



A c a d é m i e Hassan II des Sciences & Techniques



Crystallography for the Next Generation

Rabat, Morocco 22-24 April 2015

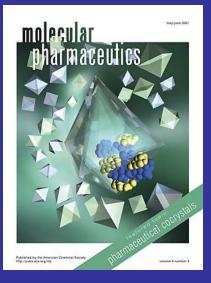
#### Polymorphs and Cocrystals in Pharmaceutical Development (and salts, hydrates, eutectics)

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## This talk is about ...



80% drugs are sold as tablets



- 40% drugs in the market have low solubility
- 80% drug candidates in the pipeline (NCEs) will pose a solubility problem

Crystal engineering of active pharmaceutical ingredients. P. York, Adv. Drug Del. Rev., 2007, 59, 617-630. R. Hilfiker, Polymorphism in the Pharmaceutical Industry; Wiley-VCH, 2006. 2

## **BCS classification**

BCS class	Solubility	Permeability	% Drugs on market	% Drugs in pipeline
I.	High	High	35	5-10
II	Low	High	30	60-70
III	High	Low	25	5-10
IV	Low	Low	10	10-20

	Solubility enhancement
	Particle size reduction, soluble salts, solid dispersions, self emulsifying systems, addition of surfactants, nano-particles, cyclodextrin complexes, pH adjustment, salting in.
Ш	V Solubility enhancement
Absorption enhancing excipients, efflux inhibitors, lipid filled capsules, Gi motility	Prodrugs, salt forms, cosolvents, solubilization by surfacants, lipid filled capsules, nano-particles, liposomes, lyophilization.

Solubility (mg/L)	Classifi- cation	Comments
<20	Low	will have solubility problems
20-65	Moderate	may have solubility problems
>65	High	no solubility problem

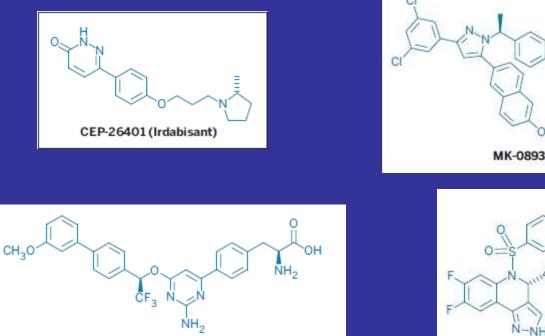
GI permeability

# NCE discovery and Solubility

- Discovery of new drug molecules is a long and expensive marathon with very low success rates to the finish line
- Combi-Chem and HTS and CADD and of course synthesis of medicinal molecules are essential inputs
- ADME, TOX, Stability, Tableting, etc.
- Critical trend (and opportunity) in last decade
- "the solubility of new drug molecules has decreased sharply. While a value of less than 20 µg/mL for the solubility of a NCE were practically unheard of until 1980s, the situation has been changed so much that in the present day drug candidates with solubilities of <1 µg/mL are common."

Serajuddin, Adv. Drug. Del. Rev., 2007, 603-616

### 2011 new drug molecules Focus on the molecule





OCH.

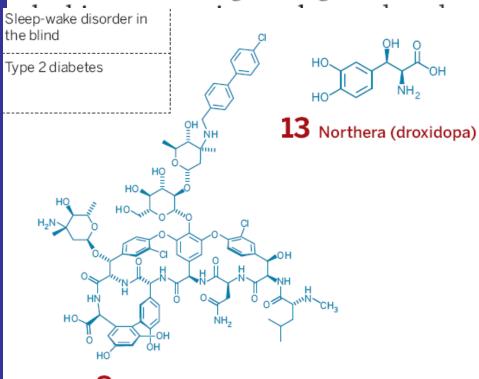
Highly lipophilic molcules – "grease ball" •

LX1031

- Tight and specific nM binding yes •
- Lipinski rules ??  $\mathbf{O}$
- Salts may not be obvious to make •

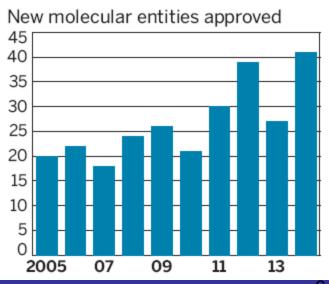
## 2014 was a record year

**OR THE PHARMACEUTICAL** industry, 2014 was one for the record books: sky-high merger and acquisition activity, unprecedented levels of financing, and, last but not least, a peak in new drug approvals. The Food & Drug Administration's green light for 41 new molecular entities—

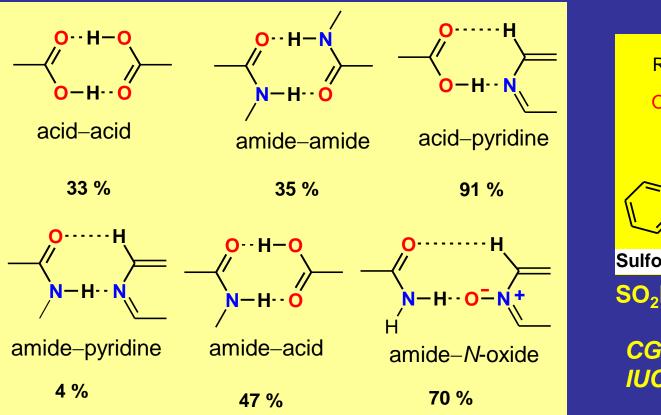


Orbactiv (oritavancin)

ignaled a return to ears ago seemed stagnant.



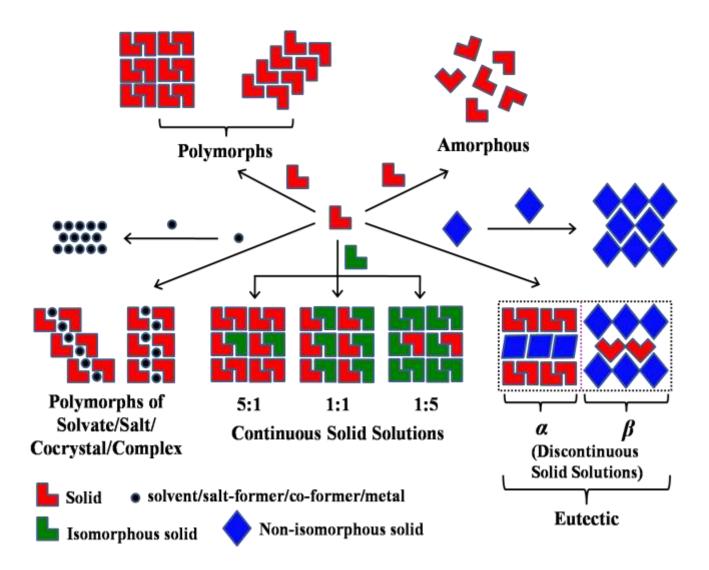
#### Supramolecular Synthons Homo- and Heterosynthons



 $R_{R}, O_{H}, O_{H}, O_{H}, O_{H}, O_{H}, O_{H}, O_{S}, O_{R}$ Sulfonamide-N-oxide SO<sub>2</sub>NH<sub>2</sub>...CONH<sub>2</sub> CGD, 2011, 1930 *JUCRJ*, in press

Desiraju, Angew. Chem. Int. Ed. **1995** 34 2311-2327 Allen, New J. Chem. **1999** 23 25-34 Zaworotko, Chem. Commun. **2003** 186-187

## **Eutectics and Solid solution**



## Isomorphous and Isostructural

Two crystals are said to be *isomorphous* if (*a*) both have the same space group and unit cell dimensions and (*b*) the types and the positions of atoms in both are the same except for a replacement of one or more atoms in one structure with different types of atoms in the other (isomorphous replacement), such as heavy atoms, or the presence of one or more additional atoms in one of them (*isomorphous addition*). Isomorphous crystals can form *solid solutions*.

Two crystals are said to be <u>isostructural</u> if they have the same structure, but not necessarily the same cell dimensions nor the same chemical composition, and with a 'comparable' variability in the atomic coordinates to that of the cell dimensions and chemical composition. For instance, calcite CaCO<sub>3</sub>, sodium nitrate NaNO<sub>3</sub> and iron borate FeBO<sub>3</sub> are isostructural. One also speaks of *isostructural series*, or of *isostructural polymorphs* or *isostructural phase transitions*.

A solid mixture containing a minor component uniformly distributed within the crystal lattice of the major component is a **solid solution**.

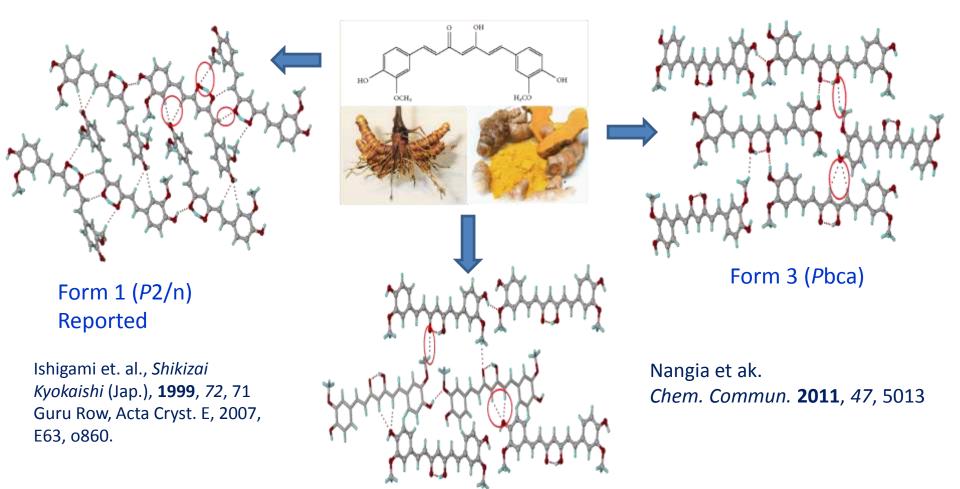
Kalman, Acta Cryst. B49, 1993, 1039; Adv. Mol. Struct. Res., 1997, 3, 189.

## **Curcumin Biological Activity**

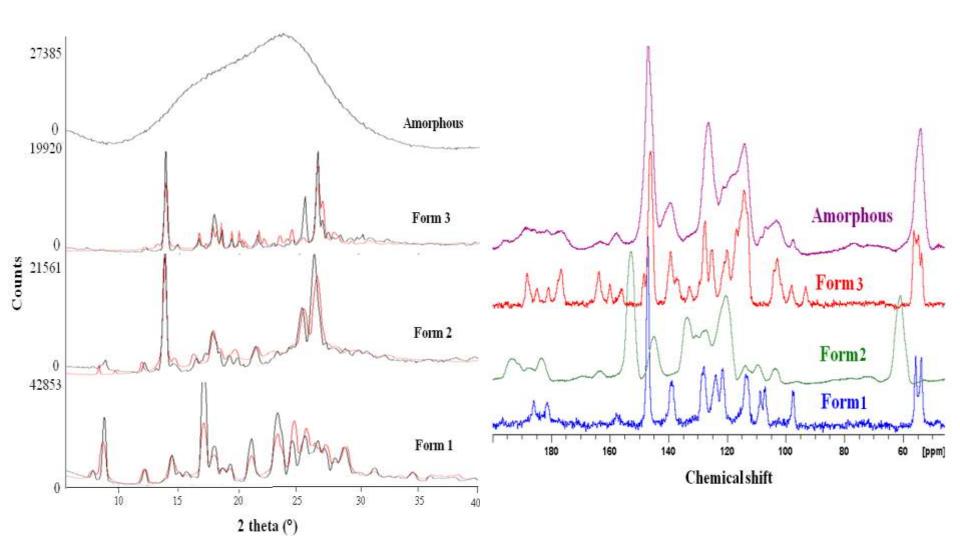
- Principal curcuminoid of popular Indian spice turmeric (haldi)
- Pharmacokinetics and biological activity of curcumin tested in cancer patients at 0.2-2 g/d dose in Phase I clinical for 3 mo
- Chemo-preventive and chemotherapeutic activity in animal and human trials convincingly demonstrated
- Curcumin is totally safe even at high doses of up to 12 g/day
- Can modulate multiple cellular targets and gene regulation
- Not approved as approved drug?
  - Stable in acidic medium, but decomposes at alkaline pH
  - Very low solubility in water (7.8 mg/L) at acidic or neutral pH
  - More soluble in alkaline medium, but decomposes to 90% extent within 30 min in 0.1 M phosphate buffer at pH 7.2 and 37 °C
  - Poor bioavailability (0.051 µg/mL) due to rapid metabolism in liver and intestinal wall (elimination half life < 2h)</li>

## Curcumin polymorphs

Curcumin is principal Curcuminoid of the popular Indian spice turmeric. Antioxidant, anti-inflammatory, antimicrobial, antimalarial and anticancer activity.



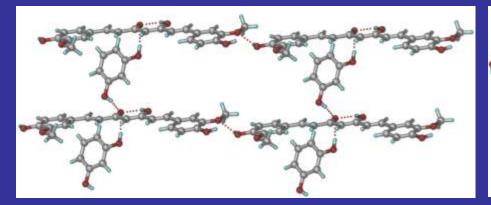
#### **PXRD** and ss-NMR lines

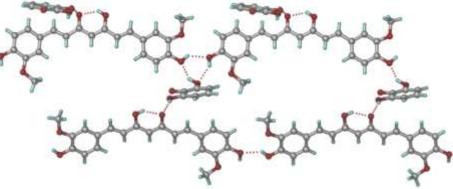


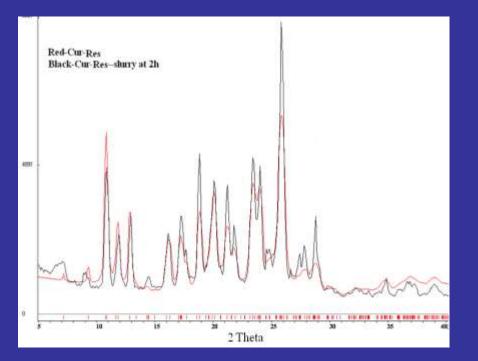


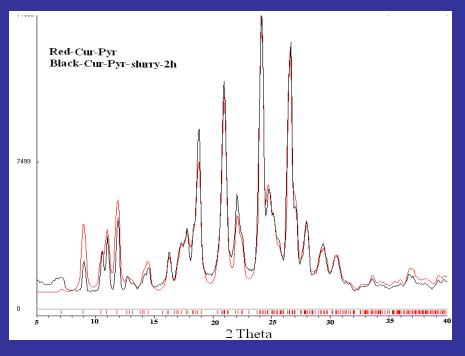
- Two polymorphs of curcumin and amorphous phase
- Two cocrystals of curcumin with pyrogallol and resorcinol
- Objective to improve stability and solubility via solid form modification
- Stability and solubility correlate inversely
- Can we make a stable, soluble curcumin for oral formulation?

## X-ray diffraction

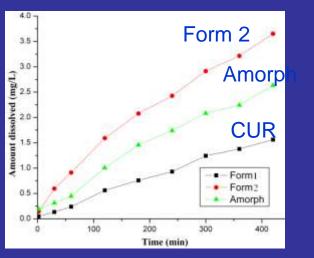


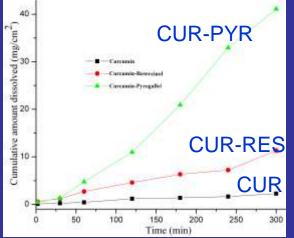


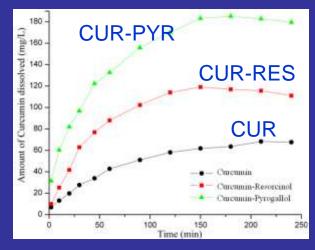




# Solubility Profile







IDR (tablet solubility)

#### IDR (tablet solubility)

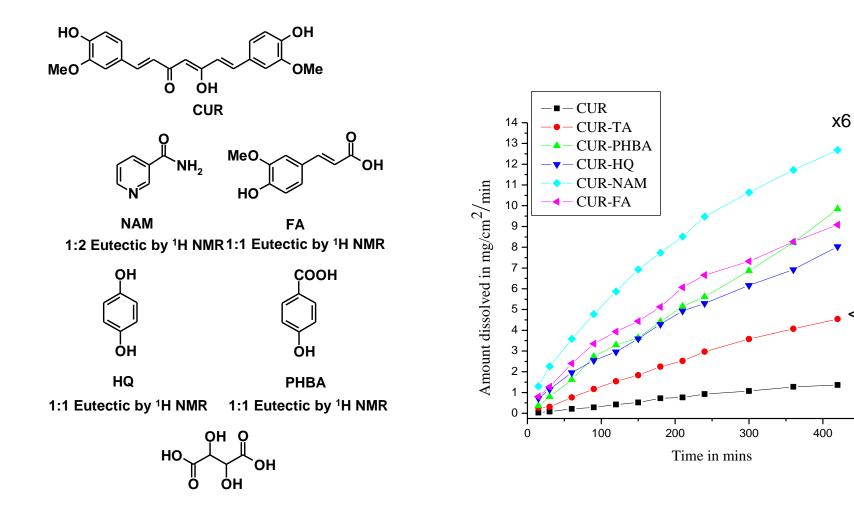
Polymorph 2 is about 4 times fast dissolving in 40% EtOH-H2O

CUR-PYR is 14x and CUR-RES is 6x more soluble than curcumin PD (capsule solubility)

AUC<sub>0-4h</sub> = 12.2 g h/L for CUR 23.3 g h/L CUR-RES 36.5 g h/L CUR-PYR

- Stability wise CUR-PYR and CUR-RES > fast dissolving polymorph 2 >> amorphous powder in EtOH-water medium
- Commercial curcumin most stable but least soluble
- Can CUR-PYR lead to a new anti-cancer combo drug?

## From Cocrystals to Eutectics



L -TA 1:1 Eutectic by <sup>1</sup>H NMR

500

X3-4

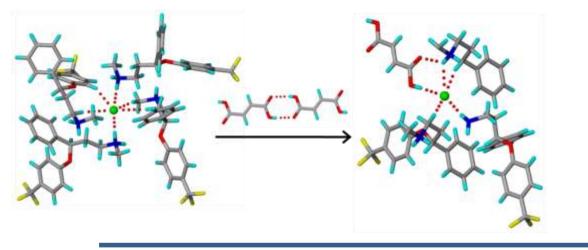
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# Cocrystal, Eutectic ??

The X-ray crystal structure of a cocrystal is different from that of the individual components whereas the unit cell of a solid solution is similar to that of one of the components. Eutectics are closer to the latter species in that their crystalline arrangement is similar to the parent components but they are different with respect to their structural integrity. A solid solution possesses structural homogeneity throughout the structure (single phase) but a eutectic is a heterogeneous ensemble of individual components whose crystal structures are like discontinuous solid solutions (phase separated). Thus, a eutectic may be better defined as a conglomerate of solid solutions. A structural analysis of cocrystals, solid solutions, and eutectics has led to an understanding that materials with strong adhesive (hetero) interactions between the unlike components will lead to cocrystals whereas those having stronger cohesive (homo/self) interactions will more often give rise to solid solutions (for similar structures of components) and eutectics (for different structures of components).

