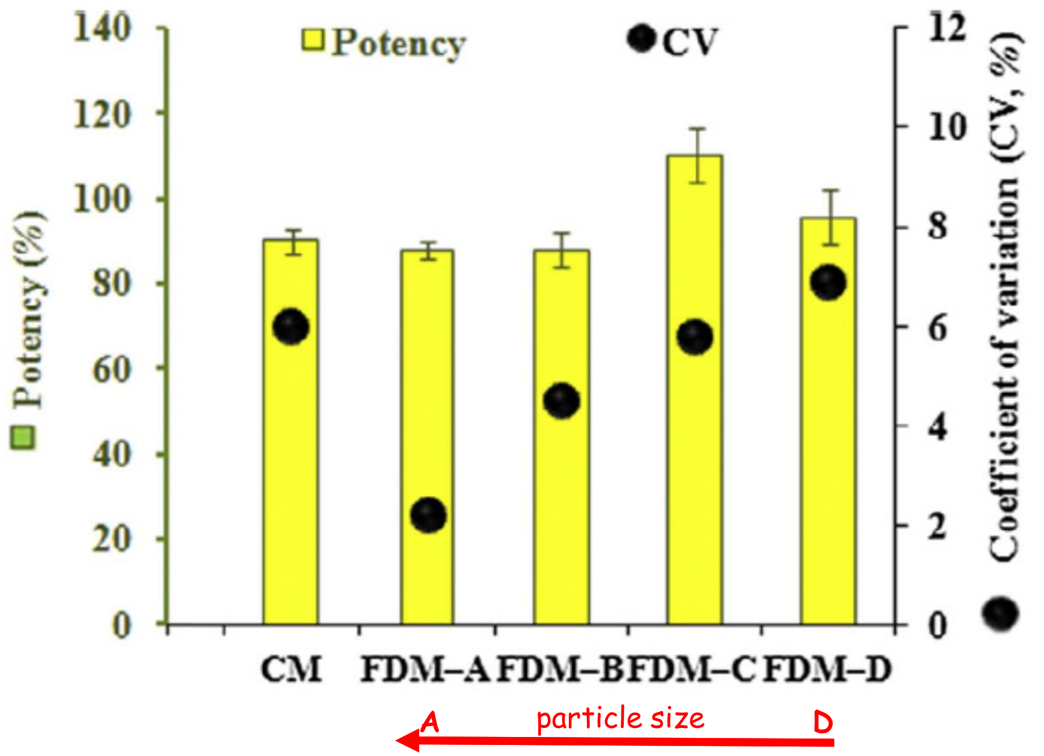
CI (%)	17.7 ± 1.7	17.7 ± 1.4	24.5 ± 3.4	26.0 ± 0.8	27.5 ± 1.7
Flow	good	good	poor	poor	poor

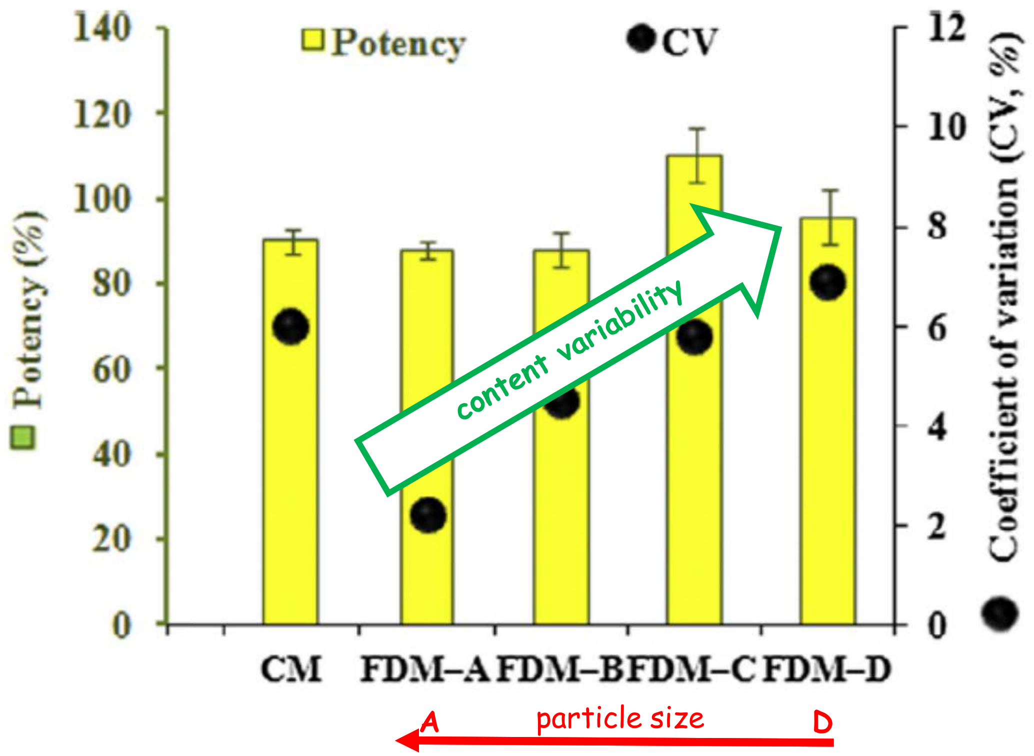
blending with API

Potency and homogeneity of formulations



% potency (□) and % coefficient of variation (●, CV) for dry powder inhaler (DPI) formulations composed of salbutamol sulphat eblended with CM and freeze-dried mannitol products sieved to different size fractions, i.e. FDA (90-125 µm), FDB (63-90 µm), FDC (45-63 µm), and FDD (20-45 µm)

Potency and homogeneity of formulations



% potency (□) and % coefficient of variation (●, CV) for dry powder inhaler (DPI) formulations composed of salbutamol sulphate blended with CM and freeze-dried mannitol products sieved to different size fractions, i.e. FDA (90-125 µm), FDB (63-90 µm), FDC (45-63 µm), and FDD (20-45 µm)

Caratteristiche fisiche API

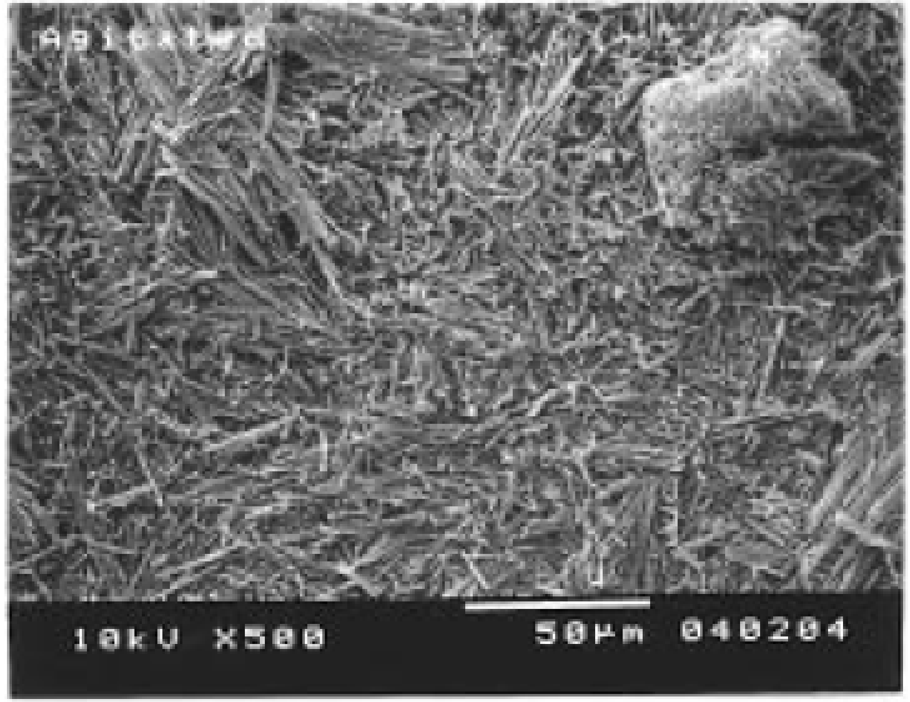
✓ granulometria /morfologia particellare