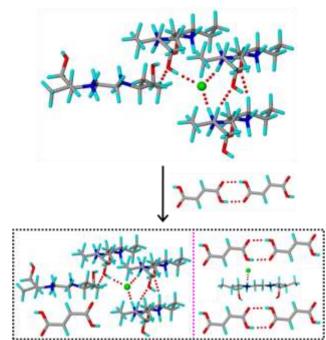
Chem. Commun. 2014, 906-923. Feature article

### Cocrystal vs. Eutectic



Fluoxetine HCI + FA/SA C-H...Cl- interactions in API salt

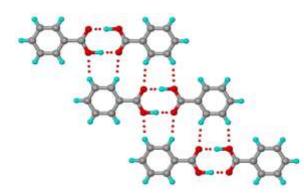
Cocrystal N-H/OH...Cl- interactions in salt-cocrystal



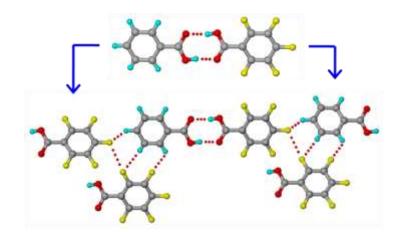
Ethambutol HCI + FA/SA

Eutectic N-H/OH...Cl- interactions in salt-cocrystal

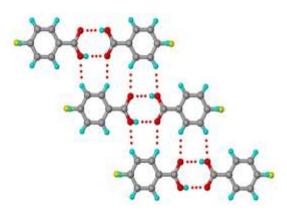
#### Solid solutions to Eutectics



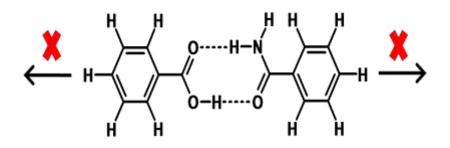
Benzoic acid – single crystal O-H...O hydrogen bonds



Benzoic acid–Pentafluorobenzoic acid Numerous C-H...F and π-stacking And strong O-H...O. Cocrystal



Benzoic acid–4-fluorobenzoic acid No strong and dominant C-H…F Solid soln. 25:75, 45:55



Benzoic acid-Benzamide Strong O-H...O & N-H...O H bonds No auxiliary interactions, Eutectic

## Elaborated this empirical model

ноос-\_\_соон

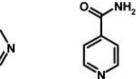
Succinic acid (SA)

HOOC-

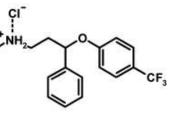
Succinamic acid (SNA)

Succinamide (SM)

H,NOC-







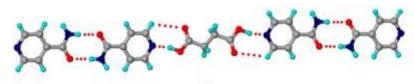
CONH.

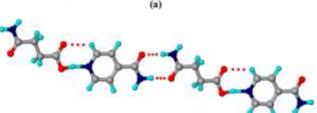
4,4'-Bipyridine (BP)

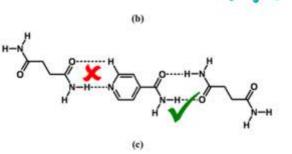
Isonicotinamide (INAM)

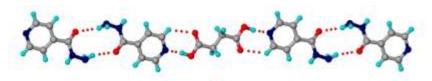
Isoniazid (INH)

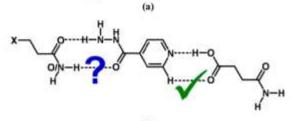
Fluoxetine hydrochloride (FL)

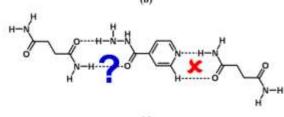




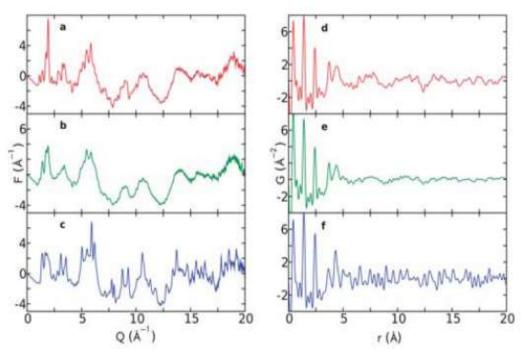




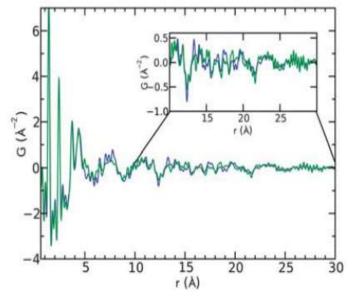




## Characterizing 'local' order PDF instead of PXRD



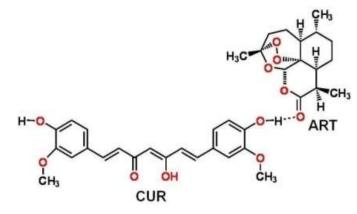
Total scattering diffraction F(Q) patterns and TSPDFs G(r) of CBZ samples. Panels (a) and (d) correspond to CBZ III, (b) and (e) to the meltquenched sample and (c) and (f) to CBZ I; (a), (b), (c) show the F(Q) whilst (d), (e), (f) show G(r).

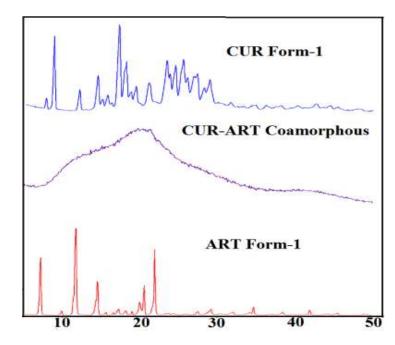


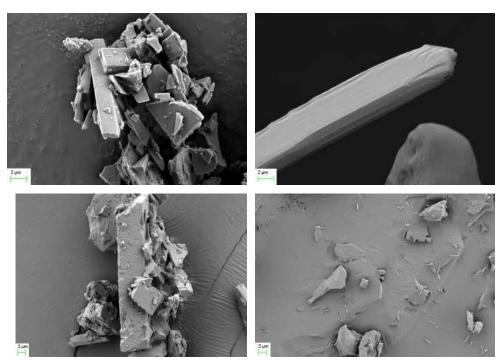
Comparison of G(r) of the meltquenched sample (green) with CBZ III (blue) shows excellent correlation (PolySNAP correlation coefficient is 0.8601) and match of the nanocrystallite material with CBZ III.

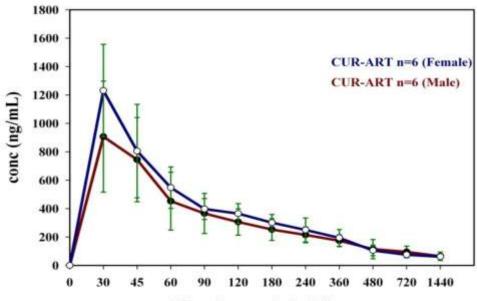
Billinge, Florence, Shankland, CrystEngComm, 2010, 12, 1366

#### **Curcumin-Artemisinin Coamorphous**





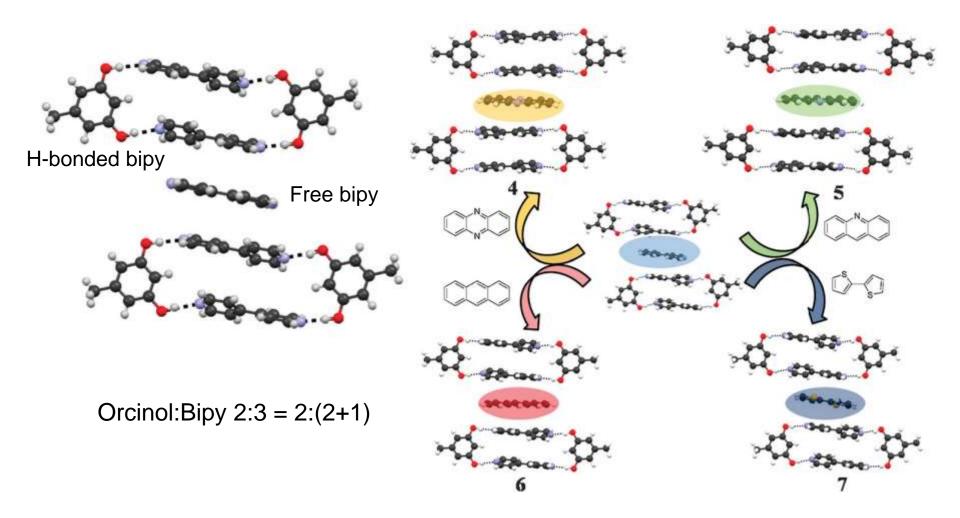




**Time Intervals In Minutes** 

CUR-ART	Female rats		Male rats	
Parameters	n=6	S.D.	n=6	S.D.
T <sub>max</sub> (hr)	0.5	0	0.5	0
C <sub>max</sub> (µg/mL)	1.23	0.33	0.9	0.39
T <sub>1/2</sub> (hr)	6.7	0.68	7.0	1.66
AUC <sub>(0-24)</sub> (µg.hr/mL)	3.69	0.69	3.45	0.83
AUC <sub>(0-∞)</sub> (µg.hr/mL)	36.4	6.00	35.4	15.64

### Binary to ternary cocrystals using structural mimicry

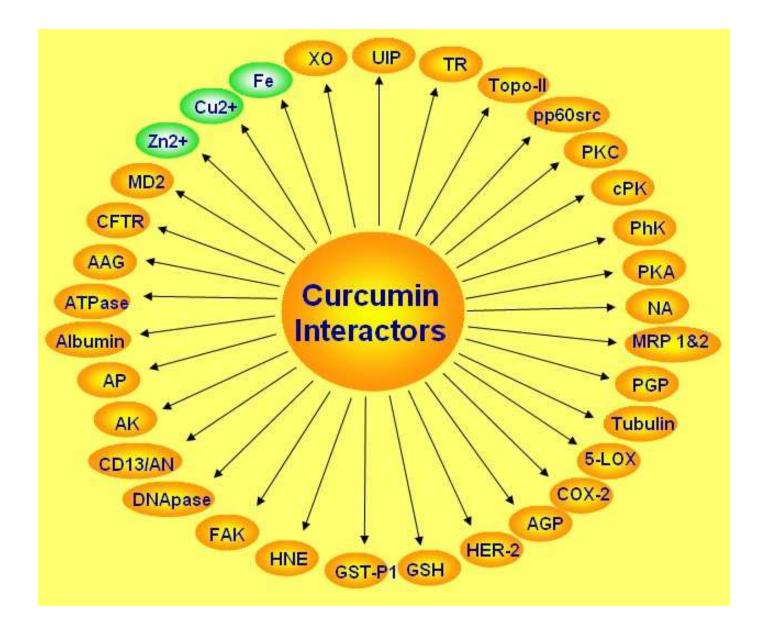


Desiraju, Chem. Commun., 2011, 47, 12080-12082

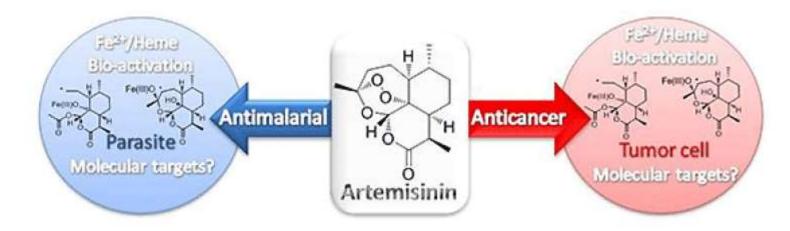


XXIV Congress and General Assembly of the International Union of Crystallography 21 - 29 August 2017, Hyderabad, India

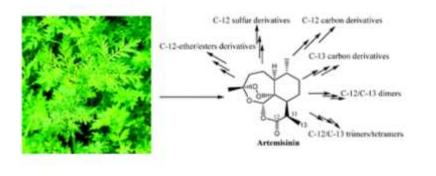




Cancer Letters 269 (2008) 199-225



In this *tutorial review*, an effort towards presentation of a comprehensive account of the recent developments on various kinds of artemisinin derivatives including artemisinin dimers, trimers and tetramers has been made and their efficacy towards malaria parasites and different cancer cells lines was compared with that of artemisinins, and various other anti-malarial and anticancer drugs. It is expected that this review will provide first-hand information on artemisinin chemistry to organic/medicinal chemists, and pharmacologists working on anticancer and anti-malarial drug development.



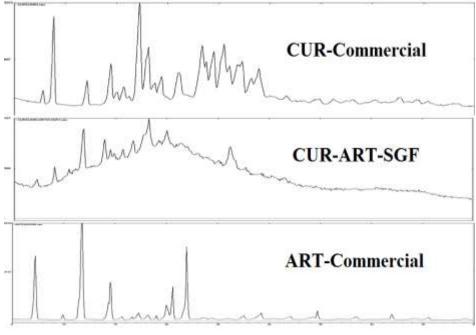
An Artemisinin-Derived Dimer Has Highly Potent Anti-Cytomegalovirus (CMV) and Anti-Cancer Activities

Boger, Johns Hopkins Univ.

PLoS ONE 2011, 6, e24334

SLs in clinical trials are artemisinin, thapsigargin and parthenolide and many of their synthetic derivatives. These drugs are selective toward tumor and cancer stem cells by targeting specific signaling pathways, which make them lead compounds in cancer therapy.

#### Stability in SGF and SIF media at 24 h in slurry conditions

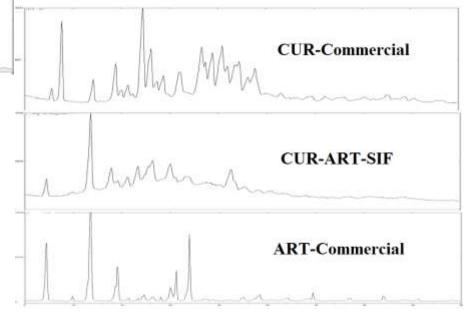


#### SGF pH = 1.2

Sodium chloride (0.2 g) was added to a 100 mL flask and dissolved in 50 mL of water. Then 0.7 mL of 10 M HCl was added to adjust the pH of the solution to 1.2. To this, 0.32 g of pepsin was added and dissolved with gentle shaking and the volume made up to 100 mL with water.

#### SIF pH = 6.8

Monobasic potassium phosphate (0.68 g) was dissolved in 25 mL of water, then 7.7 mL of 0.2 N NaOH was added to adjust the pH to 6.8. To this, 1 g of pancreatin was added and shaken gently until dissolved and the volume adjusted to 100 mL with water.



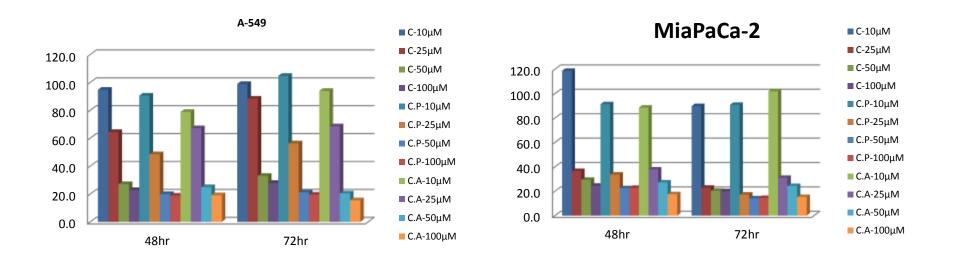
## Comparison of performance

Table	C <sub>max</sub> , T <sub>max</sub> , AUC for soluble curcumin oral forms					
Curcumin form	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (min)	Dose (mg/kg)	AUC <sub>0-∞</sub> (µg. h /mL)	Relative performance <sup>b</sup>	Ref.
CUR-ART coamorph.	1003	30	200	24.7	100, 2.5	This work
CUR liposome	43	30	100	0.1	8, 0.02	18a
CUR cryst.	35	80	100	11.0	7, 2.2	20a
CUR cryst. disp.	194	55	20	36.2	194, 36	20a
CUR amorph. disp.	147	60	20	27.1	147, 27	20a
Nano CUR	451	9	20	20.0	451, 20	20a
CUR powder	37	120	300	0.1ª	2.5, 0.006	20b
Thera CUR	1697	120	300	9.3ª	113, 0.62	20b

<sup>a</sup> Estimated for 24 h from Fig. 3 of ref. 20b.

<sup>b</sup> Based on a dose of 20 mg/kg and assuming linear profile. This comparison is qualitative because different additives and solubilizers and polymers are added to each formulation.

## Pancreatic and Lung cancer cell lines

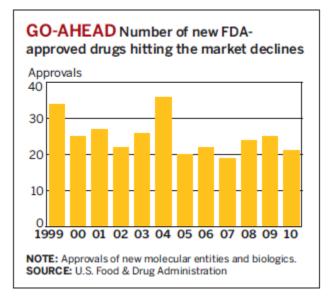


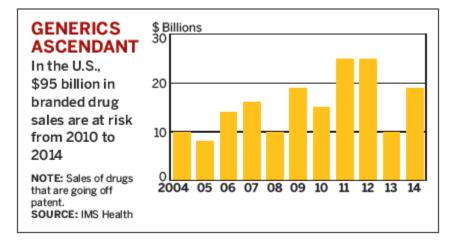
- A-549 (Lung carcinoma) and MiaPaca-2 (Pancreas)
- Cell survival rate <20% at drug conc. 50-100  $\mu$ M
- By itself more of validation but useful start point to next phase Xenograft model study in rats

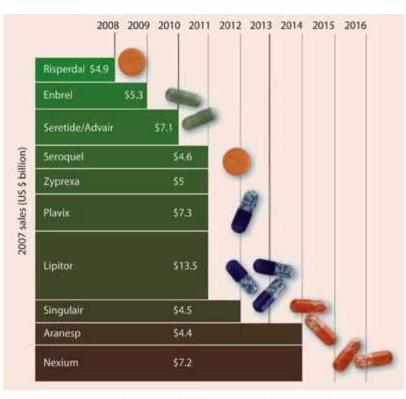
## Summary and Outlook

- Crystal engineering of pharma cocrystals: Improving (property) without changing (drug)
  - Hydration stability and color Temozolomide
  - Biochemical stability Andrographolide
  - Solubility improvement Curcumin
  - Polymorphs screen for Acedapsone
- Crystal structure to physicochemical property
- Correlation of structure-property non-obvious
- Cocrystals and Eutectics represent useful materials with tunable properties in medicine
- Fill gap for declining NCEs, poorly soluble drugs & modulate properties of problem formulation



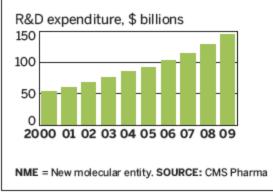


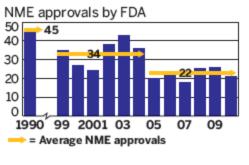




The pharma industry will see over \$63 billion of annual income washed away due to patent erosion by 2014

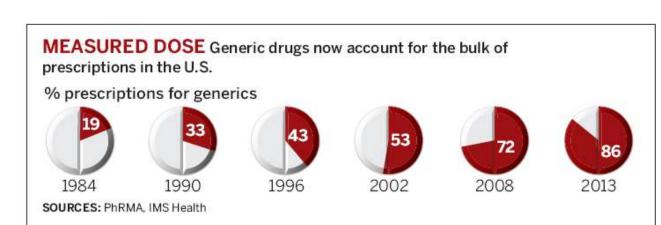
#### DIVERGENCE As R&D spending rises, drug approvals are declining

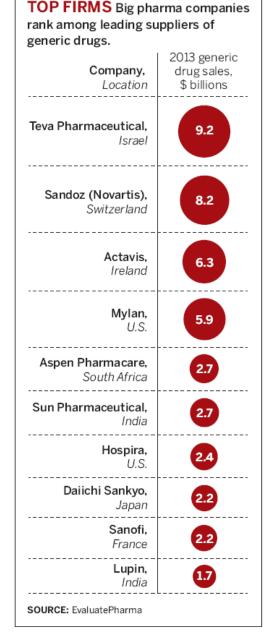




#### **NEW DRUG APPROVALS SOAR**

In an encouraging sign of the health of the pharmaceutical industry, new drug approvals soared to an 18-year high in 2014. The Food & Drug Administration gave the green light to 41 new molecular entities last year, up from 27 in 2013. In years past, a surge in new approvals often meant a flood of "me-too" drugs had made it onto the market. But the 2014 class of new drugs is ripe with innovation: The list includes 16 first-in-class treatments, compared with just nine drugs with a novel mechanism of action approved in 2013. Last year was the best year ever for rare disease drug approvals, FDA said, with orphan drugs accounting for roughly 40% of the new drugs approved. Other highlights were 12 new treatments for infectious diseases, including four much-needed new antibiotics. And eight new cancer drugs hit the market, a crop that included several immunotherapies that represent major advances for patients. FDA crammed seven of those new drug approvals into the last month of the year.—LJ





## Temozolomide

- Chemotherapy for treatment of glioblastoma multiforme (GBM); Primary malignant brain and CNS tumors
- Discovered at Aston Univ. UK in 1980s in lab of Prof. Malcom Stevens (Richard Stone PhD student)
- Approved for treatment of malignant glioma in US and EU in 1999
- Temodar/ Temodal is Schering-Plough molecule; Now Merck. Locally Temonat of Natco
- TMZ prodrug, Active species is MTIC (CH3N2+)
- By product of hydrolysis is AIC, which is brown colored
- Discoloration of active from white to pink to tan
- Can we address stability of Temo by pharma cocrystal?