PROCESSABILITA'

Scorrevolezza	*mescolazione, ripartizione polveri*
Impaccamento/Volume apparente	*filtrazione, ripartizione polveri, stoccaggio*
Capacita' di compattazione	*produzione di compresse*
Velocità di sedimentazione	*allestimento di sospensioni (stabilità fisica)*
Solubilità apparente	*dissoluzione*
…………..	………………

Aspartame: morfologia dei cristalli

cristalli piccoli,
igroscopici con scarsa
resistenza meccanica



needle-like crystals

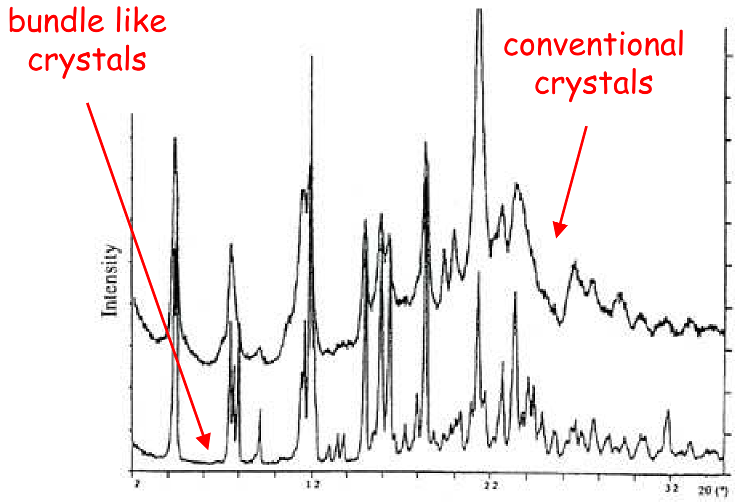
problemi nelle operazioni di **filtrazione** ed essiccamento e, in generale, nella lavorazione di questo materiale

Characterization of Aspartame Crystals
A. Kishishita et al., Ind.Eng.Chem. Res.,38(5), 2166-2170 (1999)

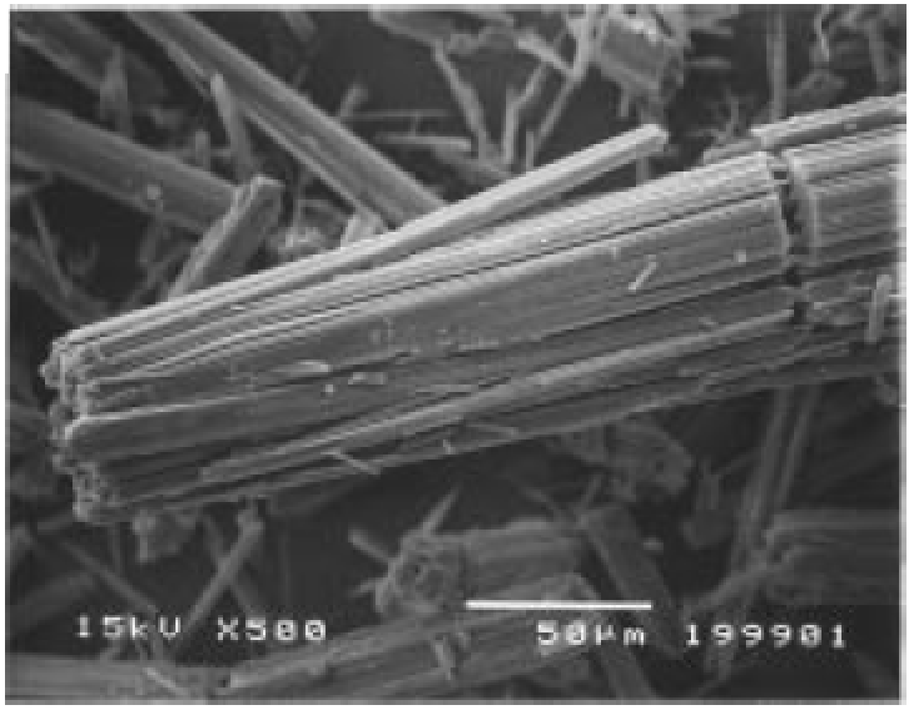
Aspartame: morfologia dei cristalli

nuovo metodo di cristallizazione per raffreddamento di una soluzione acquosa SENZA agitazione (Brevetto Ajimoto)

stessa forma cristallina, diversa morfologia



Vantaggi: maggior grado di cristallinità, densità apparente, resistenza meccanica, minor contenuto di umdità



bundle-like crystals

Caratteristiche fisiche API

- ✓ granulometria /morfologia particellare
- ✓ forma cristallina

PROCESSABILITA'

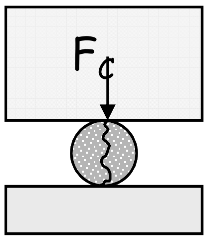
Scorrevolezza	*mescolazione, ripartizione polveri*
Impaccamento/Volume apparente	*filtrazione, ripartizione polveri, stoccaggio*
Capacita' di compattazione	*produzione di compresse*
Velocità di sedimentazione	*allestimento di sospensioni (stabilità fisica)*
Solubilità apparente	*dissoluzione*
…………..	………………