#### (19) United States

#### (12) Patent Application Publication (10) Pub. No.: US 2006/0222792 A1 Braverman et al. (10) Pub. Date: Oct. 5, 2006

#### (54) TEMOZOLOMIDE STORAGE SYSTEM

(75) Inventors: Oleg Braverman, Beer-Sheva (IL); Rimma Feinshtein, Beer-Sheva (IL); Alex Weisman, Kiriat Ekron (IL); Joseph Kaspi, Givatayim (IL)

> Correspondence Address: LEYDIG VOIT & MAYER, LTD TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE CHICAGO, IL 60601-6780 (US)

- (73) Assignee: CHEMAGIS LTD., Bnei Brak (IL)
- (21) Appl. No.: 11/409,345
- (22) Filed: Apr. 21, 2006

#### **Publication Classification**

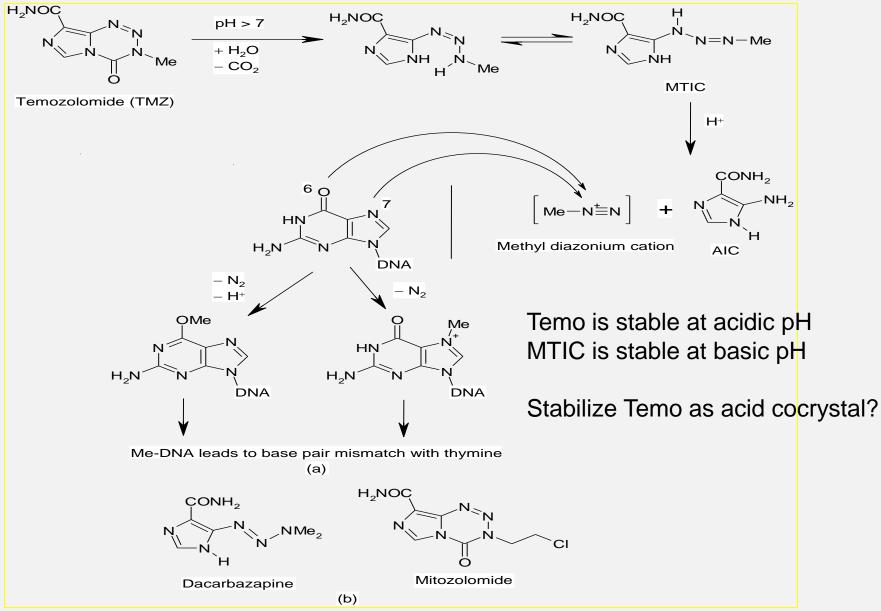
(51) Int. Cl. B32B 27/32 (2006.01)
(52) U.S. Cl. 428/35.2

#### (57) ABSTRACT

The present invention provides an improved storage system for temozolomide, which preferably includes one or more bags (e.g., 3 bags, optionally containing a desiccant interposed between two of the bags). The storage system of the present invention can maintain temozolomide as a white, stable, and dry material after long periods of storage. The present invention also provides methods of producing and storing temozolomide as a stable, white solid.

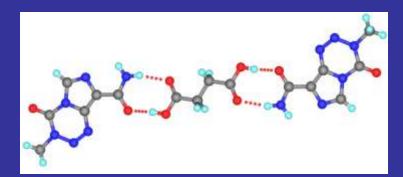
**[0004]** A process for preparing temozolomide is described in US 2002/0095036. According to the teaching of Example 1 of US 2002/0095036, temozolomide is obtained as a white precipitate. However, the Temodar® drug leaflet and the Physician Desk Reference 60<sup>th</sup> Ed. (2006) state that the material is "a white to light tan/light pink powder." The light tan/pink color is indicative of degradation.

**[0005]** In view of the apparent tendency of temozolomide to degrade, as evidenced by the change in color, there exists a need for products and methods, which improve the stability or shelf life of temozolomide. The present invention provides such products and methods.

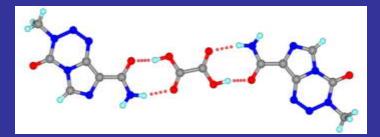


Crystal structure	Stoichiometry	Predominant Synthon	Conformer				
Hydrolyzed TMZ							
Hydrolyzed TMZ · H <sub>2</sub> O	1:1	Amide-water (X)	Α				
TMZ · Methanolyzed TMZ	1:1	Amide-tetrazinone VI	A				
		Amide catemer (II)					
Ethanolyzed TMZ		Amide-imidazole (V)	2				
	TMZ solvates						
$TMZ \cdot H_2O$	1:1	Amide-tetrazinone	Α				
(55)		(VI)					
TMZ · MeNO <sub>2</sub>	1:1	Amide-amide (I)	A				
TMZ · DMSO	1:0.5	Amide-amide (I)	A				
TMZ cocr	ystals with COOH	partners					
TMZ · Formic acid · H <sub>2</sub> O	2:1:1	Amide-acid (XI)	A + B				
and the second		Amide-amide (I)	993.021.00438				
TMZ · Acetic acid	1:1	Amide-acid (XI)	A				
TMZ · Oxalic acid	1:0.5	Amide-acid (XI)	A				
TMZ · Succinic acid	1:0.5	Amide-acid (XI)	A				
TMZ · DL Malic acid	1:0.5	Amide-acid (XI)	A				
TMZ · p-Aminobenzoic acid ·	3:1:1	Amide-acid (XI)	A				
H <sub>2</sub> O		Amide-amide (I)					
TMZ · Fumaric acid · H <sub>2</sub> O	1:0.5:1	Amide-amide (I)	A				
		Amide-tetrazinone					
		(VI)	2550				
TMZ · Salicylic acid	1:1	Amide-acid (XI)	В				
TMZ · Hydrolyzed TMZ ·	3:1:1:1	Amide-amide (XI)	A + B				
Cinnamic acid · H <sub>2</sub> O		Acid-imidazole (XIII)					
TMZ cocrystals with CONH2 partners							
TMZ · Isonicotinamide	2:1	Amide-amide (I)	A + B				
TMZ · Nicotinamide	2:1	Amide-amide (I)	A + B				
TMZ · Pyrazinam ide	1:1	Amide-pyrazine (III)	A				
<i></i>		Amide-imadazole (IV)					
TMZ · 4-hydroxybenzamide	2:1	Amide-amide (I)	A				
TMZ · Saccharin	1:0.5	Amide-amide (I)	В				

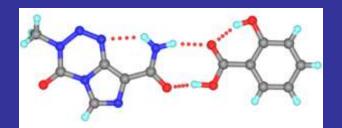
## TMZ Cocrystals with CO<sub>2</sub>H CCFs



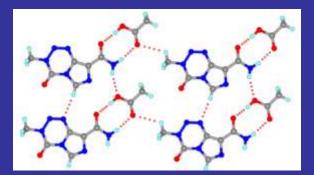
TMZ-Succinic acid (1:0.5)  $pK_a = 4.2, 5.6$ 



TMZ·Oxalic acid (1:0.5)  $pK_a = 1.2, 4.2$ 



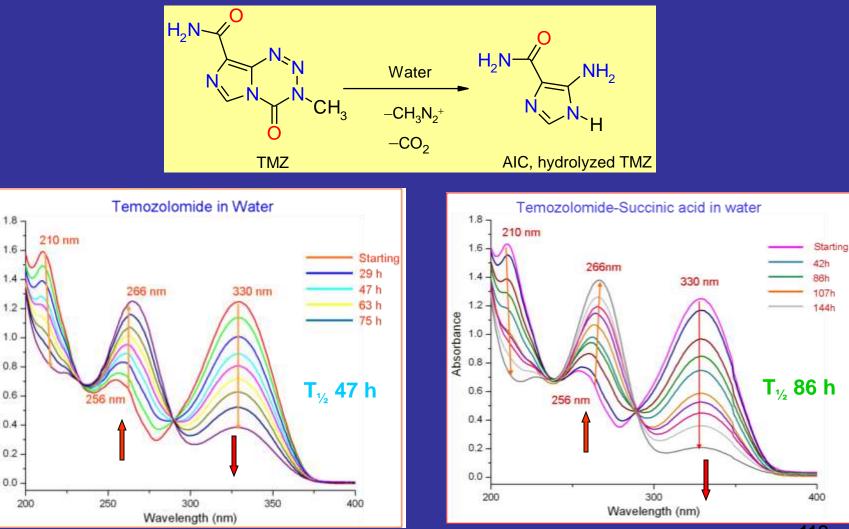
TMZ·Salicylic acid (1:1)  $pK_a = 2.9$ 



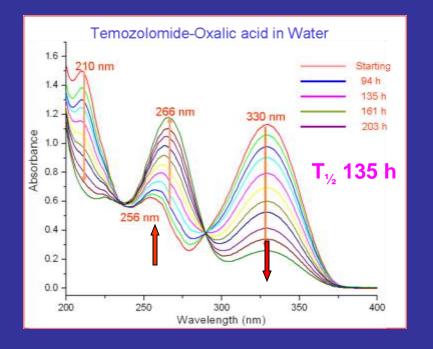
TMZ·Acetic acid (1:1)  $pK_a = 4.7$ 

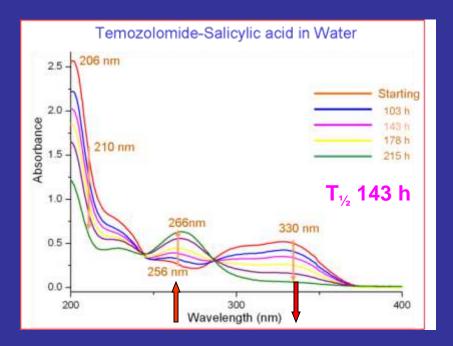
With the knowledge that TMZ is stable at acidic pH < 5 but labile at pH > 7, it was co-crystallized with GRAS organic acids as pH adjusters to improve API stability.

## API and API•COOH stability



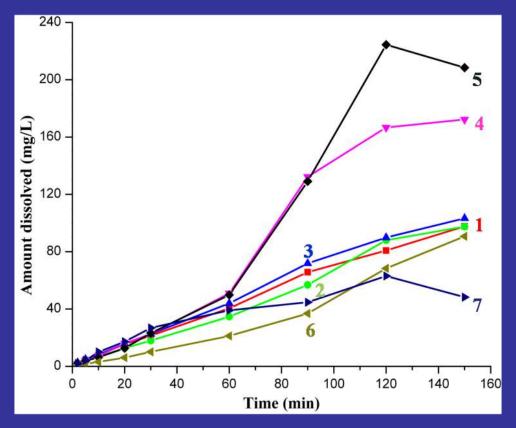
Absorbance





- Stability studies at 25  $\mu$ g/mL conc. High T<sub>½</sub> (47 h) of TMZ at higher conc. compared to reported value from *in vivo* studies
- Mean  $T_{\frac{1}{2}}$  at plasma conc. 1.8 h (1.7-1.9 h)
- Repeated stability measurements at 10 μg/mL, pH 7.0 buffer 37 °C
- T<sub>1/2</sub> = TMZ 1.7 h, T<sup>1</sup>/<sub>2</sub> cocrystals : anth 2.2, suc 2.3, d,l-tart 2.5 h, d,l-malic 2.7, oxal 3.5, salic 3.6 h
- No discoloration of TMZ•Succinic acid CC even after <u>1 year of storage</u>

## Dissolution of cocrystals is good



1. TMZ, 2. TMZ-oxalic, 3. TMZ-succinic,

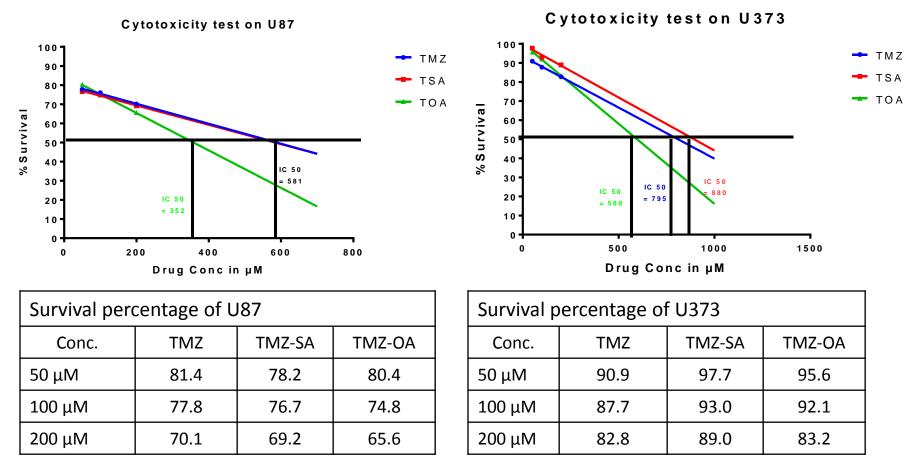
- 4. TMZ-salicylic, 5. TMZ-malic,
- 6. TMZ-anthranilic, 7. TMZ-tartaric acid

Stability and Dissolution criteriaTMZ-succinicTMZ-oxalic > TMZ-salicylic > TMZ-malic

Chem. – An Asian J. 7, 2274-2285 (2012)

#### Results – Cell culture inhibition

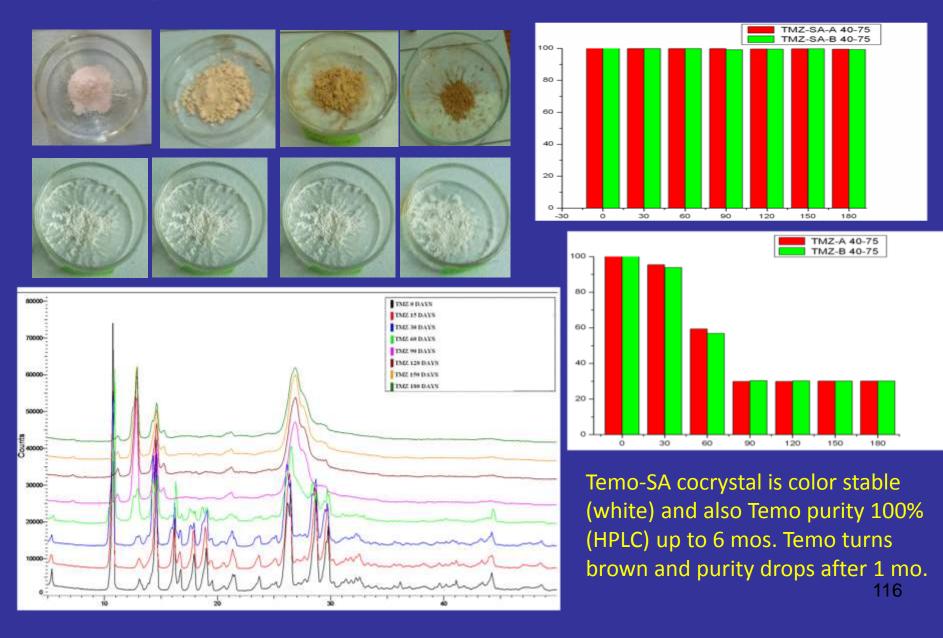
Proc. Natl. Acad. Sci., India, 2014, 84, 321–330



 $\Rightarrow$  Readings were taken on 96 well plate TECAN ELISA reader attached to UV-Vis detector at 570 and 600 nm using AB dye. Standardized protocols followed.

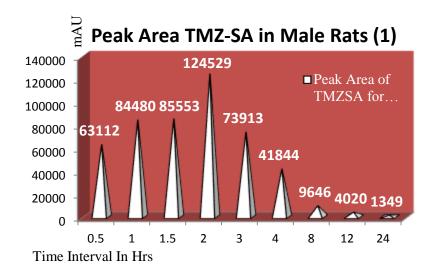
 $\Rightarrow$  Survival cells %age and IC50 on higher side but consistent with lit. reports. May be due to fact that Temo is a pro-drug and hydrolysis will release the active CH3N2+ species

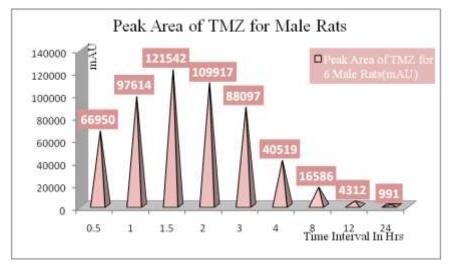
#### Progress results – Color and Form stability



#### TMZ and TMZ-SA Male rats

PK profile and Bioavailability in Sprague Dawley rats weight 200-250 g

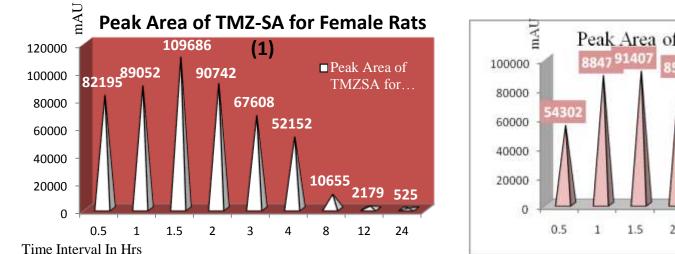


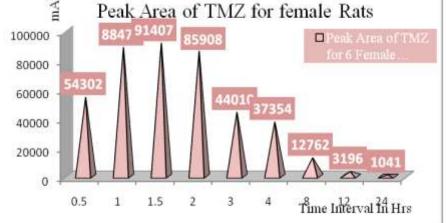


S. No	Test Parameter	TMZ-SA	TMZ
1	AUC <sub>(0-24)</sub>	21.74 µg.hr/mL	24.00 µg.hr/mL
2	C <sub>max</sub>	5.39 μg.hr/mL	5.37 µg.hr/mL
3	T <sub>max</sub>	2 hr	1.5 hr
4	K <sub>e</sub>	0.14 /hr	0.18 /hr
5	T <sub>1/2</sub>	4.9 hr	3.8 hr
6	AUC <sub>(0-∞)</sub>	21.98 µg.hr/mL	24.12 μg.hr/mL

#### TMZ and TMZ-SA Female Rats

PK profile and Bioavailability in Sprague Dawley rats weight 200-250 g





S. No.	Parameter	TMZ-SA	TMZ
1	AUC <sub>(0-24)</sub>	21.84 µg.hr/mL	18.66 µg.hr/mL
2	C <sub>max</sub>	4.76 µg.hr/mL	4.12 μg.hr/mL
3	T <sub>max</sub>	1.5 hr	1.5 hr
4	K <sub>e</sub>	0.17 /hr	0.15 /hr
5	T <sub>1/2</sub>	4 hr	4.5 hr
6	AUC <sub>(0-∞)</sub>	21.99 µg.hr/mL	18.83 µg.hr/mL

#### **Compare with reported data** J. Pharmacol. Experiment. Therap. 2007, 321, 265.

#### TABLE 1

 $PK \ parameters \ of \ TMZ \ in \ plasma \ and \ tumor \ IF \ in \ SF188V+ \ tumor-bearing \ athymic \ rats \ receiving \ multiple \ i.v. \ administrations \ of \ TMZ \ at \ a \ dose \ level \ of \ either \ 18 \ mg/kg \ (CD \ regimen) \ or \ 3.24 \ mg/kg \ (MD \ regimen)$ 

Values are means  $\pm$  S.D.

D (	CD(n = 7)		MD $(n = 9)$	
Parameters	Day 1	Day 5	Day 1	Day 28
Plasma				
$C_{\rm max^{*}p}$ ( $\mu g/ml$ )	$24.1 \pm 3.7$	$21.6 \pm 3.2$	$3.17 \pm 0.26$	$3.33 \pm 0.54$
$AUC_{0\to\infty,p}$ (µg·h/ml)	$24.1 \pm 2.6$	$25.0 \pm 5.7$	$4.27 \pm 1.45$	$3.72 \pm 0.89$
$V_{\rm p} (l/kg)$	$0.91 \pm 0.30$	$0.98 \pm 0.44$	$1.14 \pm 0.18$	$1.18 \pm 0.41$
$CL_{p}(l/h/kg)$	$0.73 \pm 0.11$	$0.75 \pm 0.15$	$0.85 \pm 0.22$	$0.92 \pm 0.21$
$K_{\rm e}  ({\rm h}^{-1})$	$0.87 \pm 0.26$	$0.86 \pm 0.29$	$0.75 \pm 0.16$	$0.81 \pm 0.12$
$t_{1/2}$ (h)	$0.85 \pm 0.20$	$0.89 \pm 0.28$	$0.97 \pm 0.27$	$0.87 \pm 0.13$
Tumor IF				
$C_{\rm max,t}$ (µg/ml)	$10.6 \pm 3.6$	$11.1 \pm 5.9$	$4.85 \pm 4.08$	$2.03 \pm 0.58$
$t_{\rm max,t}$ (h)	$0.51 \pm 0.21$	$0.77 \pm 0.22$	$0.44 \pm 0.23$	$0.45 \pm 0.34$
$AUC_{0\to\infty,t}$ (µg·h/ml)	$21.0 \pm 5.4$	$31.7 \pm 15.1$	$6.59 \pm 4.16$	$4.55 \pm 2.56$
$V_{\rm t}$ (ml)	$1.22 \pm 0.30$	$1.33 \pm 0.32$	$1.13 \pm 0.20$	$1.41 \pm 0.61$
$AUC_{0\rightarrow\infty}$ ratio				
$AUC_{tumor}/AUC_{plasma}$	$0.90 \pm 0.35$	$1.22 \pm 0.49$	$1.56 \pm 1.01$	$1.31 \pm 0.84$
Intercompartmental rate constant				
$K_{\rm pt}$ (h <sup>-1</sup> )	$4.30 \pm 5.00$	$2.69 \pm 1.30$	$6.68 \pm 7.50$	$6.77 \pm 3.21^*$
$K_{\rm tp}^{\rm pt}$ (h <sup>-1</sup> )	$3.02 \pm 2.28$	$1.88 \pm 1.47$	$5.01 \pm 3.96$	$5.13 \pm 5.07$

\*P < 0.01 comparing with the CD group on day 5 using the Wilcoxon rank-sum test.

CD = 18 mg/kg (conventional dose) for 5 days = 200 mg in human MD = 3.23 mg/kg (metronomic dose) for 28 days

#### BBB study in rats

PK Bioavail. Table	Female rats TMZ-SA TMZ		Male rats TMZ-SA TMZ	
T <sub>max</sub> (hr)	1.50	1.50	2.00	1.50
C <sub>max</sub> (µg/mL)	4.76	4.12	5.39	5.37
T <sub>1/2</sub> (hr)	4.0	4.5	4.9	3.8
AUC <sub>(0-24)</sub> (µg.hr/mL)	21.84	18.66	21.74	24.00

#### Average of 6 readings for each test

- 1. Test cocrystal and reference drug are bioequivalent (+/-10%).
- 2. There is no significant difference in test cocrystal and ref. drug.
- 3. Cmax, AUC and Tmax values between test cocrystal and ref. drug are similar values.
- 4. No TMZ detected in rat brain after 15 days.
- 5. Test cocrystal TMZ-SA PK-PD readings are slightly better that ref. drug Temo.

#### Current Science, under revision

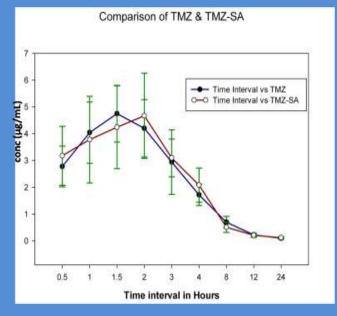
BBB st	tudy	TMZ-SA		TMZ	
Rat code	Brain mass (gm)	AUC in brain (mAU)	Conc. (µg/ 0.6g)	AUC brain (mAU)	Conc. (µg/ 0.6g)
1M	0.6	10830	0.135	4065	0.057
2M	0.6	25845	0.295	420	0.023
3M	0.6	14095	0.169	2257	0.043
4F	0.6	6226	0.085	5974	0.083
5F	0.6	7630	0.100	17867	0.210
6F	0.6	6270	0.086	41867	0.466
Av. 6 r	dgs.	11816	0.145	12075	0.147

Ref. in humans BBB at tumor tissue = 0.117  $\mu$ g/g <u>Temo-SA meets the requirement of FDA defn.</u>

#### Summary of Data TMZ-SA & TMZ

PK profile and Bioavailability in Sprague Dawley rats weight 200-250 g

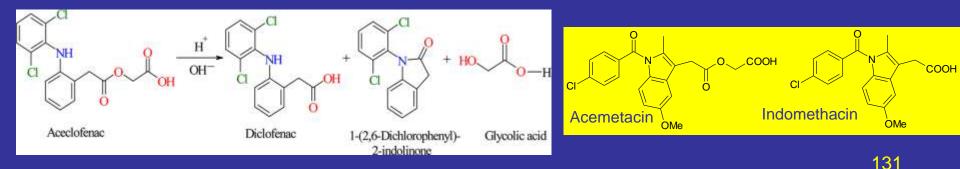
- Stability of TMZ-SA longer than 6 mo, ~1 yr
- PK-PD-Bioavail of test cocrystal 100-110% of ref. drug Temo
- Temo-SA meets the requirement of FDA defn
- Sub chronic and acute toxicity, hematology and histo-pathology results are good

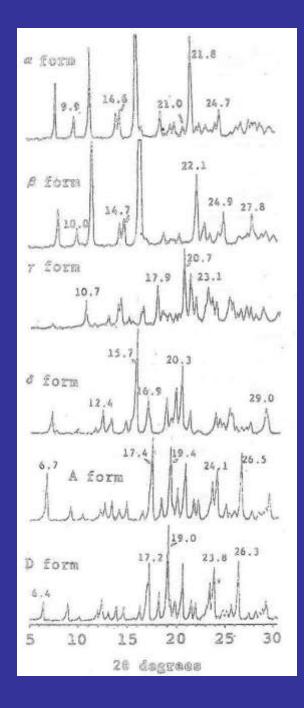


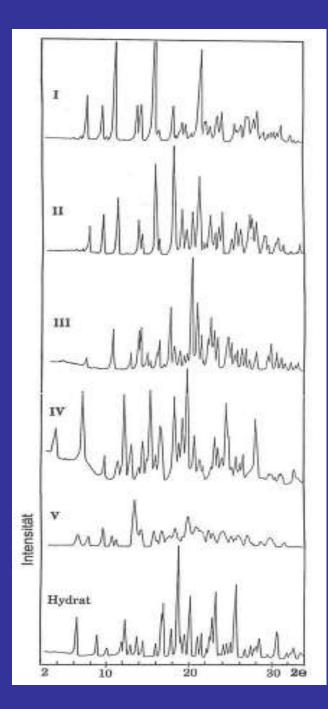
S. No	Test Parameter	TMZ-SA	TMZ
1	AUC <sub>(0-24)</sub>	21.79 µg.hr/mL	21.33 µg.hr/mL
2	C <sub>max</sub>	4.67 μg.hr/mL	4.75 μg.hr/mL
3	T <sub>max</sub>	2.0 hr	1.5 hr
4	K <sub>e</sub>	0.15 /hr	0.17 /hr
5	T <sub>1/2</sub>	4.6 hr	4.1 hr
6	AUC <sub>(0-∞)</sub>	21.98 µg.hr/mL	21.47 μg.hr/mL

## Acemetacin

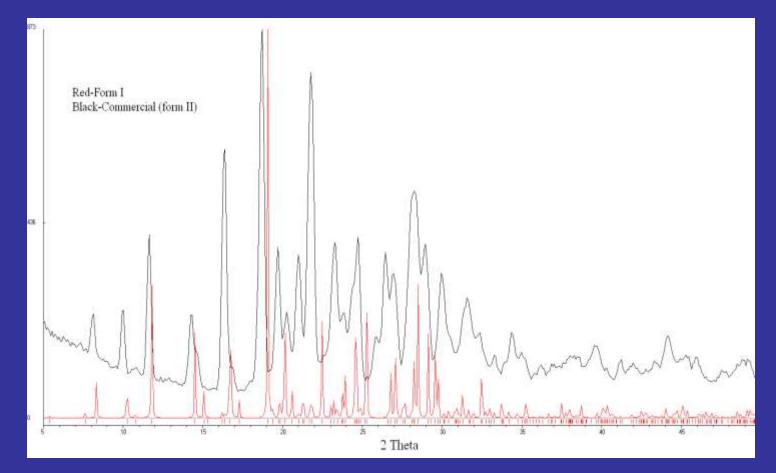
- Popular NSAID drug. Glycolic acid ester of Indomethacin. Reduces gastric acidity. Aceclofenac has same moiety.
- Acemetacin exists in several polymorphic forms (5) and a hydrate form.
- Solubility 23 mg/L at pH 5; 1.95 g/L at pH 7.4.
- Monohydrate is stable form and is obtained in normal crystallization.
- Must use super anhydrous or solvent-free conditions for ACM polymorphs.





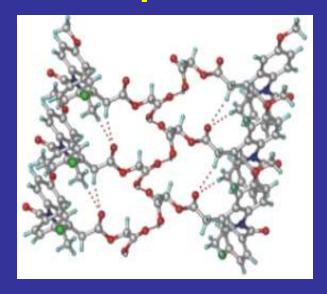


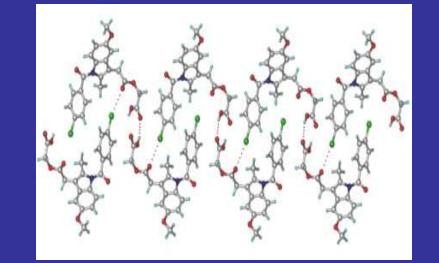
## **Our studies**

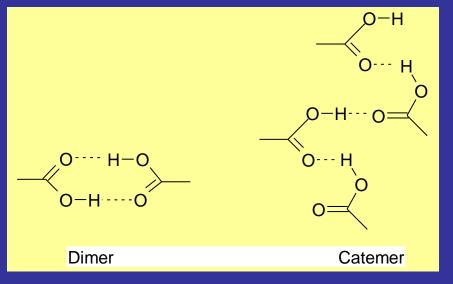


PXRD comparison of commercial acemetacin purchased from Dalian Hong Ri Dong Sheng Co. China (form II) with the calculated X-ray diffraction lines of form I crystal structure indicates that these two phases are not the same.

### **Reported X-ray structure I**





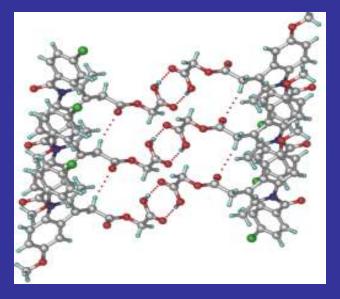


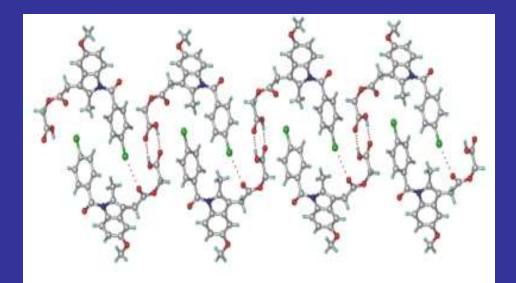
Dimer is the more common synthon in COOH crystal strutcures. Catemer chain is very rare <5% strs. Acemetacin has catemer str.(form I) but indomethacin has dimer structure

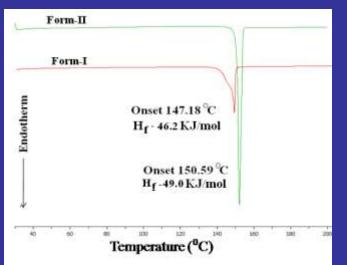
## Acemetacin form II

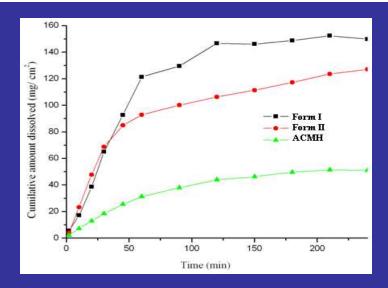
- The as received bulk material is different from polymorph I solved catemer structure
- Unable to crystallize the same material because obtained form I or the hydrate
- The crystalline powder structure was solved by SDPD (structure determination form powder XRD line pattern)
- Collaboration with Prof. Alok Mukherjee of Jadavpur Univ.

### Stable Form II structure



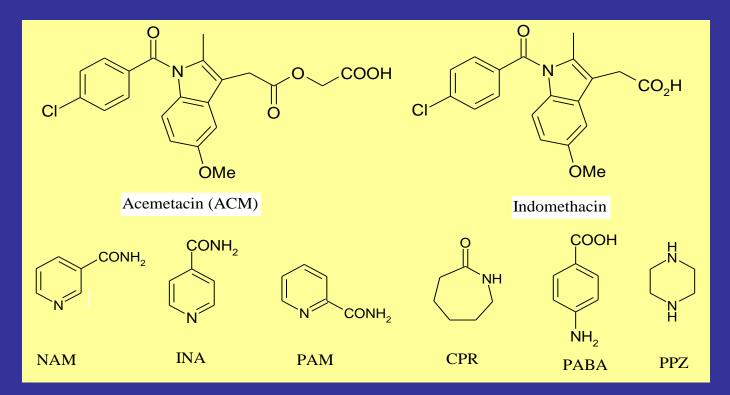






### Acemetacin salts and cocrystals

- ACM solubility is pH dependent being a COOH drug. Lowering of pH from 7.4 to 5.0, solubility decreases from 1.95 g/L to 23 mg/L.
- Explored salts and cocrystals for IDR.



#### Are the **SDPD** methods reliable?

Yes, they are! One recent example – Carvedilol dihydrogen phosphate hemihydrate,  $C_{24}H_{27}N_2O_4^+$ .  $H_2PO_4^-$ . 0.5 $H_2O_4$ **Single-crystal** OН **SDPD** Н HN CCDC refcode XOZJOM01 CCDC refcode **XOZJOM** (Vogt *et al.*, **2010**) (Chernyshev *et al.*, **2009**) a = 26.60 Å b = 12.38 Å *c* = 16.51 Å *β*= 106.66°  $V = 5207 \text{ Å}^3$ C2/cZ = 8 Z' = 1

#### Acemetacin

Three crystal structures were solved by **SDPD** methods

#### ACM-PPZ, ACM-PAM & ACM-CPR

The powder pattern were measured with the laboratory diffractometer EMPYREAN (PANalytical)

#### The first very important step – **INDEXING**

Three indexing programs were used – TREOR90, ITO & AUTOX

- **ACM-PPZ** indexed routinely by each program,
- **ACM-PAM** indexed with efforts,
- **ACM-CPR** indexed with great efforts after two weeks, several patterns were measured for indexing purposes.

#### Unit cell dimensions

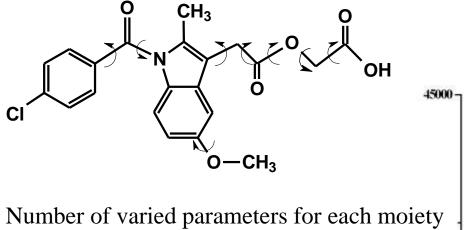
	ACM-PPZ	ACM-PAM	ACM-CPR
Empirical formula	$(C_4H_{12}N_2)^{2+} \cdot 2(C_{21}H_{17}CINO_6^{-})$	$C_{21}H_{18}CINO_6 \cdot C_6H_6N_2O$	$C_{21}H_{18}CINO_6 \cdot C_6H_{11}NO$
Space group	P-1	$P2_1$	<i>P-1</i>
<i>a</i> , Å	7.3994(15)	21.7202(15)	11.9406(16)
b, Å	25.6703(19)	5.0077(14)	21.3081(19)
<i>c</i> , Å	5.8254(17)	11.8457(17)	5.1030(14)
α, °	90.162(17)	90	92.373(15)
β, °	98.598(16)	93.954(13)	93.003(16)
γ, <sup>0</sup>	98.315(19)	90	85.308(17)
V, Å <sup>3</sup>	1082.2(4)	1285.4(4)	1291.3(4)

One parameter is significantly shorter than two others – an additional obstacle in the correct indexing from powder data.

In collaboration with Prof. Vladimir Chernyshev, Moscow Univ, RAS

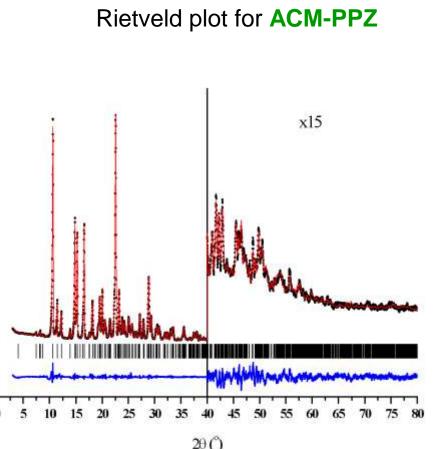
# Search for structure solution (simulated annealing) and subsequent Rietveld refinement

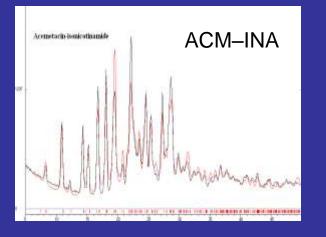
Program MRIA (Zlokazov & Chernyshev, 1992)

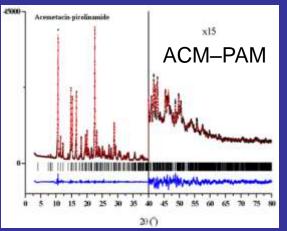


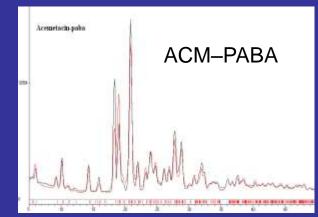
Number of varied parameters for each molety in a search for structure solution: ACM – 11 (3 translational + 3 orientational + 8 torsional), CPR – 6 (3 trans + 3 orient), PAM – 5 (2 trans + 3 orient; y - fixed in P2<sub>1</sub>),<sup>0-</sup>

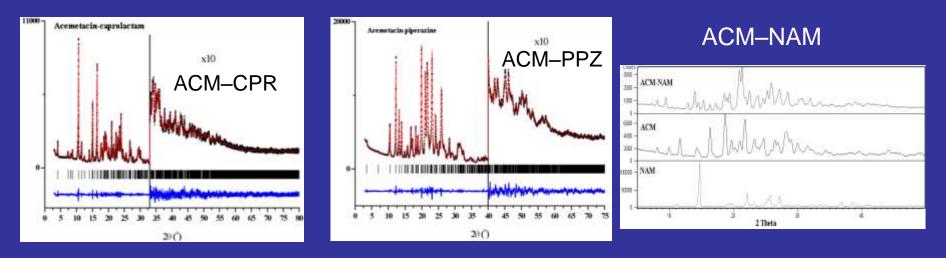
**PPZ – 3** (orientational; resides on  $\underline{1}$ ).