Forma fisica & capacità di compattazione

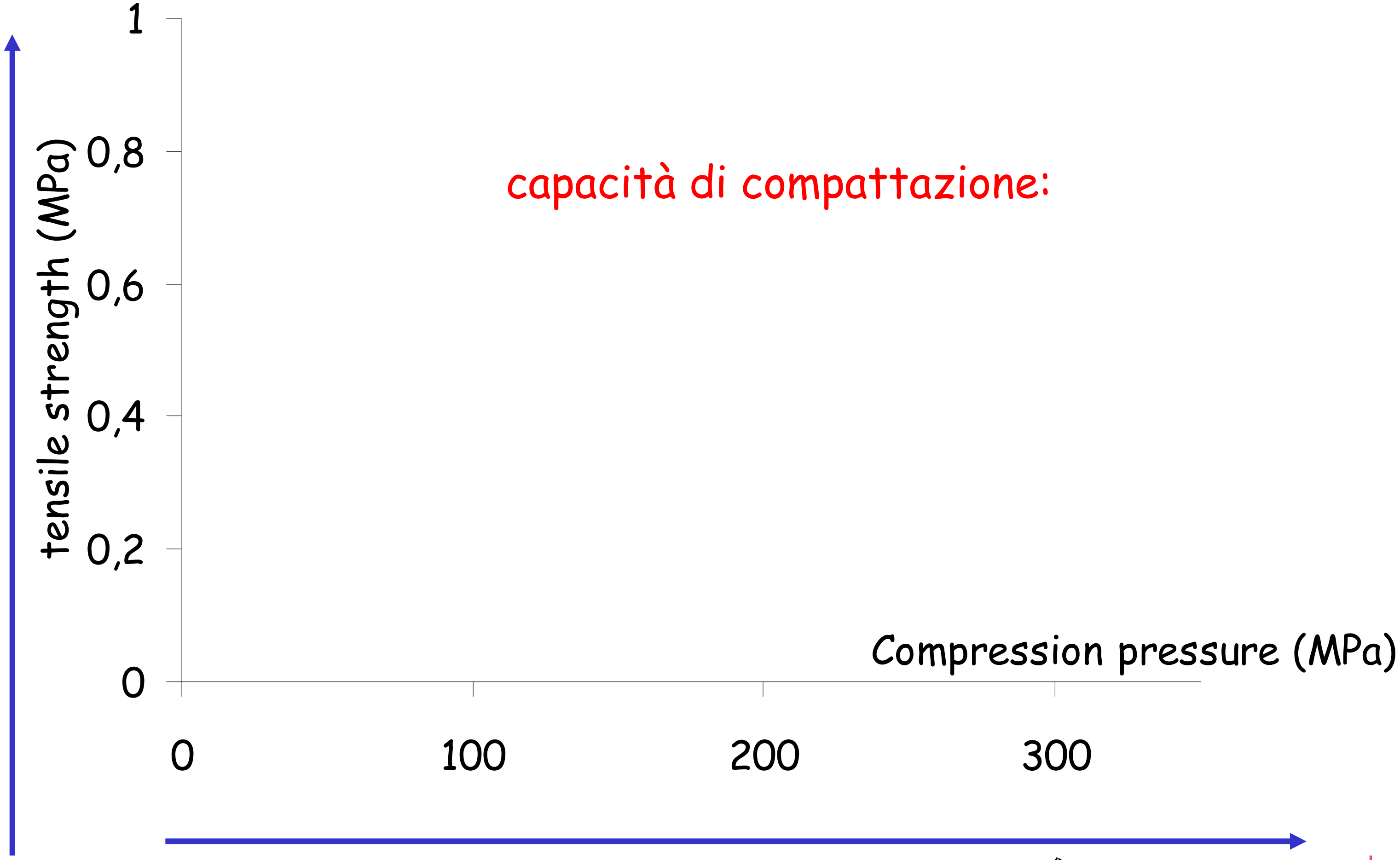
capacità di compattazione:

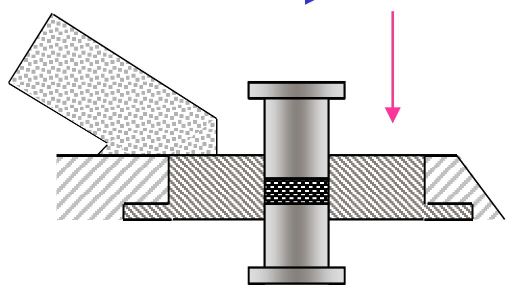
capacità di dar luogo a un compatto coerente (resistenza meccanica) per effetto dell'applicazione di una forza

Forma fisica & capacità di compattazione

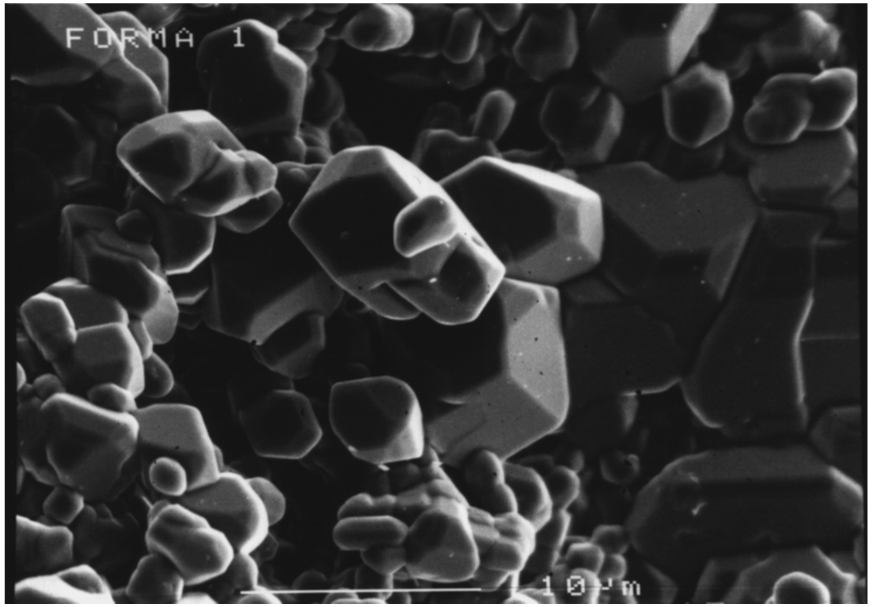


capacità di compattazione:

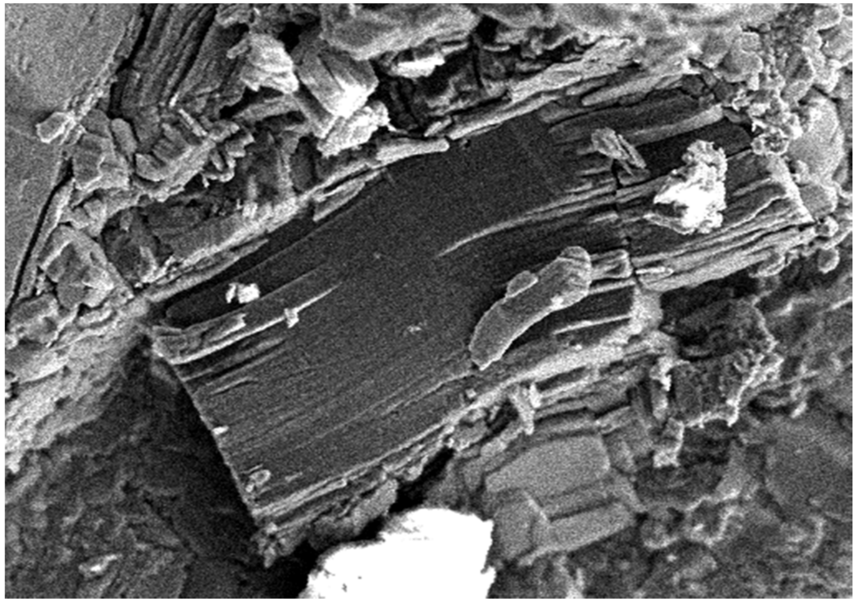




Paracetamolo: forme polimorfe



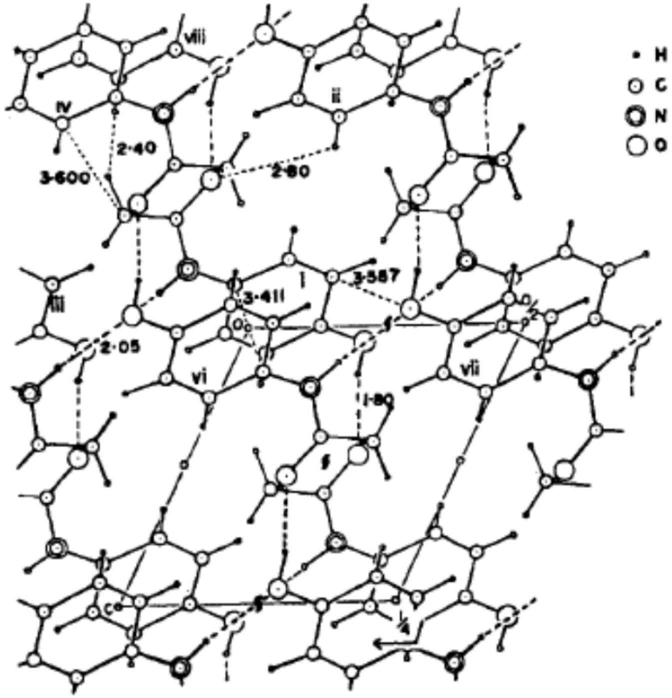
forma I, monocliana



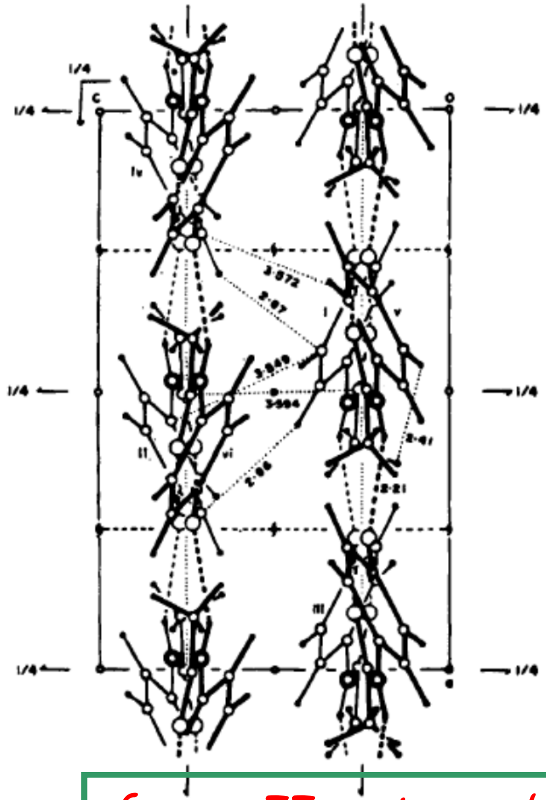
forma II, ortorombica

Adattato da: Compression behavior of orthorhombic paracetamol
E. Joiris et al., Pharm. Res.,15(7); 1121-1130, (1998)

Paracetamolo: forme polimorfe

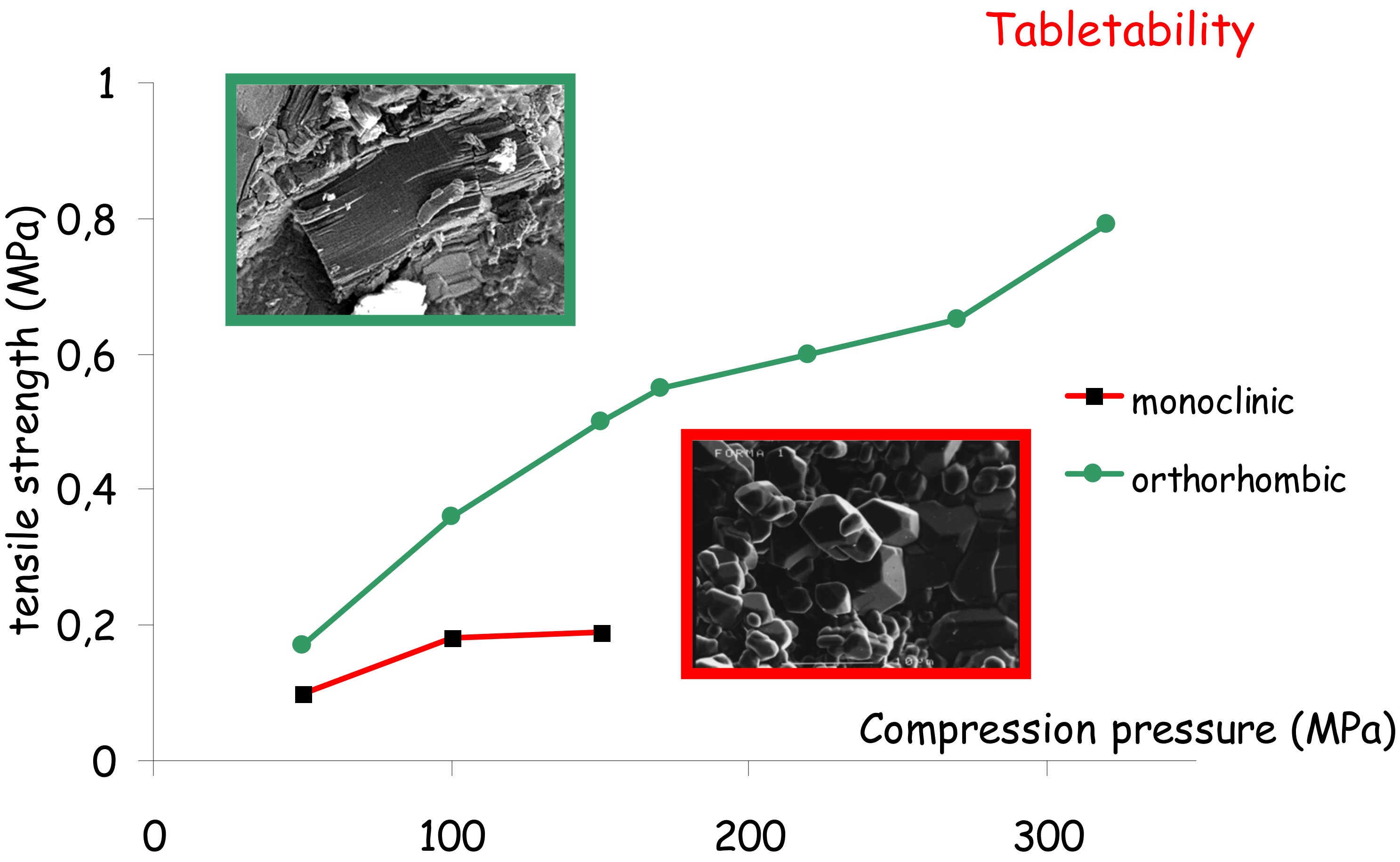


forma I, monocliana



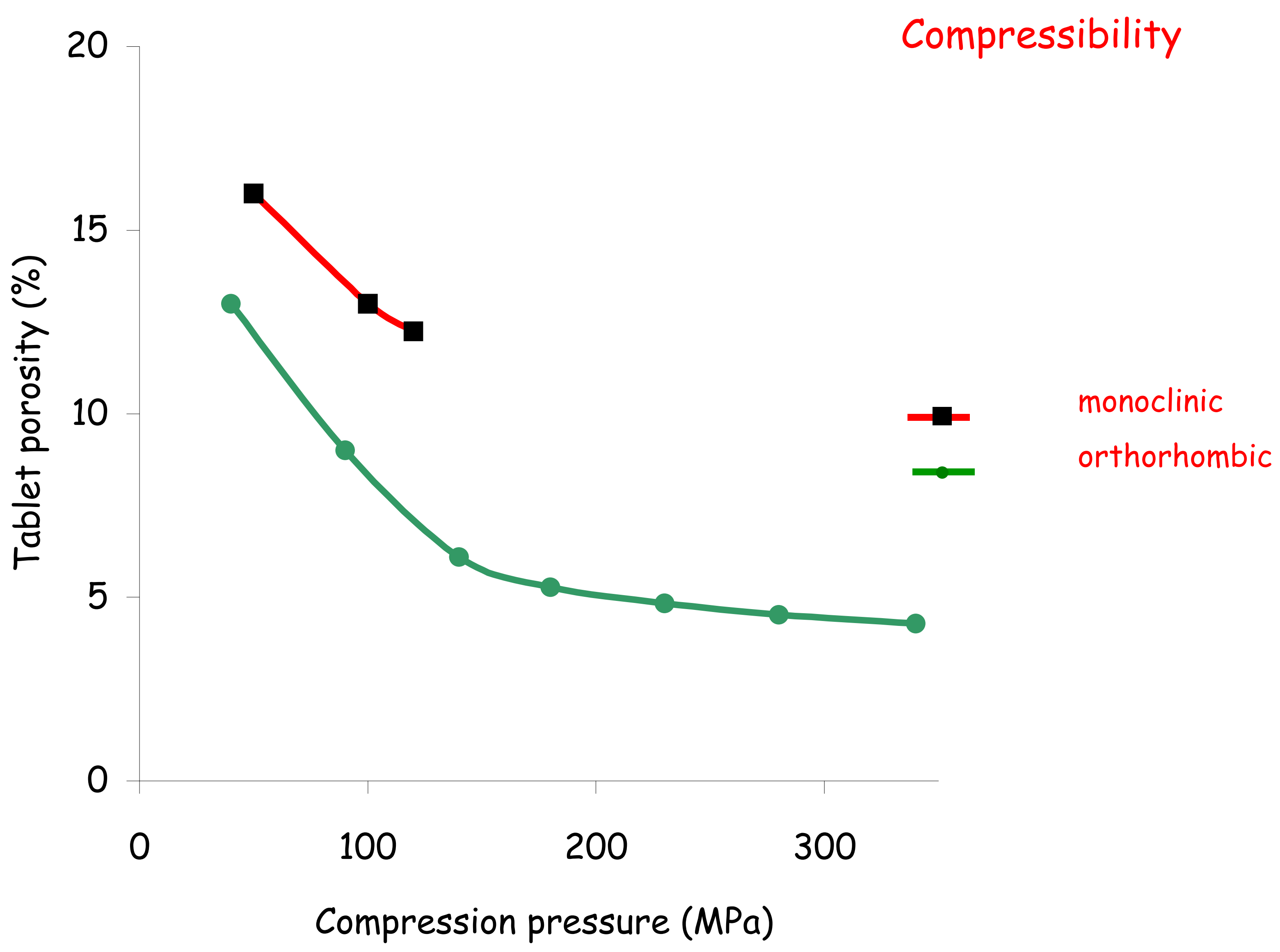
forma II, ortorombica

Projection, viewed along the *b* axis, of the crystal structure of monoclinic (left) and orthorhombic (right) paracetamol. Broken lines show hydrogen bonds, dotted lines intermolecular contacts.



Le differenze di comportamento meccanico e coesivo delle particelle dipendono dal crystal packing a livello molecolare.

Adattato da: Compression behavior of orthorhombic paracetamol
E. Joiris et al., Pharm. Res.,15(7); 1121-1130, (1998)

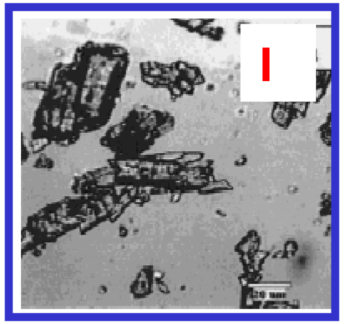


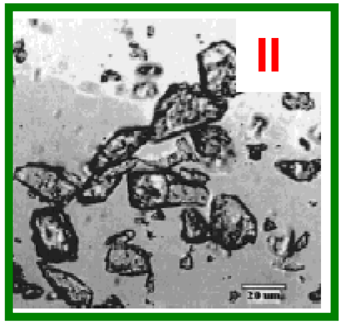
Adattato da: Compression behavior of orthorhombic paracetamol
E. Joiris et al., Pharm. Res.,15(7); 1121-1130, (1998)

Sulfamerazina

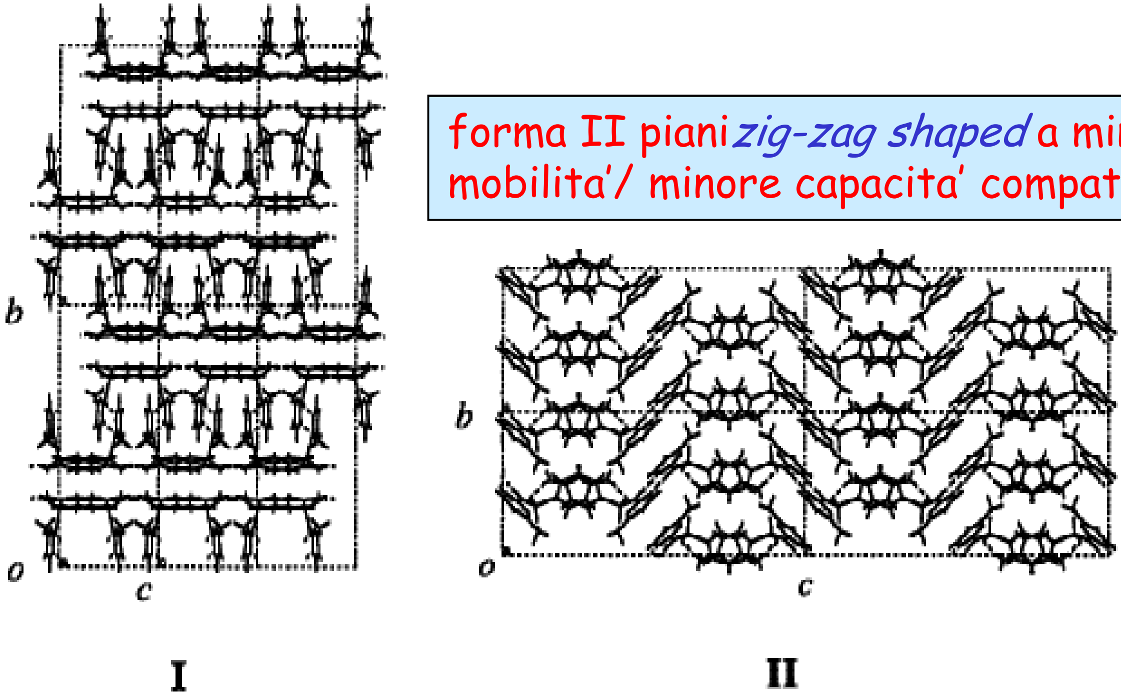
Influence of crystal structure on the tableting properties of sulfamerazine polymorphs
C.Sun and D.J.W.Grant, Pharm. Res.,18(3), 274-280, (2001)

struttura forma I *slip planes* paralleli piu' mobili





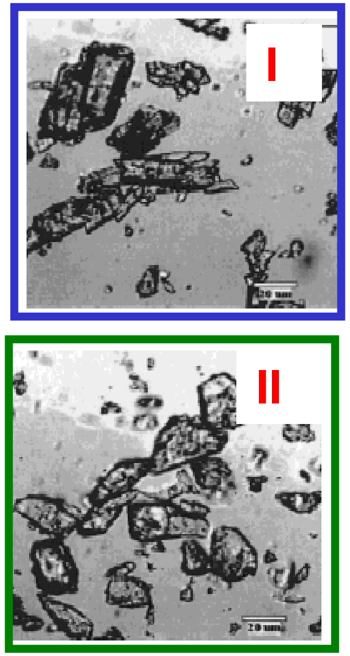
forma II piani *zig-zag shaped* a minore mobilita'/ minore capacita' compattazione