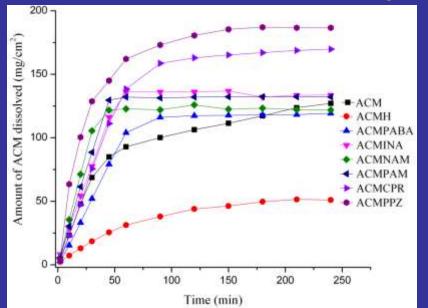




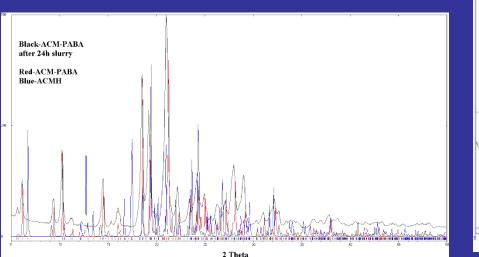


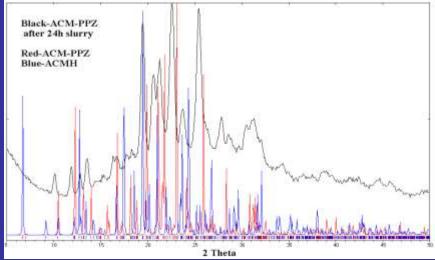
ACM-INA and ACM-PABA solved by SC-XRD ACM-PAM, ACM-CPR and ACM-PPZ solved by SDPD ACM-NAM is partially solved only

## Solubility and Stability

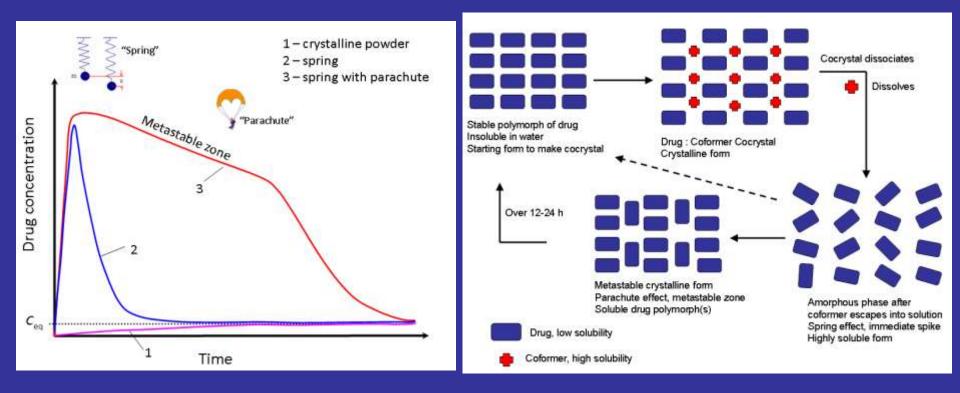


ACM-PABA and ACM-PPZ salts are showing high solubility, faster IDR and also good stability as salts Other cocrystals ACM-INA, ACM-PAM, ACM-CPR and ACM-NAM transformed to ACM hydrate in solubility slurry medium ACM-PPZ (1:0.5) appears to be optimal





### Theory of fast dissolution for cocrystals and polymorphs compared to pure API Spring and Parachute



Cryst. Growth Des. 2011, 2662

## Summary

- There are acidic (and basic) drugs for which simple salts are not an option to improve solubility
- Crystal engineering using weaker bases/ coformers is a viable strategy
- SDPD is now advanced to level of simplicity and accuracy for routine use in XRD
- By enhancing the bioavailability of complex drug molecules, thicken the pipeline for new drugs from insoluble lead molecules
- The supramolecular modification of drugs to control physico-chemical properties is the pharmacy answer to "patent cliffs"

## Acknowledgments

- University of Hyderabad
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  - D Maddileti
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  - Saikat Roy
  - Sreenivas Reddy
  - Srinivasulu A.
  - Balakrishna Reddy
  - Vishweshwar Peddy

- Funding
  - DST
  - CSIR



- UGC
- UPE and PURSE
- Ramanna Fellowship
- JC Bose Fellowship
- TBI@UOH
- LSI@IKP

#### Structure Determination from Powder Diffraction (SDPD)

**SDPD** methods can help to determine crystal structure in the cases when compounds did not produce single crystals suitable for X-ray diffraction, their growing procedures resulted only in polycrystalline powders.

David, W. I. F.; Shankland, K.; McCusker, L. B.; Baerlocher, C., Eds. *Structure Determination from Powder Diffraction Data*. Oxford University Press/International Union of Crystallography: Chester, U.K., 2002.

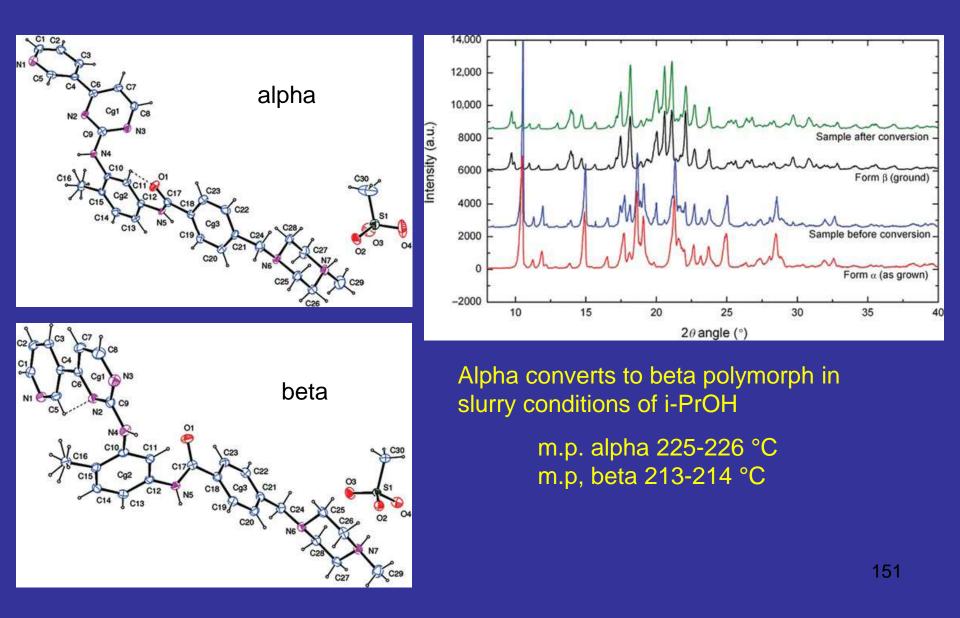
An internal limitation of SDPD - 3D crystal structure is extracted from 1D experimental data set (powder pattern).

In the single-crystal diffraction – **3D** crystal structure from **3D** data set  $\{F^2(hkl)\}$ .

### The Gleevec case

- Imatinib mesylate is the active ingredient of Gleevec, a Novartis patented drug for the treatment of CML (Chronic Myeloid Leukemia) and GIST (Gastrointestinal Stromal Tumors)
- Known to exist in several polymorphs of which two are common, alpha and beta
  - $-\alpha$  crystals are needles and hygroscopic and metastable and difficult to handle
  - β crystals are uniform morphology and easy to process and thermodynamically stable 150

# X-ray crystal structures



# The Supreme Court ruling

The story of the patent begins with Jurg Zimmerman's invention of derivatives of Nphenyl-2- pyrimidine-amine, one of which in freebase form was called "Imatinib," and together constituted a U.S. patent application (no. 5,521,184) granted on May 28, 1996 (which, the judgment terms "the Zimmermann Patent"). Subsequently, a European patent was also acquired. Later, a patent application was filed for the beta crystalline form of Imatinib Mesylate (the subject in dispute) in January 2000. Initially rejected, the patent was awarded in May 2005 following Novartis's appeal to a U.S. appellate court. What is interesting is that the filings for new drug approval, submitted in April 1998, was for Gleevec, and a filing for original drug approval in February 2001 was for Imatinib Mesylate. Confusing as this may seem, the judgment highlights this to establish that Imatinib Mesylate was covered by the Zimmerman patent and that Gleevec was its market name. Any remaining doubt, the judgment notes, is extinguished by the application for patent term extension: "This application leaves no room for doubt that Imatinib Mesylate, marketed under the name Gleevec, was submitted for drug approval as covered by the Zimmermann patent."

Evidence in a widely cited study by the National Institute of Health Care Management, Changing Patterns of Pharmaceutical Innovation, is telling. Between 1989 and 2000, the U.S. Food and Drug Authority approved 1,035 new drug applications — of these, 65 per cent contained active ingredients that were already on the market (i.e. incrementally modified drugs), 11 per cent were identical and only 15 per cent were considered a "highly innovative drug." Mischief like this results in a patent thicket around a single molecule to delay generic entry which Section 3(d) seeks to avoid. Consequently, the Supreme Court heralds Section 3(d) as a "second tier of qualifying standards for chemical substances/ pharmaceutical products in order to leave the door open for true and genuine inventions but, at the same time, to check any attempt at repetitive patenting or extension of the patent term on spurious grounds."

"Section 3(d) states, the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance (<u>therapeutic efficacy</u>) or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such process results in a new product or employs at least one new reactant."

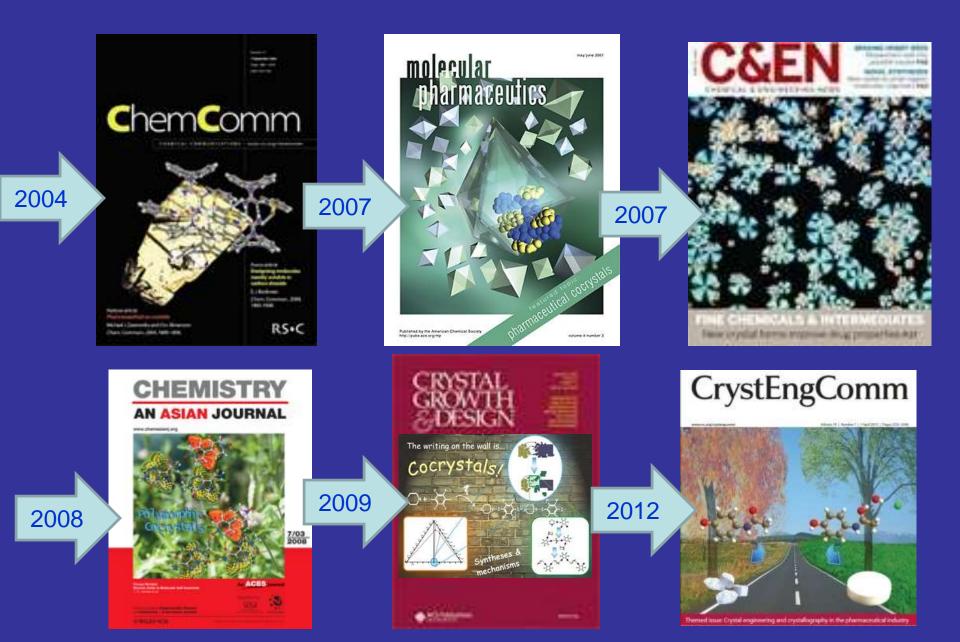
A final aspect of the judgment that needs highlighting is the pronouncement concerning drafting. The careful interrogation of the sequence of events leading to the patent application for the beta crystalline form of Imatinib Mesylate opened up gaping holes in the claims made by Novartis. These included that Gleevec was "disclosed" in the Zimmerman patent

Novartis argued that even while Gleevec could be claimed by the Zimmerman patent, it was not fully disclosed in an enabling manner. Thus, seeking to differentiate between claims and disclosure. This wonderful legalese was eloquently rejected by the Supreme Court; both, in terms of U.S. legal history that was cited and in terms of the argument's merits. And it's useful to quote at length: "We certainly do not wish the law of patent in this country to develop on lines where there may be a vast gap between the coverage and the disclosure under the patent; where the scope of the patent is determined not on the intrinsic worth of the invention but by the artful drafting of its claims by skilful lawyers, and where patents are traded as a commodity not for production and marketing of the patented products but to search for someone who may be sued for infringement of the patent."

# Summary and Conclusions

- The current decade is witnessing reorganizations in Pharma R&D
- Decline in many blockbuster drugs
- Rise of generics, biologics, repurposing
- Shift in focus form MedChem to PharmDev
- Exploit patent islands around the innovator IP – drug derivatives, solid-state forms
- In India, a balance between Patent and Patient, or Innovation and Affordability

#### A Decade of Cocrystals and Solid State Forms



#### http://www.crystalin.co.in/



#### CRYSTALIN RESEARCH PVT. LTD.

Pharmaceutical Solid State Innovation R&D Laboratory

#### **Our Services**

Crystalin Research

**API Characterization** 

Form Screen

PC/PK/PD Improvement

Phase Behavior

#### Computations

#### Patent Advice

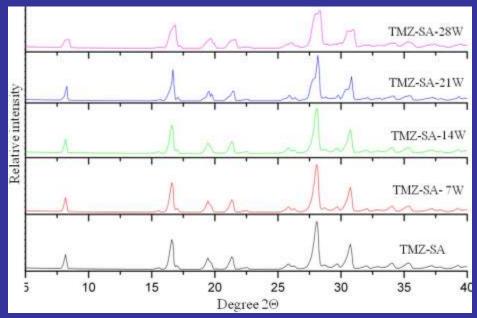


#### Who We are

Crystalin Research is a new scientific enterprise started at the Technology Business Incubator facility on University of Hyderabad campus. Crystalin will leverage Scientific Inventions and Innovations through Pharmaceutical R&D and transform into platform technologies and novel drug products. We provide reliable solutions to polymorphism and crystallization problems through in-depth knowledge and expertise of the solid-state for over a decade. Our motto is to create Intellectual Property through R&D.

The business theme of Crystalin is Chalk2Salt – to take insoluble drug molecules like chalk dust and transform them into high solubility solid forms as table salt. The discovery of novel drug forms and selection of the stable formulation is guided under the expert mentorship of Professor Ashwini Nangia, author of 180 research publications and 12 patents.

# ICH 40 °C, 75% RH stability







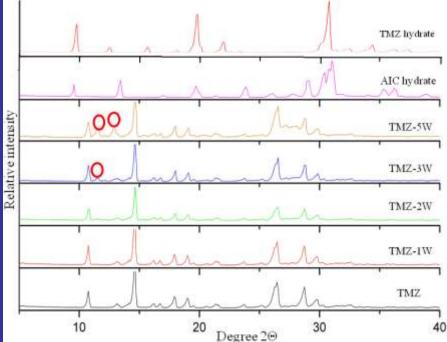


Impurity profile confirmed by HPLC and NMR









# Temozolomide – birth of a blockbuster

The history of anticancer drug temozolomide can be traced back over 30 years -

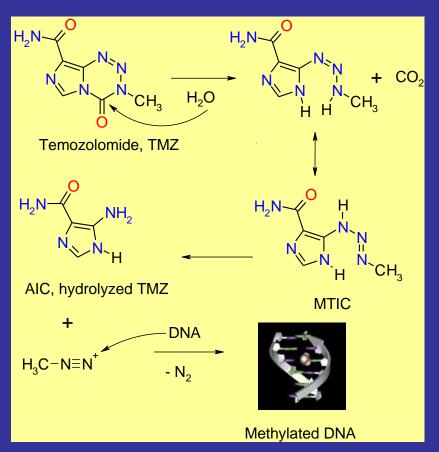
Scientists gathered from across the world in October 2008 to celebrate the 30<sup>th</sup> anniversary of the start of the research project which led to the discovery of Temodal, at Aston University, Birmingham, UK.



**Malcolm Stevens** 



**Richard Stone** 



Chemistry World, 2009, 48.

US Patent 5,260,291, 1993.

# Acknowledgments

#### University of Hyderabad

- Palash Sanphui
- Rajesh Goud
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- D Maddileti
- Sudalai Kumar
- B Geeta
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- Ranjit Thakuria
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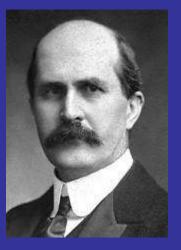


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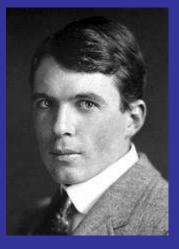
# The History of X-ray Diffraction



Max von Laue MVL German 1879-1960 1914 Physics Laue diffraction of X-rays by crystals



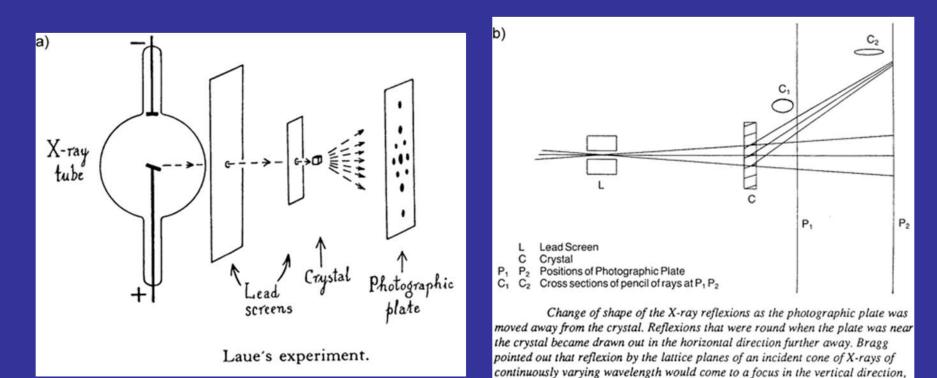
William Henry Bragg WHB England 1862-1942 1915 Physics Design of X-ray spectrometer



William Lawrence Bragg WLB Australia-England 1890-1971 1915 Physics Famous Bragg's Law  $n\lambda = 2d \sin\theta$ 

#### 2014 – IYCr In celebration of Bragg Centenary

### Laue's experiment

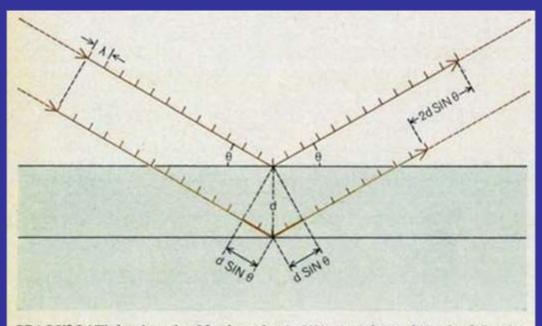


#### Note the elliptical spots on Laue's diffraction experiment

Bragg realized that the <u>diffraction</u> of Xrays (in Laue experiment) was nothing but the <u>reflection</u> of the rays from the atomic planes in the crystal

but would spread out in the horizontal direction

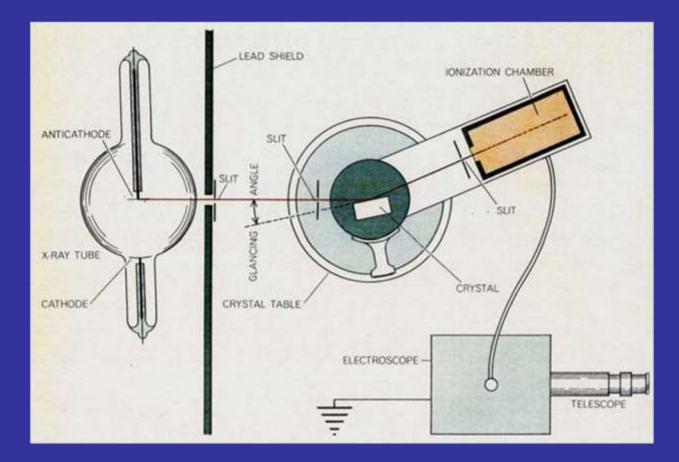
#### WLB – Bragg's Law $n\lambda = 2d \sin \theta$



BRAGG'S LAW, first formulated by the author in 1912, states the condition for diffraction of an incident beam of monochromatic X rays by the successive sheets of atoms in a crystal. In general terms the law states that if the path difference for waves reflected by successive sheets of atoms is a whole number of wavelengths, the wave trains will combine to produce a strong reflected beam. In more formal geometric terms, if the spacing between the reflecting planes of atoms is d and the glancing angle of the incident X-ray beam is  $\theta$ , the path difference for waves reflected by successive planes is  $2d \sin \theta$ . In this diagram the extra path followed by the lower ray (heavy colored line at bottom) is four wavelengths long, which is exactly equal to the path difference of  $2d \sin \theta$  between the two diffracted rays (upper right).

Original equation was  $n\lambda = 2d \cos \theta$ 

### WHB – Designed the spectrometer

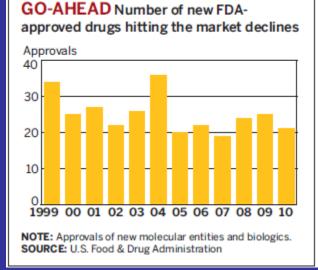


X-ray diffractometer was designed by WHB and used by WLB to record the reflections of chemical compounds NaCl, KCl, ZnS, CaF2, CaCO3, FeS2 and Diamond!

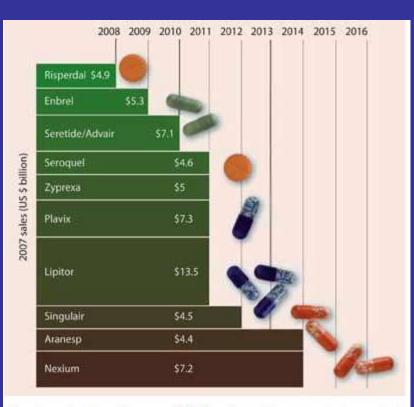


# The Current Crisis in Pharma Industry

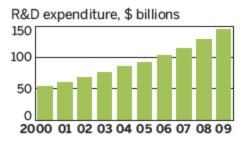
- R&D costs rising exponentially
- Number of new drug molecules falling
- Blockbuster drugs falling off patent cliff
- Advanced drug candidates of poor solubility
- Downsizing of BIG Pharma R&D
- M&A with small biotech/ innovation start ups
- Shift in R&D from MedChem to PharmDev



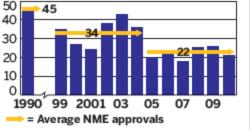
#### GENERICS \$ Billions 30 ASCENDANT In the U.S., \$95 billion in 20 branded drug sales are at risk 10 from 2010 to 2014 0 NOTE: Sales of drugs 2004 05 06 07 08 09 10 11 12 13 14 that are going off patent. SOURCE: IMS Health



DIVERGENCE As R&D spending rises, drug approvals are declining



NME approvals by FDA



NME = New molecular entity. SOURCE: CMS Pharma

#### "The engine behind pharmaceutical innovation is broken."

The pharma industry will see over \$63 billion of annual income washed away due to patent erosion by 2014

### MedChem–PharmDev cross talk

MC: I gave you that micromolar (sometime nanomolar) active compound. I only have a few mgs after an 8 step synthesis. How's the solubility looking? I have several analogs in the same series.

PD: Ya, your compound doesn't dissolve in anything except DMSO. Its like "brick dust" (chalk powder) in water. Can you not put some functional groups for making salts, like heterocycle or COOH.



# BCS class of drugs in market

Class I – High solubility, High permeability

Propranolol, Metoprolol, Diltiazem, Verapamil, Theophyline, Paracetamol, Pseudoephedrine sulfate, Motformin hydrochloride Class II – Low solubility, High pormeability

Danazol, Ketoconazole, Mefanimic acid, Nisoldipine, Nifedipine, Nicardipine, Felodipine, Atovaquone, Griseofulvin, Troglitrazone, Glibenclamade, Carbamazepine

Class III – High solubility, Low permeability

Acyclovir, Neomycin, Captopril, Enalprilate, Alendronate, Atenolol, Cimetidine, Ranitidine Class IV – Low solubility, Low permeability

Chlorothiazine, Furosemide, Tobramycin, Cefuroxime, Itraconazole, Cyclosporin

# **Drug solubility**

- Good solubility of drug is important for sufficient bioavailability of parenterals
- Problem is acute in last decade due to complex, lipophilic molecules of HTS, navigate in limited patent space, and improve specificity/ potency of drugs
- Common methods to improve solubility are salts, amorphous, micronization, CDs, nanoparticles, cocrystals, polymorphs, ...

# Solubility and Dissolution

- Solubility and Dissolution are Different
- Solubility is a thermodynamic (equilibrium) phenomenon (C<sub>s</sub>)
  - Solubility is the concentration of the substance in solution that is at chemical equilibrium with an excess of the undissolved substance
- Dissolution is the Rate at which this equilibrium state is reached (IDR, J)
- Apparent Solubility (C<sub>m</sub>) is the rate at which the metastable form dissolves with respect to the stable form, multiplied by the solubility of the stable form

$$-$$
 C<sub>m</sub> = C<sub>s</sub> × (J<sub>m</sub> / J<sub>s</sub>)

# Talk plan

- Why drug solubility is important
- Crystal Engineering
  - Heterosynthons in cocrystal design
  - Cocrystals of Temozolomide, Fluoroquinolones, Olanzapine, Curcumin, Nitrofurantoin, ....
- Modify PC and PK drug profile
  - Stability improvement in Temozolomide
  - Solubility enhancement in Norflox/ Ciproflox
  - Solubility of curcumin cocrystal polypill
- New improved medicines

# Temozolomide

- Chemotherapy for treatment of glioblastoma multiforme (GBM); Primary malignant brain and CNS tumors
- Discovered at Aston Univ. UK in 1980s in lab of Prof. Malcom Stevens (Richard Stone PhD student)
- Approved for treatment of malignant glioma in US and EU in 1999
- Temodar/ Temodal is Schering-Plough molecule; Now Merck
- TMZ prodrug, Active species is MTIC (CH3N2+)
- By product of hydrolysis is AIC, which is brown colored
- Discoloration of active from white to pink to tan

#### (19) United States

#### (12) Patent Application Publication (10) Pub. No.: US 2006/0222792 A1 Braverman et al. (10) Pub. Date: Oct. 5, 2006

#### (54) TEMOZOLOMIDE STORAGE SYSTEM

(75) Inventors: Oleg Braverman, Beer-Sheva (IL); Rimma Feinshtein, Beer-Sheva (IL); Alex Weisman, Kiriat Ekron (IL); Joseph Kaspi, Givatayim (IL)

> Correspondence Address: LEYDIG VOIT & MAYER, LTD TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE CHICAGO, IL 60601-6780 (US)

- (73) Assignee: CHEMAGIS LTD., Bnei Brak (IL)
- (21) Appl. No.: 11/409,345
- (22) Filed: Apr. 21, 2006

#### **Publication Classification**

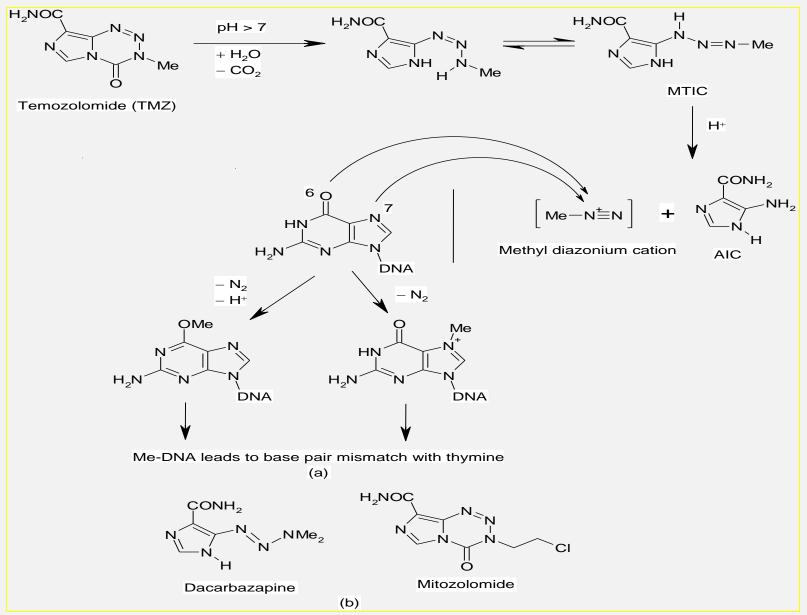
(51) Int. Cl. B32B 27/32 (2006.01)
(52) U.S. Cl. 428/35.2

#### (57) ABSTRACT

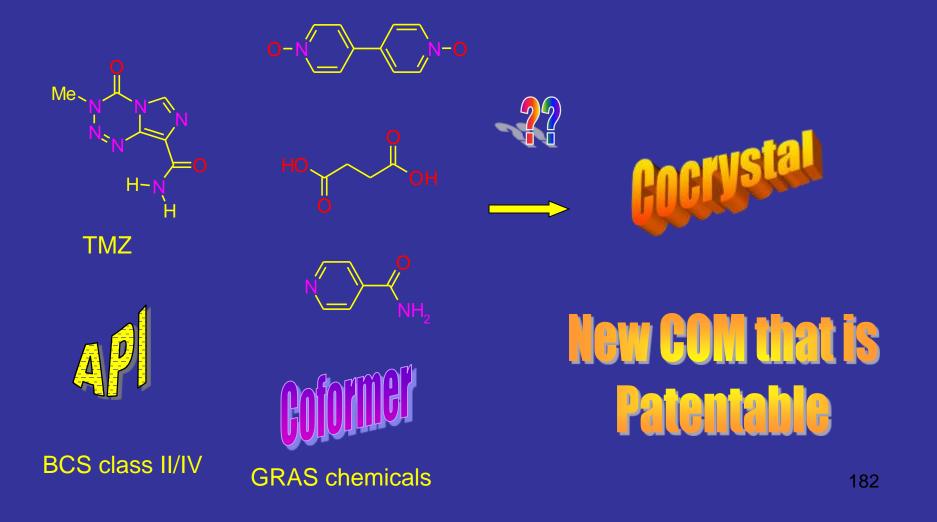
The present invention provides an improved storage system for temozolomide, which preferably includes one or more bags (e.g., 3 bags, optionally containing a desiccant interposed between two of the bags). The storage system of the present invention can maintain temozolomide as a white, stable, and dry material after long periods of storage. The present invention also provides methods of producing and storing temozolomide as a stable, white solid.

**[0004]** A process for preparing temozolomide is described in US 2002/0095036. According to the teaching of Example 1 of US 2002/0095036, temozolomide is obtained as a white precipitate. However, the Temodar® drug leaflet and the Physician Desk Reference 60<sup>th</sup> Ed. (2006) state that the material is "a white to light tan/light pink powder." The light tan/pink color is indicative of degradation.

**[0005]** In view of the apparent tendency of temozolomide to degrade, as evidenced by the change in color, there exists a need for products and methods, which improve the stability or shelf life of temozolomide. The present invention provides such products and methods.