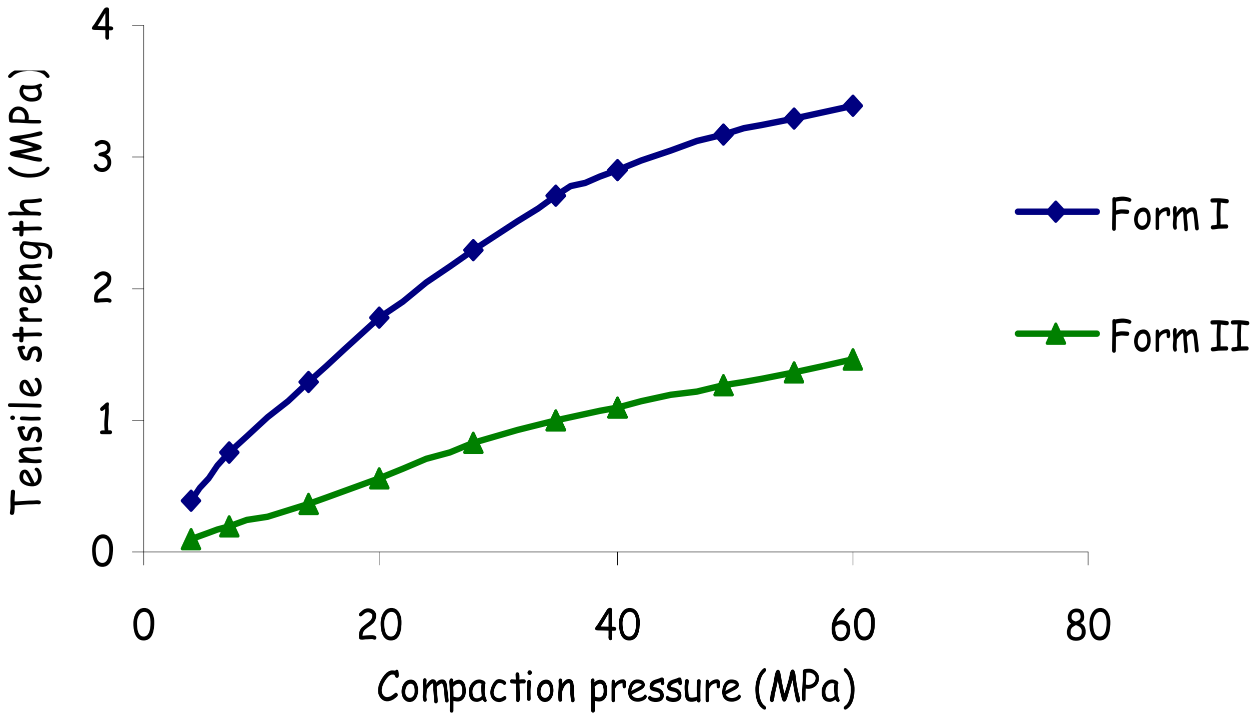


The crystal structures of sulfamerazine polymorphs looking into the *a* axis; left polymorph **I** in which the slip planes are parallel to the *ac* plane of the unit cell; right, polymorph **II** in which no slip plane is observed. The hydrogen bonds are indicated by dotted lines between molecules

Sulfamerazina

Influence of crystal structure on the tableting properties of sulfamerazine polymorphs
C.Sun and D.J.W.Grant, Pharm. Res.,18(3), 274-280, (2001)





Influence of crystal structure on the tableting properties of sulfamerazine polymorphs
C.Sun and D.J.W.Grant. Pharm. Res.,18(3), 274-280, (2001)

Influence of crystal shape on the tableting properties of L-lysine monohydrochloride dihydrate
C.Sun and D.J.W.Grant. J. Pharm. Sci.,90(5), 569-579, (2001)

Improved tableting properties of p-Hydroxybenzoic acid by water of crystallization: a molecular insight
C.Sun and D.J.W.Grant. Pharm. Res.,21(2), 382-386, (2004)

Effect of initial particle size on the tableting properties of L-lysine monohydrochloride dihydrate powder
C.Sun and D.J.W.Grant. Int. J. Pharm.,215, 221-228, (2001)

Caratteristiche fisiche API

- ✓ morfologia particellare

PROCESSABILITA'

Scorrevolezza	*mescolazione, ripartizione polveri*
Impaccamento/Volume apparente	*filtrazione, ripartizione polveri, stoccaggio*
Capacita' di compattazione	*produzione di compresse*
Velocità di sedimentazione	*allestimento di sospensioni* *(stabilità fisica)*
Solubilità apparente	*dissoluzione*
…………..	………………

Habitus & stabilità

Trimetoprim sospensione

(Crystal I) thin rods

(Crystal II) thick rods

(Crystal III) polyhedra

(Crystal IV) cubes

(PD, commercial product)

Da: Influence of Crystal Habit on Trimethoprim Suspension Formulation. A.K. Tiwary and G.M. Panpalia, Pharma. Res.; 16 (2); 261-265 (1998)

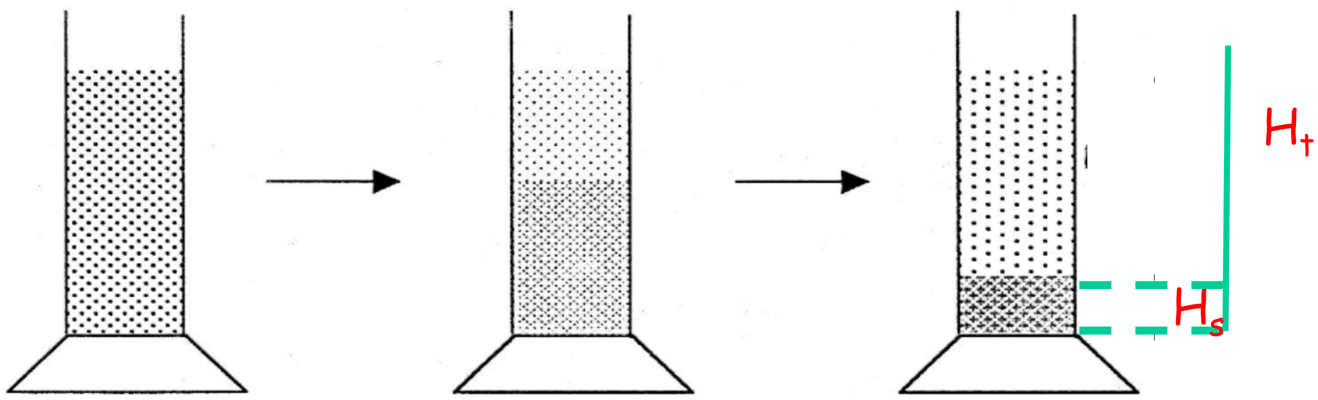
Trimetoprim sospensione

Crystal n°	**cosolvent**	**Crystallization conditions Co-solvent:water** ratio	temp	cooling	**Crystal habit**
I	DMF	1:10	RT-RT	RT	thin rods
II	PEG200	1:5	RT-RT	RT	thick rods
III	DMF	1:10	70-70	RT	polyhedra
IV	DMF	1:20	RT-70	RT	cubes
PD	-	-	-	-	irregulars

Sospendente: PEG400, HPMC 2% w/v acqua distillata

Stability testing (45°C, 60 days)

Sedimentation volume (Hs/Hi)



Stability testing (45°C, 60 days)