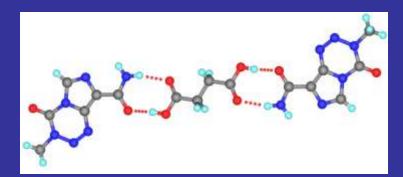


### TMZ Cocrystals Experiments planned

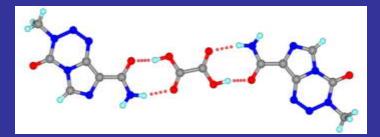


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Ethanolyzed TMZAmide-imidazole (V)TMZ vH2O1:1Amide-imidazole (V)TMZ vH2O1:1Amide-amide (I)A(VI)TMZ vMeNO21:1Amide-amide (I)ATMZ vMeNO21:1Amide-amide (I)TMZ cocrystals with COOH partnersTMZ cocrystals with COOH partnersTMZ vAcetic acid · H2O2:1:1Amide-acid (XI)AAmide-acid (XI)AAmide-acid (XI)ATMZ vAcetic acid1:1Amide-acid (XI)ATMZ vAcetic acid1:1.1Amide-acid (XI)ATMZ vAcetic acid1:1.1Amide-acid (XI)ATMZ vAcetic acid1:1.1Amide-acid (XI)ATMZ vPAminobenzoic acid ·3:1:1Amide-acid (XI)ATMZ vFumaric acid · H2O1:0:5:1Amide-acid (XI)ATMZ vSalicylic acid1:1Amide-acid (XI)ATMZ vSalicylic acid1:1Amide-acid (XI)A <td>TMZ · Methanolyzed TMZ</td> <td>1:1</td> <td>the first of a set at the set of the set of</td> <td>A</td>	TMZ · Methanolyzed TMZ	1:1	the first of a set at the set of	A	
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$\begin{array}{ccccc} \mathrm{TMZ} \cdot \mathrm{H_2O} & 1:1 & \mathrm{Amide-tetrazinone} & A \\ \mathrm{(VI)} \\ \mathrm{TMZ} \cdot \mathrm{MeNO_2} & 1:1 & \mathrm{Amide-amide} (\mathrm{I}) & A \\ \mathrm{TMZ} \cdot \mathrm{DMSO} & 1:0.5 & \mathrm{Amide-amide} (\mathrm{I}) & A \\ \hline \mathrm{TMZ} \cdot \mathrm{Cocrystals} \ \text{with COOH partners} \\ \mathrm{TMZ} \cdot \mathrm{Formic} \ \mathrm{acid} \cdot \mathrm{H_2O} & 2:1:1 & \mathrm{Amide-acid} (\mathrm{XI}) & A + B \\ & \mathrm{Amide-amide} (\mathrm{I}) \\ \mathrm{TMZ} \cdot \mathrm{Acetic} \ \mathrm{acid} & 1:1 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{TMZ} \cdot \mathrm{Oxalic} \ \mathrm{acid} & 1:0.5 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{TMZ} \cdot \mathrm{Oxalic} \ \mathrm{acid} & 1:0.5 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{TMZ} \cdot \mathrm{Succinic} \ \mathrm{acid} & 1:0.5 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{TMZ} \cdot \mathrm{Succinic} \ \mathrm{acid} & 1:0.5 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{TMZ} \cdot \mathrm{DL} \ \mathrm{Malic} \ \mathrm{acid} & 1:0.5 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{TMZ} \cdot \mathrm{DL} \ \mathrm{Malic} \ \mathrm{acid} & 1:0.5 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{TMZ} \cdot \mathrm{PAminobenzoic} \ \mathrm{acid} \cdot & 3:1:1 & \mathrm{Amide-acid} (\mathrm{XI}) & A \\ \mathrm{H_2O} & & & & & & & & & & & & & & & & & & &$	Ethanolyzed TMZ		Amide-imidazole (V)	-	
$\begin{array}{c cccc} (VI) \\ TMZ \cdot MeNO_2 & 1:1 & Amide-amide (I) & A \\ TMZ \cdot DMSO & 1:0.5 & Amide-amide (I) & A \\ \hline TMZ \ cocrystals with COOH partners \\ TMZ \cdot Formic \ acid \cdot H_2O & 2:1:1 & Amide-acid (XI) & A + B \\ & Amide-amide (I) \\ TMZ \cdot Acetic \ acid & 1:1 & Amide-acid (XI) & A \\ TMZ \cdot Oxalic \ acid & 1:0.5 & Amide-acid (XI) & A \\ TMZ \cdot Succinic \ acid & 1:0.5 & Amide-acid (XI) & A \\ TMZ \cdot Succinic \ acid & 1:0.5 & Amide-acid (XI) & A \\ TMZ \cdot DL \ Malic \ acid & 1:0.5 & Amide-acid (XI) & A \\ TMZ \cdot DL \ Malic \ acid & 1:0.5 & Amide-acid (XI) & A \\ TMZ \cdot DL \ Malic \ acid & 1:0.5 & Amide-acid (XI) & A \\ TMZ \cdot DL \ Malic \ acid & 1:0.5 & Amide-acid (XI) & A \\ TMZ \cdot P-Aminobenzoic \ acid \cdot & 3:1:1 & Amide-acid (XI) & A \\ H_2O & Amide-acid (XI) & A \\ H_2O & Amide-acid (XI) & A \\ TMZ \cdot Fumaric \ acid \cdot H_2O & 1:0.5:1 & Amide-acid (XI) & A \\ TMZ \cdot Salicylic \ acid & 1:1 & Amide-acid (XI) & B \\ TMZ \cdot Salicylic \ acid & 1:1 & Amide-acid (XI) & A \\ TMZ \cdot Salicylic \ acid \ A$	TMZ solvates				
$\begin{array}{c cccc} \mathrm{TMZ}\cdot\mathrm{MeNO}_2 & 1:1 & \mathrm{Amide-amide}\left(I\right) & A \\ \mathrm{TMZ}\cdot\mathrm{DMSO} & 1:0.5 & \mathrm{Amide-amide}\left(I\right) & A \\ \hline \mathrm{TMZ}\operatorname{cocrystals} \operatorname{with}\operatorname{COOH}\operatorname{partners} \\ \mathrm{TMZ}\cdot\operatorname{Formic}\operatorname{acid}\cdot\mathrm{H}_2\mathrm{O} & 2:1:1 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A + B \\ & \mathrm{Amide-amide}\left(I\right) \\ \mathrm{TMZ}\cdot\operatorname{Acetic}\operatorname{acid} & 1:1 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{TMZ}\cdot\operatorname{Oxalic}\operatorname{acid} & 1:0.5 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{TMZ}\cdot\operatorname{Oxalic}\operatorname{acid} & 1:0.5 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{TMZ}\cdot\operatorname{Succinic}\operatorname{acid} & 1:0.5 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{TMZ}\cdot\operatorname{Succinic}\operatorname{acid} & 1:0.5 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{TMZ}\cdot\operatorname{DL}\operatorname{Malic}\operatorname{acid} & 1:0.5 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{TMZ}\cdot\operatorname{DL}\operatorname{Malic}\operatorname{acid} & 1:0.5 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{TMZ}\cdot\operatorname{p-Aminobenzoic}\operatorname{acid} \cdot 3:1:1 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A \\ \mathrm{H}_2\mathrm{O} & \mathrm{Amide-acid}\left(\mathrm{I}\right) & A \\ \mathrm{H}_2\mathrm{O} & \mathrm{Amide-acid}\left(\mathrm{I}\right) & A \\ \mathrm{H}_2\mathrm{O} & \mathrm{I}:0.5:1 & \mathrm{Amide-acid}\left(\mathrm{I}\right) & A \\ \mathrm{Amide-tetrazinone} & (\mathrm{VI}) \\ \mathrm{TMZ}\cdot\operatorname{Salicylic}\operatorname{acid} & 1:1 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & B \\ \mathrm{TMZ}\cdot\mathrm{Hydrolyzed}\operatorname{TMZ}\cdot & 3:1:1:1 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & A + B \\ \mathrm{Cinnamic}\operatorname{acid}\cdot\mathrm{H_2\mathrm{O}} & \mathrm{Acid-imidazole}\left(\mathrm{XII}\right) \\ \hline & \mathrm{TMZ}\operatorname{cocrystals}\operatorname{with}\operatorname{CONH_2}\operatorname{partners} \\ \hline & \mathrm{TMZ}\cdot\mathrm{Isonicotinamide} & 2:1 & \mathrm{Amide-amide}\left(\mathrm{I}\right) & A + B \\ \mathrm{TMZ}\cdot\mathrm{Nicotinamide} & 2:1 & \mathrm{Amide-amide}\left(\mathrm{I}\right) & A + B \\ \hline & \mathrm{TMZ}\cdot\mathrm{Nicotinamide} & 2:1 & \mathrm{Amide-amide}\left(\mathrm{I}\right) & A + B \\ \hline & \mathrm$	$TMZ \cdot H_2O$	1:1	Amide-tetrazinone	A	
TMZ · DMSO1:0.5Amide-amide (I)ATMZ cocrystals with COOH partnersTMZ · Formic acid · H2O2:1:1Amide-acid (XI) $A + B$ Amide-amide (I)Amide-acid (XI) $A$ TMZ · Acetic acid1:1Amide-acid (XI) $A$ TMZ · Oxalic acid1:0.5Amide-acid (XI) $A$ TMZ · Succinic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · p-Aminobenzoic acid ·3:1:1Amide-acid (XI) $A$ H2OAmide-acid (XI) $A$ $A$ TMZ · Fumaric acid · H2O1:0.5:1Amide-acid (XI) $A$ TMZ · Salicylic acid1:1Amide-acid (XI) $B$ TMZ · Hydrolyzed TMZ ·3:1:1:1Amide-acid (XI) $A + B$ Cinnamic acid · H2OTMZ cocrystals with CONH2 partnersTMZ cocrystals with CONH2 partnersTMZ · Isonicotinamide2:1Amide-amide (I) $A + B$ TMZ · Nicotinamide2:1Amide-amide (I) $A + B$	10000				
TMZ cocrystals with COOH partnersTMZ · Formic acid · $H_2O$ 2:1:1Amide-acid (XI) $A + B$ Amide-amide (I)Amide-acid (XI) $A$ TMZ · Acetic acid1:1Amide-acid (XI) $A$ TMZ · Oxalic acid1:0.5Amide-acid (XI) $A$ TMZ · Succinic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · p-Aminobenzoic acid ·3:1:1Amide-acid (XI) $A$ H <sub>2</sub> OAmide-acid (XI) $A$ ATMZ · Fumaric acid · H <sub>2</sub> O1:0.5:1Amide-amide (I) $A$ TMZ · Fumaric acid · H <sub>2</sub> O1:0.5:1Amide-amide (XI) $A$ TMZ · Salicylic acid1:1Amide-acid (XI) $B$ TMZ · Hydrolyzed TMZ ·3:1:1:1Amide-amide (XI) $A + B$ Cinnamic acid · H <sub>2</sub> OTMZ cocrystals with CONH <sub>2</sub> partnersTMZ cocrystals with CONH <sub>2</sub> partnersTMZ · Isonicotinamide2:1Amide-amide (I) $A + B$ TMZ · Nicotinamide2:1Amide-amide (I) $A + B$	$TMZ \cdot MeNO_2$		Amide-amide (I)	A	
TMZ · Formic acid · $H_2O$ 2:1:1Amide-acid (XI) $A + B$ Amide-amide (I)TMZ · Acetic acid1:1Amide-acid (XI) $A$ TMZ · Oxalic acid1:0.5Amide-acid (XI) $A$ TMZ · Succinic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · p-Aminobenzoic acid ·3:1:1Amide-acid (XI) $A$ H <sub>2</sub> OAmide-acid ·1:0.5:1Amide-amide (I)TMZ · Fumaric acid · H <sub>2</sub> O1:0.5:1Amide-amide (I) $A$ TMZ · Salicylic acid1:1Amide-acid (XI) $B$ TMZ · Hydrolyzed TMZ ·3:1:1:1Amide-amide (XI) $A + B$ Cinnamic acid · H <sub>2</sub> OTMZ cocrystals with CONH <sub>2</sub> partnersTMZ · Isonicotinamide2:1TMZ · Isonicotinamide2:1Amide-amide (I) $A + B$	TMZ · DMSO	1:0.5	Amide-amide (I)	A	
TMZ · Formic acid · $H_2O$ 2:1:1Amide-acid (XI) $A + B$ Amide-amide (I)TMZ · Acetic acid1:1Amide-acid (XI) $A$ TMZ · Oxalic acid1:0.5Amide-acid (XI) $A$ TMZ · Succinic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · DL Malic acid1:0.5Amide-acid (XI) $A$ TMZ · p-Aminobenzoic acid ·3:1:1Amide-acid (XI) $A$ H <sub>2</sub> OAmide-acid ·3:1:1Amide-acid (XI) $A$ TMZ · Fumaric acid · H <sub>2</sub> O1:0.5:1Amide-amide (I) $A$ TMZ · Salicylic acid1:1Amide-acid (XI) $B$ TMZ · Hydrolyzed TMZ ·3:1:1:1Amide-amide (XI) $A + B$ Cinnamic acid · H <sub>2</sub> OTMZ cocrystals with CONH <sub>2</sub> partnersTMZ cocrystals with CONH <sub>2</sub> partnersTMZ · Isonicotinamide2:1Amide-amide (I) $A + B$	TMZ cocrystals with COOH partners				
$\begin{array}{ccccc} {\rm TMZ} \cdot {\rm Acetic\ acid} & 1:1 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm Oxalic\ acid} & 1:0.5 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm Succinic\ acid} & 1:0.5 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm DL\ Malic\ acid} & 1:0.5 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm DL\ Malic\ acid} & 1:0.5 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm p-Aminobenzoic\ acid} \cdot & 3:1:1 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm p-Aminobenzoic\ acid} \cdot & 3:1:1 & {\rm Amide-acid\ (XI)} & A \\ {\rm H}_2{\rm O} & {\rm Amide-acid\ (XI)} & A \\ {\rm H}_2{\rm O} & {\rm Amide-amide\ (I)} \\ {\rm TMZ} \cdot {\rm Fumaric\ acid} \cdot {\rm H}_2{\rm O} & 1:0.5:1 & {\rm Amide-amide\ (I)} & A \\ {\rm Amide-tetrazinone\ (VI)} \\ {\rm TMZ} \cdot {\rm Salicylic\ acid} & 1:1 & {\rm Amide-acid\ (XI)} & B \\ {\rm TMZ} \cdot {\rm Hydrolyzed\ TMZ} \cdot & 3:1:1:1 & {\rm Amide-amide\ (XI)} & A + B \\ {\rm Cinnamic\ acid} \cdot {\rm H}_2{\rm O} & {\rm Acid-imidazole\ (XII)} \\ \end{array} $				A + B	
$\begin{array}{ccccc} {\rm TMZ} \cdot {\rm Oxalic\ acid} & 1:0.5 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm Succinic\ acid} & 1:0.5 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm DL\ Malic\ acid} & 1:0.5 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm pAminobenzoic\ acid} \cdot & 3:1:1 & {\rm Amide-acid\ (XI)} & A \\ {\rm TMZ} \cdot {\rm p-Aminobenzoic\ acid} \cdot & 3:1:1 & {\rm Amide-acid\ (XI)} & A \\ {\rm H}_2{\rm O} & {\rm Amide-amide\ (I)} \\ {\rm TMZ} \cdot {\rm Fumaric\ acid} \cdot {\rm H}_2{\rm O} & 1:0.5:1 & {\rm Amide-amide\ (I)} & A \\ {\rm Amide-amide\ (I)} & {\rm Amide-tetrazinone\ (VI)} \\ {\rm TMZ} \cdot {\rm Salicylic\ acid} & 1:1 & {\rm Amide-acid\ (XI)} & B \\ {\rm TMZ} \cdot {\rm Hydrolyzed\ TMZ} \cdot & 3:1:1:1 & {\rm Amide-amide\ (XI)} & A + B \\ {\rm Cinnamic\ acid} \cdot {\rm H}_2{\rm O} & {\rm Acid-imidazole\ (XIII)} \\ \end{array}$	and the second se			9-9-52-00-0429	
TMZ · Succinic acid1:0.5Amide-acid (XI)ATMZ · DL Malic acid1:0.5Amide-acid (XI)ATMZ · p-Aminobenzoic acid ·3:1:1Amide-acid (XI)AH <sub>2</sub> OAmide-amide (I)ATMZ · Fumaric acid · H <sub>2</sub> O1:0.5:1Amide-amide (I)TMZ · Salicylic acid1:1Amide-acid (XI)BTMZ · Salicylic acid1:1Amide-acid (XI)BTMZ · Hydrolyzed TMZ ·3:1:1:1Amide-amide (XI)A + BCinnamic acid · H <sub>2</sub> OTMZ cocrystals with CONH <sub>2</sub> partnersTMZ · Isonicotinamide2:1TMZ · Nicotinamide2:1Amide-amide (I)A + B	TMZ · Acetic acid	1:1	Amide-acid (XI)	A	
TMZ · DL Malic acid1:0.5Amide-acid (XI)ATMZ · p-Aminobenzoic acid ·3:1:1Amide-acid (XI)AH <sub>2</sub> OAmide-amide (I)ATMZ · Fumaric acid · H <sub>2</sub> O1:0.5:1Amide-amide (I)ATMZ · Salicylic acid1:1Amide-acid (XI)BTMZ · Salicylic acid1:1Amide-acid (XI)BTMZ · Hydrolyzed TMZ ·3:1:1:1Amide-amide (XI)A + BCinnamic acid · H <sub>2</sub> OTMZ cocrystals with CONH <sub>2</sub> partnersTMZ · Isonicotinamide2:1TMZ · Isonicotinamide2:1Amide-amide (I)A + BTMZ · Nicotinamide2:1Amide-amide (I)A + B	TMZ · Oxalic acid	1:0.5	Amide-acid (XI)	A	
TMZ $\cdot p$ -Aminobenzoic acid $\cdot$ 3:1:1Amide-acid (XI)AH2OAmide-amide (I)Amide-amide (I)ATMZ $\cdot$ Fumaric acid $\cdot$ H2O1:0.5:1Amide-amide (I)ATMZ $\cdot$ Salicylic acid1:1Amide-acid (XI)BTMZ $\cdot$ Hydrolyzed TMZ $\cdot$ 3:1:1:1Amide-amide (XI)A + BCinnamic acid $\cdot$ H2OTMZ cocrystals with CONH2 partnersTMZ $\cdot$ Isonicotinamide2:1TMZ $\cdot$ Nicotinamide2:1Amide-amide (I)A + B	TMZ · Succinic acid	1:0.5	Amide-acid (XI)	A	
$\begin{array}{cccc} H_2O & & Amide-amide (I) \\ TMZ \cdot Fumaric acid \cdot H_2O & 1:0.5:1 & Amide-amide (I) & A \\ & Amide-tetrazinone \\ & (VI) \\ TMZ \cdot Salicylic acid & 1:1 & Amide-acid (XI) & B \\ TMZ \cdot Hydrolyzed TMZ \cdot & 3:1:1:1 & Amide-amide (XI) & A + B \\ Cinnamic acid \cdot H_2O & & Acid-imidazole (XIII) \\ \hline TMZ \ cocrystals with CONH_2 \ partners \\ \hline TMZ \cdot Isonicotinamide & 2:1 & Amide-amide (I) & A + B \\ TMZ \cdot Nicotinamide & 2:1 & Amide-amide (I) & A + B \\ \hline \end{array}$	TMZ · DL Malic acid	1:0.5	Amide-acid (XI)	A	
$\begin{array}{cccc} \mathrm{TMZ} \cdot \mathrm{Fumaric} \ \mathrm{acid} \cdot \mathrm{H_2O} & 1:0.5:1 & \mathrm{Amide-amide}\left(\mathrm{I}\right) & A \\ & \mathrm{Amide-tetrazinone} \\ & (\mathrm{VI}) \\ \mathrm{TMZ} \cdot \mathrm{Salicylic} \ \mathrm{acid} & 1:1 & \mathrm{Amide-acid}\left(\mathrm{XI}\right) & B \\ \mathrm{TMZ} \cdot \mathrm{Hydrolyzed} \ \mathrm{TMZ} \cdot & 3:1:1:1 & \mathrm{Amide-amide}\left(\mathrm{XI}\right) & A + B \\ \mathrm{Cinnamic} \ \mathrm{acid} \cdot \mathrm{H_2O} & & \mathrm{Acid-imidazole}\left(\mathrm{XIII}\right) \\ \hline \\ & \mathbf{TMZ} \ \mathrm{cocrystals} \ \mathrm{with} \ \mathrm{CONH_2} \ \mathrm{partners} \\ \hline \\ \mathrm{TMZ} \cdot \mathrm{Isonicotinamide} & 2:1 & \mathrm{Amide-amide}\left(\mathrm{I}\right) & A + B \\ \mathrm{TMZ} \cdot \mathrm{Nicotinamide} & 2:1 & \mathrm{Amide-amide}\left(\mathrm{I}\right) & A + B \\ \hline \\ \end{array}$	TMZ · p-Aminobenzoic acid ·	3:1:1	Amide-acid (XI)	A	
$\begin{array}{c c} & Amide-tetrazinone \\ (VI) \\ TMZ \cdot Salicylic acid & 1:1 & Amide-acid (XI) & B \\ TMZ \cdot Hydrolyzed TMZ \cdot & 3:1:1:1 & Amide-amide (XI) & A+B \\ Cinnamic acid \cdot H_2O & Acid-imidazole (XIII) \\ \hline TMZ \ cocrystals \ with \ CONH_2 \ partners \\ \hline TMZ \cdot Isonicotinamide & 2:1 & Amide-amide (I) & A+B \\ TMZ \cdot Nicotinamide & 2:1 & Amide-amide (I) & A+B \\ \hline \end{array}$	H <sub>2</sub> O		Amide-amide (I)		
$\begin{array}{cccc} (VI) & & & & (VI) \\ TMZ \cdot Salicylic acid & 1:1 & Amide-acid (XI) & B \\ TMZ \cdot Hydrolyzed TMZ \cdot & 3:1:1:1 & Amide-amide (XI) & A+B \\ Cinnamic acid \cdot H_2O & Acid-imidazole (XIII) \\ \hline TMZ \ cocrystals with CONH_2 \ partners \\ \hline TMZ \cdot Isonicotinamide & 2:1 & Amide-amide (I) & A+B \\ TMZ \cdot Nicotinamide & 2:1 & Amide-amide (I) & A+B \\ \hline \end{array}$	$TMZ \cdot Fumaric acid \cdot H_2O$	1:0.5:1	Amide-amide (I)	A	
$\begin{array}{cccc} \mathrm{TMZ} \cdot \mathrm{Salicylic} \ \mathrm{acid} & 1:1 & \mathrm{Amide-acid} \left(\mathrm{XI}\right) & B \\ \mathrm{TMZ} \cdot \mathrm{Hydrolyzed} \ \mathrm{TMZ} \cdot & 3:1:1:1 & \mathrm{Amide-amide} \left(\mathrm{XI}\right) & A + B \\ \mathrm{Cinnamic} \ \mathrm{acid} \cdot \mathrm{H_2O} & \mathrm{Acid-imidazole} \left(\mathrm{XIII}\right) & \\ \hline & & & & \\ \mathrm{TMZ} \ \mathrm{cocrystals} \ \mathrm{with} \ \mathrm{CONH_2} \ \mathrm{partners} & \\ \mathrm{TMZ} \cdot \mathrm{Isonicotinamide} & 2:1 & \mathrm{Amide-amide} \left(\mathrm{I}\right) & A + B \\ \mathrm{TMZ} \cdot \mathrm{Nicotinamide} & 2:1 & \mathrm{Amide-amide} \left(\mathrm{I}\right) & A + B \\ \end{array}$			Amide-tetrazinone		
$\begin{array}{ccc} \mathrm{TMZ} \cdot \mathrm{Hydrolyzed} \ \mathrm{TMZ} \cdot & 3:1:1:1 & \mathrm{Amide-amide} \ (\mathrm{XI}) & A+B \\ \mathrm{Cinnamic} \ \mathrm{acid} \cdot \mathrm{H_2O} & & \mathrm{Acid-imidazole} \ (\mathrm{XIII}) \\ & & & \\ & & $			(VI)	1000	
$\begin{array}{c c} Cinnamic acid \cdot H_2O & Acid-imidazole (XIII) \\ \hline TMZ \ cocrystals \ with \ CONH_2 \ partners \\ TMZ \cdot Isonicotinamide & 2:1 & Amide-amide (I) & A+B \\ TMZ \cdot Nicotinamide & 2:1 & Amide-amide (I) & A+B \\ \end{array}$				2000	
TMZ cocrystals with CONH2 partnersTMZ $\cdot$ Isonicotinamide2:1Amide-amide (I) $A + B$ TMZ $\cdot$ Nicotinamide2:1Amide-amide (I) $A + B$		3:1:1:1		A + B	
$TMZ \cdot Isonicotinamide2:1Amide-amide (I)A + BTMZ \cdot Nicotinamide2:1Amide-amide (I)A + B$	Cinnamic acid · H <sub>2</sub> O		Acid-imidazole (XIII)		
TMZ · Nicotinamide 2:1 Amide-amide $(I)$ $A + B$	TMZ cocrystals with CONH <sub>2</sub> partners				
이 가슴 가슴 같은 것은 이에 만든 것이 있는 것은 것이 있는 것이 있는 것은 것이 있는 것이 없는 것은 것이 있는 것이 없는 것이 있는 것이 없는 것은 것이 있는 것이 없는 것이 없는 것은 것이 있는 것이 없는 것은 것이 없는 것이 없다. 것이 없는 것이 없다. 것이 없는 것이 없다. 것이 없는 것이 없다.	TMZ · Isonicotinamide	2:1	Amide-amide (I)	A + B	
TMZ · Pyrazinamide 1:1 Amide_pyrazine (III) 4	TMZ · Nicotinamide	2:1	Amide-amide (I)	A + B	
The Pyrachian av	TMZ · Pyrazinam ide	1:1	Amide-pyrazine (III)	Α	
Amide-imadazole (IV)	~		Amide-imadazole (IV)		
TMZ · 4-hydroxybenzamide 2:1 Amide-amide (I) A	TMZ · 4-hydroxybenzamide	2:1	Amide-amide (I)	A	
TMZ · Saccharin 1:0.5 Amide-amide (I) B	TMZ · Saccharin	1:0.5	Amide-amide (I)	В	

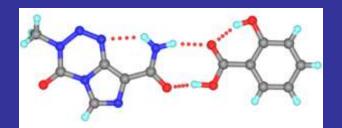
### TMZ Cocrystals with CO<sub>2</sub>H CCFs



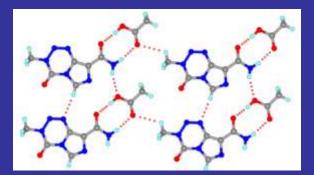
TMZ-Succinic acid (1:0.5)  $pK_a = 4.2, 5.6$ 



TMZ·Oxalic acid (1:0.5)  $pK_a = 1.2, 4.2$ 



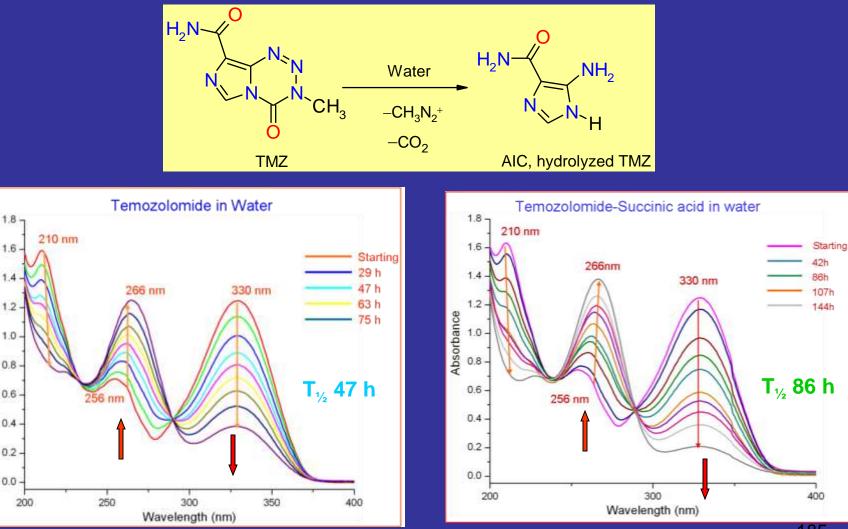
TMZ·Salicylic acid (1:1)  $pK_a = 2.9$ 



TMZ·Acetic acid (1:1)  $pK_a = 4.7$ 

With the knowledge that TMZ is stable at acidic pH < 5 but labile at pH > 7, it was co-crystallized with GRAS organic acids as pH adjusters to improve API stability.