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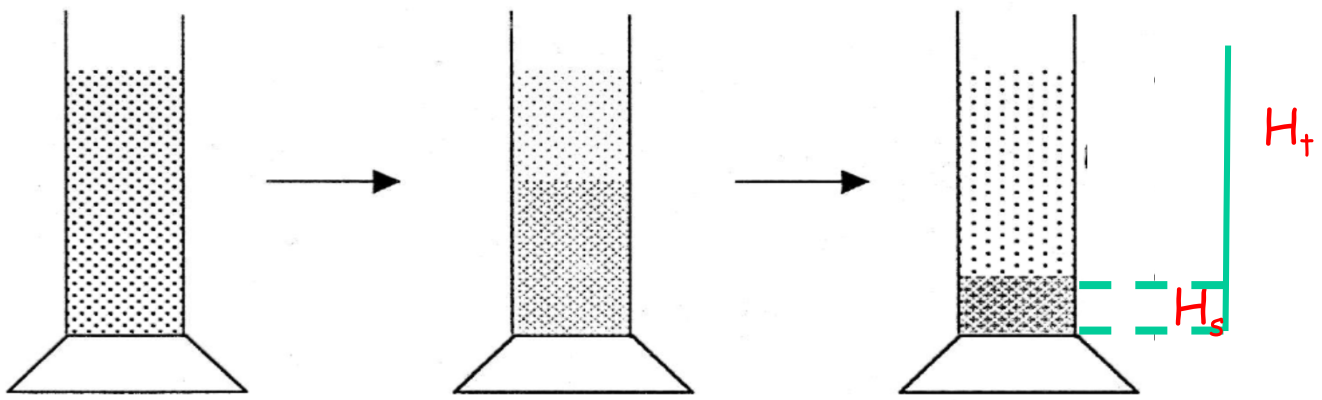
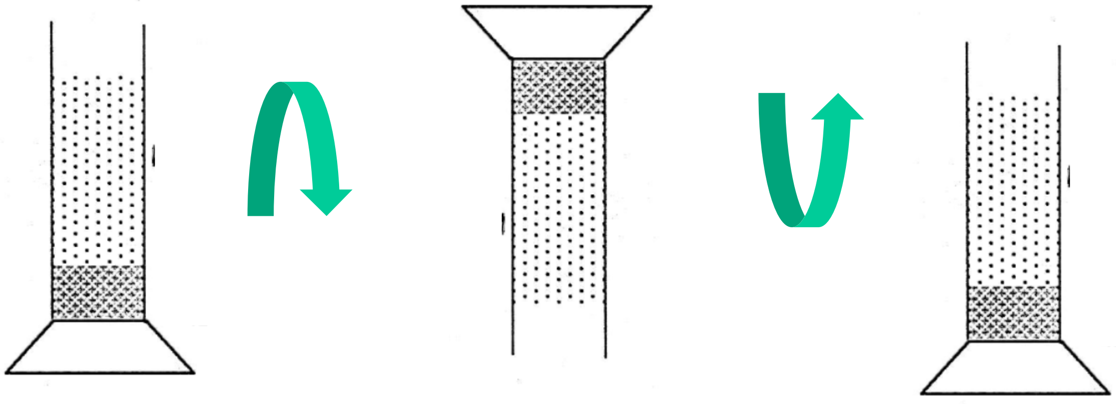
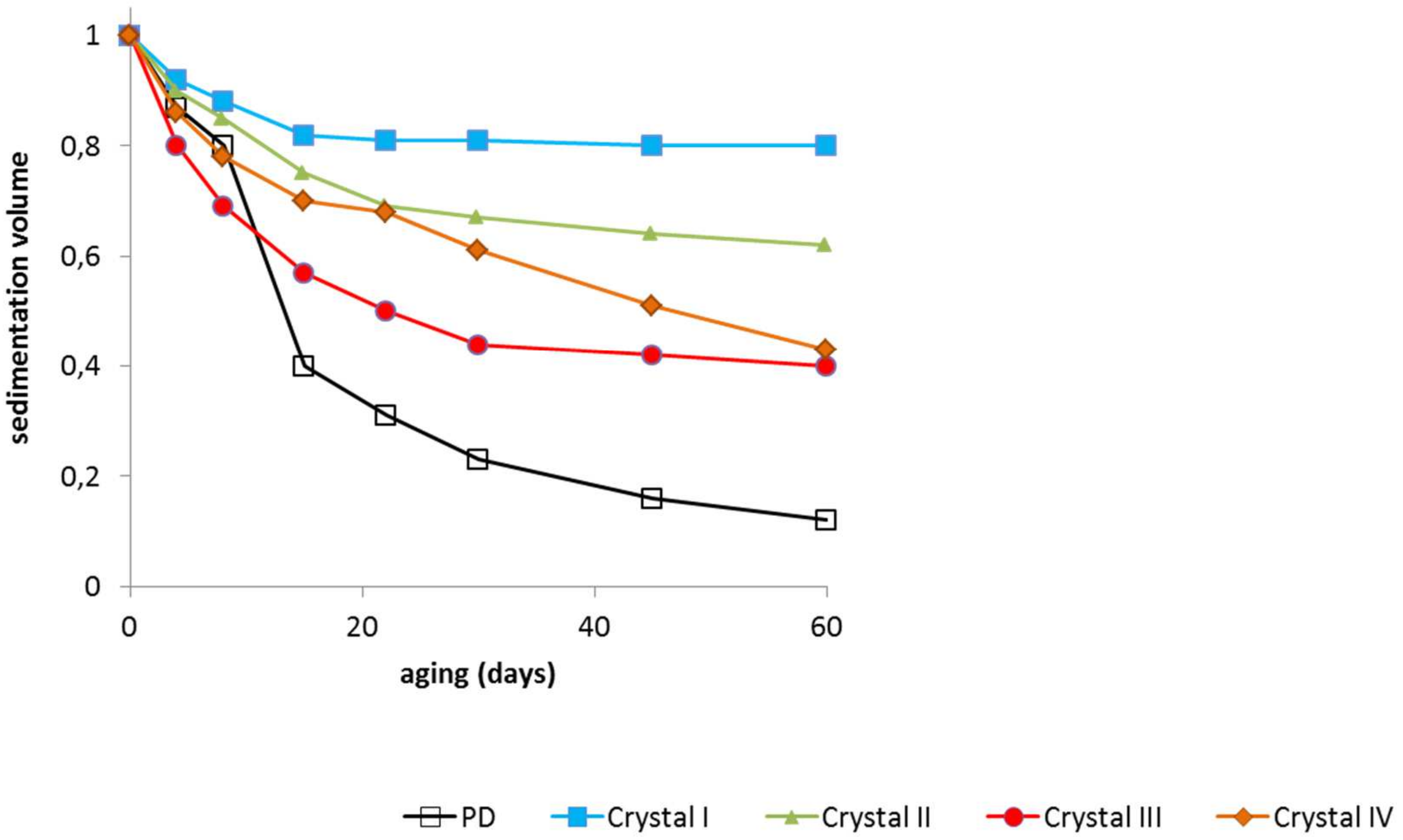


Redispersibility behaviour (n° of turns to achieve homogeneity)

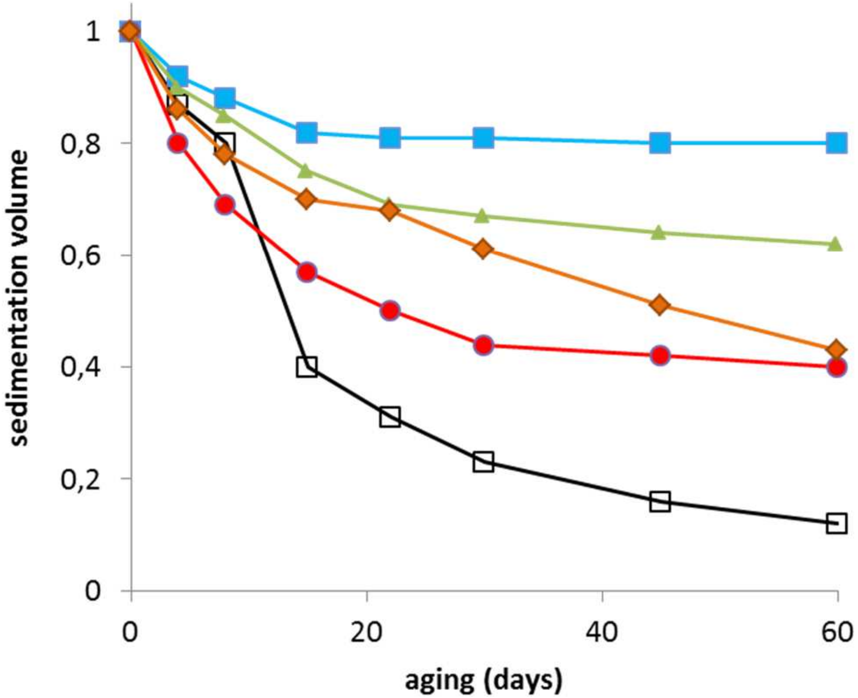


Sedimentation volume

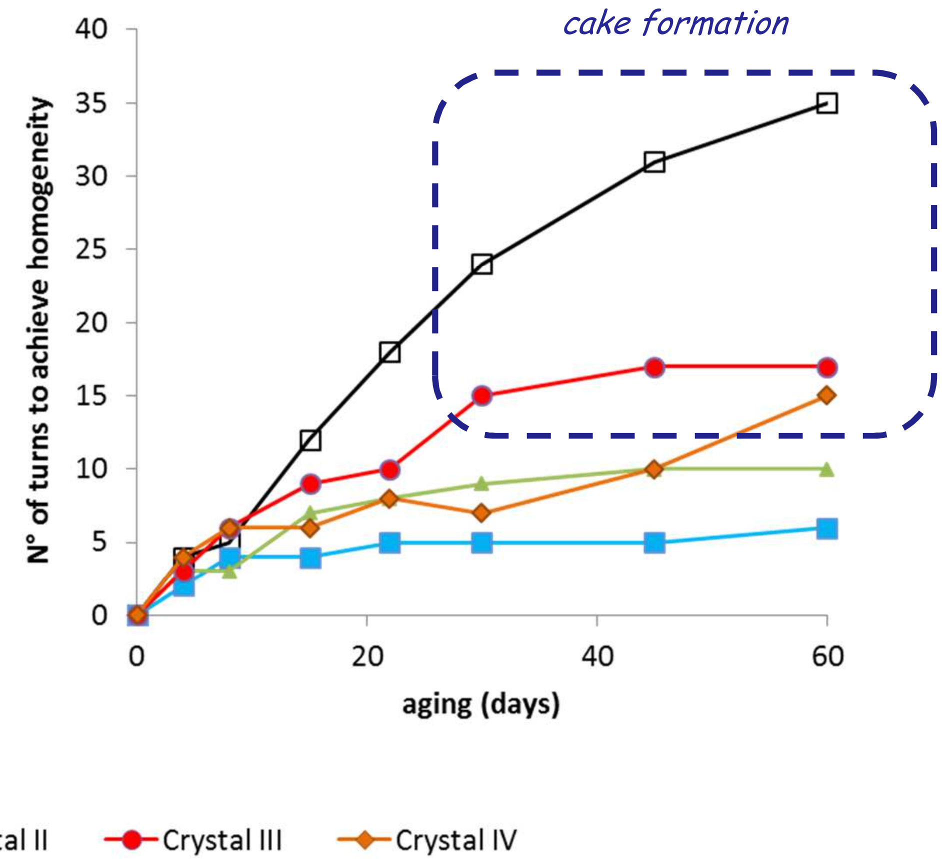


Redrawn from:A.K. Tiwary and G.M. Panpalia, Pharma. Res.; 16 (2); 261-265 (1998)

Sedimentation volume



Redispersibility behaviour



Redrawn from:A.K. Tiwary and G.M. Panpalia, Pharma. Res.; 16 (2); 261-265 (1998)

Caratteristiche fisiche API

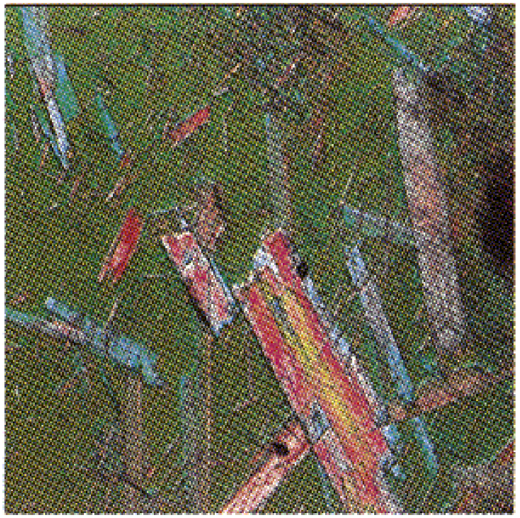
- ✓ forma cristallina

PROCESSABILITA'

Scorrevolezza	*mescolazione, ripartizione polveri*
Impaccamento/Volume apparente	*filtrazione, ripartizione polveri, stoccaggio*
Capacita' di compattazione	*produzione di compresse*
Velocità di sedimentazione	*allestimento di sospensioni (stabilità fisica)*
Solubilità apparente	*dissoluzione*
……………	………………

NORVIR [Ritonavir]

Forma I



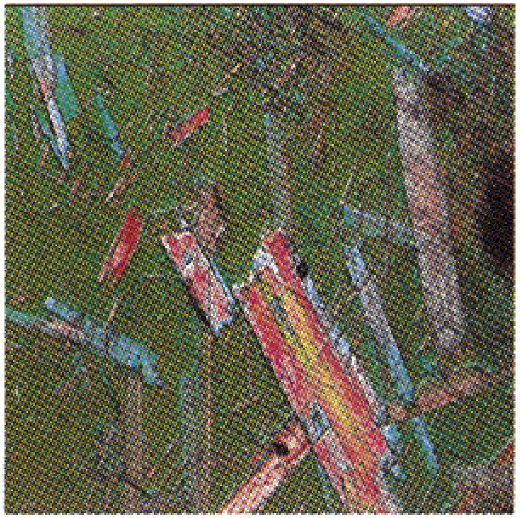
Forma II

NORVIR [Ritonavir]

Abbott informs healthcare professionals about manufacturing difficulties with the capsule formulation of their HIV protease inhibitor, Norvir.

The company has encountered an undesired formation of a Norvir crystalline structure that affects how the capsule form of Norvir dissolves.

Forma I



Forma II

MEDWATCH THE FDA MEDICAL PRODUCTS REPORTING PROGRAM July 28, 1998 (Health Professional Letter) - Abbott

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NORVIR [Ritonavir]

Abbott informs healthcare professionals about manufacturing difficulties with the capsule formulation of their HIV protease inhibitor, Norvir.

The company has encountered an undesired formation of a Norvir crystalline structure that affects how the capsule form of Norvir dissolves.

shutdown of production of the capsules
all users required to switch to the liquid formulation

MEDWATCH THE FDA MEDICAL PRODUCTS REPORTING PROGRAM July 28, 1998 (Health Professional Letter) - Abbott

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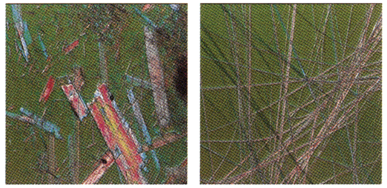
NORVIR [Ritonavir]



Abbott informs healthcare professionals about manufacturing difficulties with the capsule formulation of their HIV protease inhibitor, Norvir.

The company has encountered an undesired formation of a Norvir crystalline structure that affects how the capsule form of Norvir dissolves.

Abbott says that to date it has been unable to find a solution to the problem.

Their plan is to supply Norvir oral solution (liquid) to provide continued Norvir therapy for patients.

Abbott says that it cannot predict the impact of the problem on Norvir sales, which were expected to total $250 million in 1998.

MEDWATCH THE FDA MEDICAL PRODUCTS REPORTING PROGRAM July 28, 1998 (Health Professional Letter) - Abbott

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……molti altri esempi da proporre……

Grazie per l'attenzione !