## API and API•COOH stability



1.6

1.4

1.2

1.0

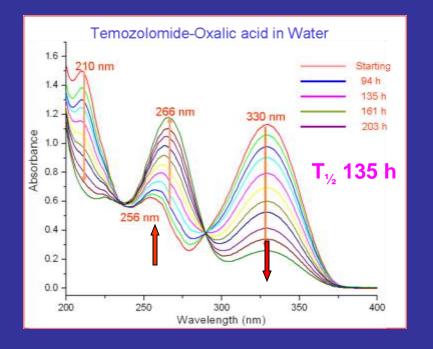
0.8

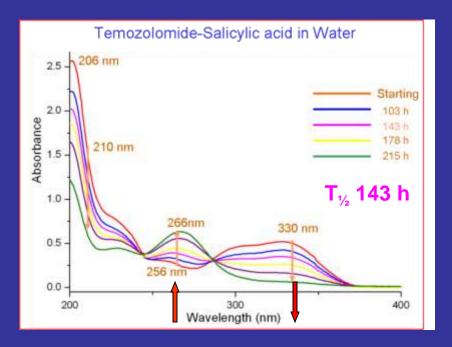
0.6

0.4

0.0

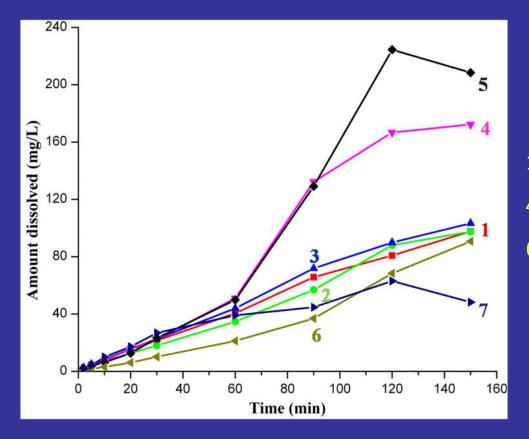
Absorbance





- Stability studies at 25  $\mu$ g/mL conc. High T<sub>½</sub> (47 h) of TMZ at higher conc. compared to reported value from *in vivo* studies
- Mean  $T_{\frac{1}{2}}$  at plasma conc. 1.8 h (1.7-1.9 h)
- Repeated stability measurements at 10 μg/mL, pH 7.0 buffer 37 °C
- T<sub>1/2</sub> = TMZ 1.7 h, T<sup>1</sup>/<sub>2</sub> cocrystals : anth 2.2, suc 2.3, d,l-tart 2.5 h, d,l-malic 2.7, oxal 3.5, salic 3.6 h
- No discoloration of TMZ•Succinic acid CC even after 1 year of storage

# Dissolution of cocrystals is good



TMZ, **2. TMZ-oxalic, 3. TMZ-succinic,** TMZ-salicylic, 5. TMZ-malic,
 TMZ-anthranilic, 7. TMZ-tartaric acid

Stability <u>and</u> Dissolution criteria <u>TMZ-succinic</u> ~TMZ-oxalic > TMZ-salicylic > TMZ-malic

Chemistry – An Asian Journal, dx.doi.org/10.1002/asia.201200205

#### Stability of cocrystal vs. TMZ Accelerated ICH study at 40 °C, 75% RH



TMZ as crystallized





TMZ TMZ-succinic acid



4 wks

7 wks - 1 yr

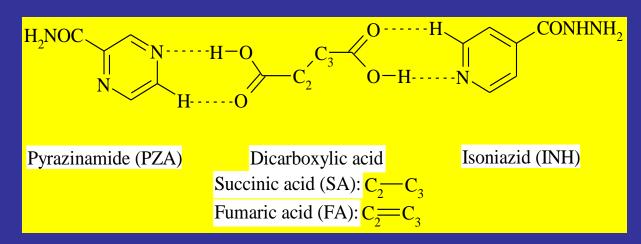
# **Chemistry to Clinic**

- FDA guidance on regulatory classification of pharma cocrystal
- Translation of Temo cocrystals through pre-clinical and clinical – BIPP support
- Development of Curcumin-Pyrogallol cocrystal as Polypill – IKP seed grant
- Technology Business Incubator @UOH

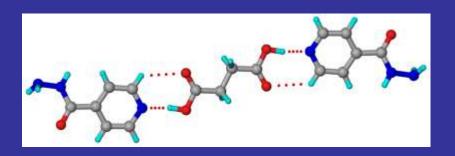
## Polymorphs, Cocrystals ...

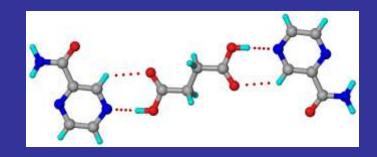
- What about Eutectics??
- Eutectic is a multi-component (2/3) constant composition low melting phase compared to the individual compounds
- Different from crystalline such as salts, cocrystals, polymorphs, and amorphous
- Drug-Drug eutectic compositions are known, e.g. paracetamol-cloperastine HCl, fenofibrate-aspirin, lidocaine-prilocaine

## Pyrazinamide and Isoniazid

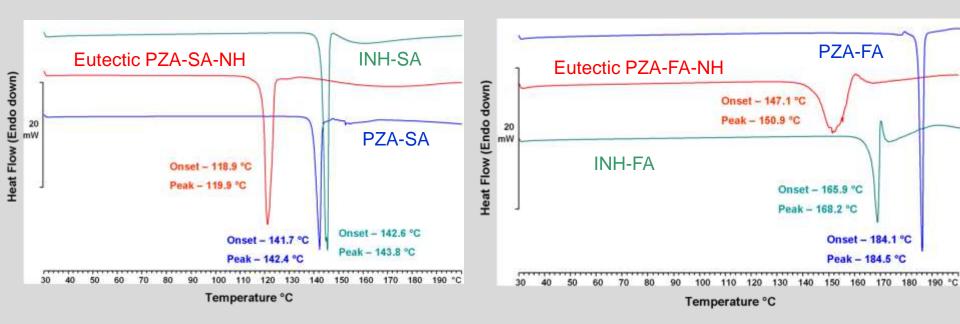


 Instead of expected ternary eutectic, eutectic of binary cocrystals were obtained



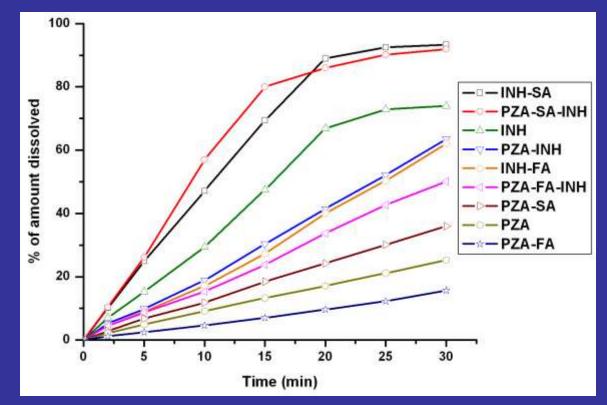


# Characterization of eutectic



- Lower m.p. of eutectic compared to individual components is surest +ve confirmation
- Ground mixture of cocrystals, physical mixture of cocrystals and physical mixture of components gave same melting endotherm in DSC
- Heating of samples lead to eutectic formation in DSC pan
- Ss NMR, PXRD and IR confirmed ternary eutectic composition of binary cocrystals

#### **Dissolution curves**



- Among INH and PZA, pyrazinamide is less soluble drug in FDC
- INH-SA cocrystal and PZA-SA-INH ternary eutectic are fast dissolving
- Dramatic improvement due to SA (cf PZA-SA-INH vs PZA-INH)
- FA reduces solubility of drug
- PZA–SA–INH dissolves 92% in 30 min (pH 1.2) = rapid dissolution

## **Summary and Future**

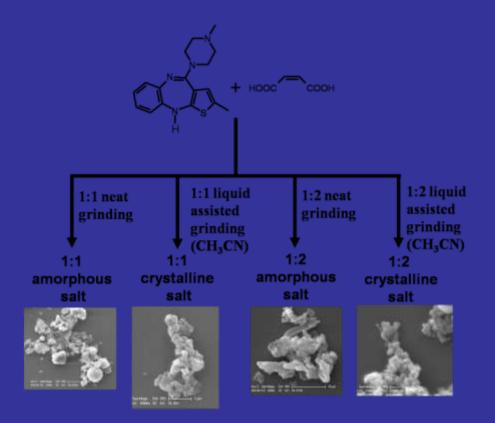
- Many potent lead molecules in pre-clinical pipeline thanks to HT screens of 1990s
- Rational crystal engineering approaches to tune PC-PK-PD of drugs
- Stability due to crystalline forms of APIs
- Improved dissolution, controlled release, better tableting, superior medicines by CE
- ICEs = improved chemical entities

#### Pharma Cocrystals – Case Studies Applicable to BCS Class II Drugs

- CBZ·COOH cocrystals Mike Z, CGD, 2003
   Cocrystals over less soluble hydrate
- CBZ·Sac cocrystal Mike Z, Almarrson, 2007
   Oral bioavailability of CC = marketed drug form
- Fluoxetine HCI·COOH S Childs, JACS, 2004
  - Cocrystals of higher dissolution profile
- Itraconazole COOH Almarsson, JACS, 2003
  - Succinic acid cocrystal = amorphous drug
- AMG517.Sorbic acid– A Bak, JPS, 2008

- 30 mg/kg of CC = 500 mg/kg of free base

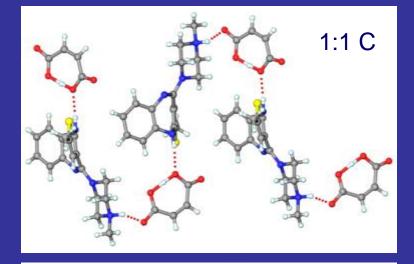
## Olanzapine – Maleic acid

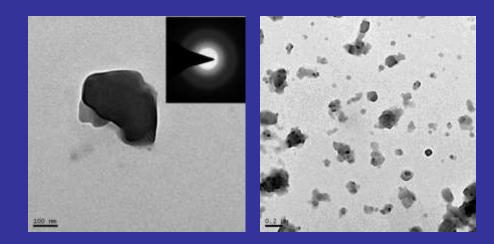


- OLN is antipsychotic drug marketed by Eli Lily
- Sol. 43 mg/L
- D<sub>o</sub> = ratio of drug dosage in 250 mL : sat. sol. of drug in water
- $D_{\rm o} = 20 \text{ mg} / 250 \text{ mL} : 43 \text{ mg/L} \approx 2$
- Cocrystals with malonic, succinic, maleic, fumaric, tartaric, adipic acid, etc.
- MA sol. 780 mg/mL
- Salt or cocrystal?  $\Delta pK_a$  rule
  - Rare case of 4 different salts of the same API counterion

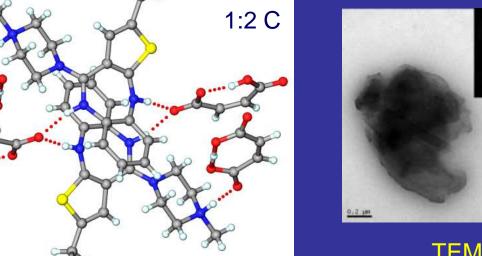
IN Patent application No. 747/CHE/2010 CrystEngComm, under revision

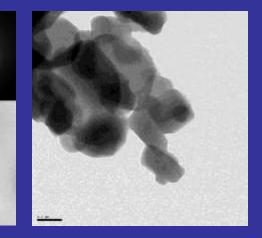
## **Olanzapine maleate salts**





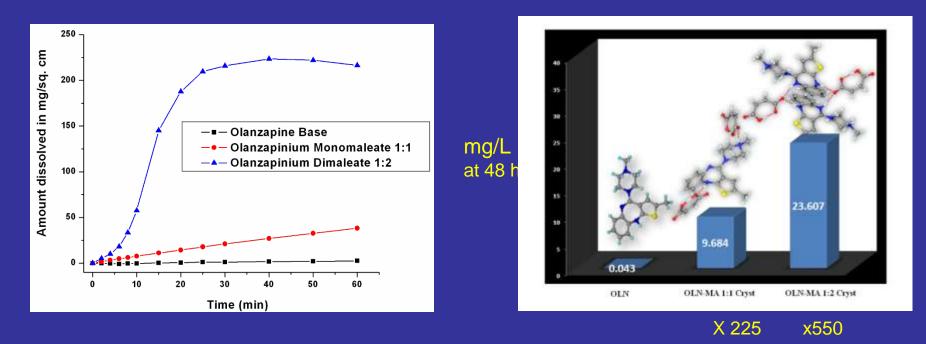
#### TEM 1:1 A, ED in inset





TEM 1:1 C, ED in inset

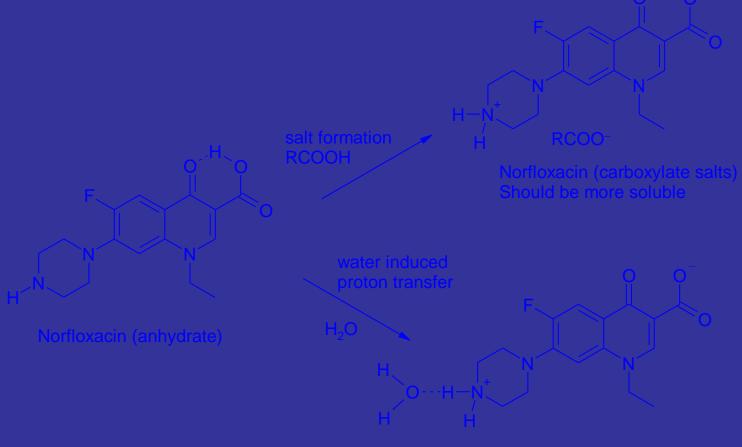
## **Solubility Enhancement**



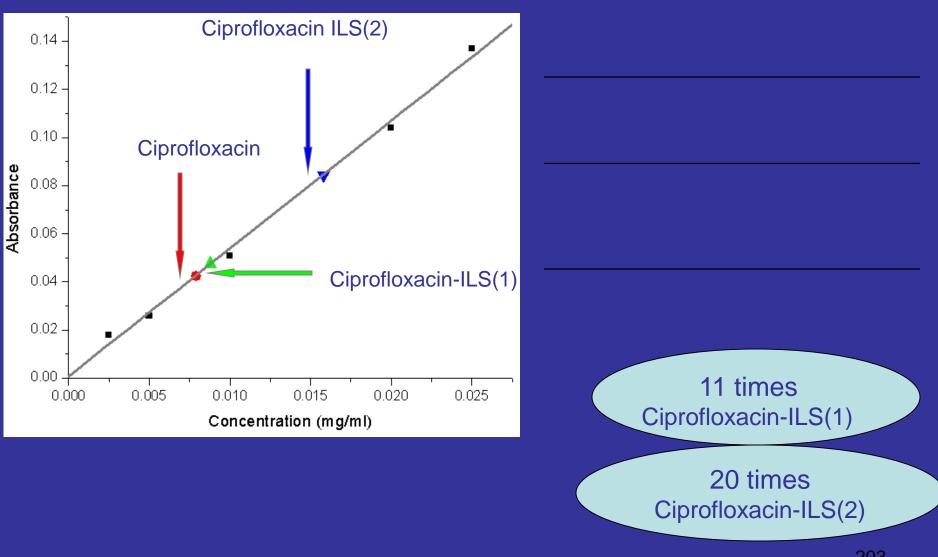
#### Why dimleate is better than monomaleate?

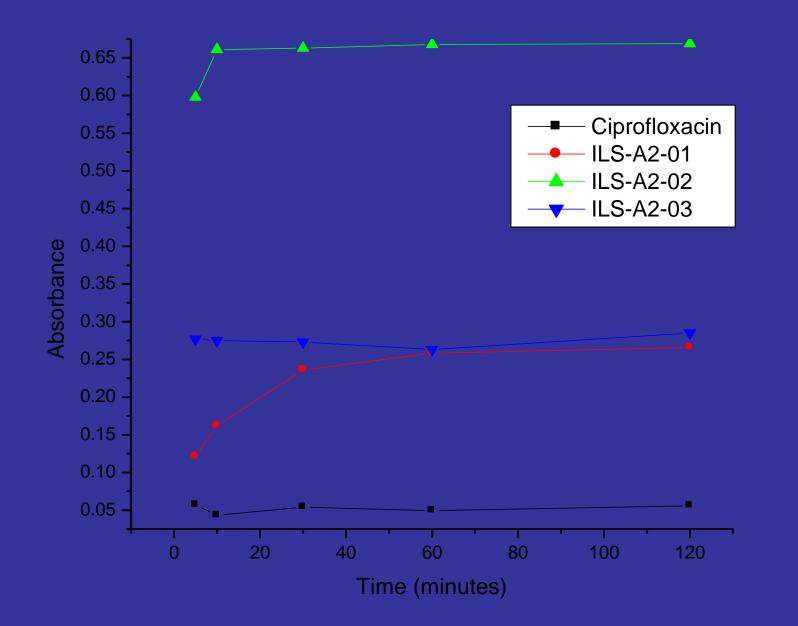
- 1. Higher charge of counterion will give better / faster hydration
- 2. 1:1 salt has infinite H bond chain; 1:2 salt has discrete aggregates
- 3. Maleate ion environment 2 HB donors in mono but 1 in dimaleate

## Norfloxacin – Neutral and Ionic Pure API and Cocrystal



Norfloxacin hydrate (zwitterionic) Highly soluble





### Sirtuin inhibitor molecules





 $23 \ \mu M$ 

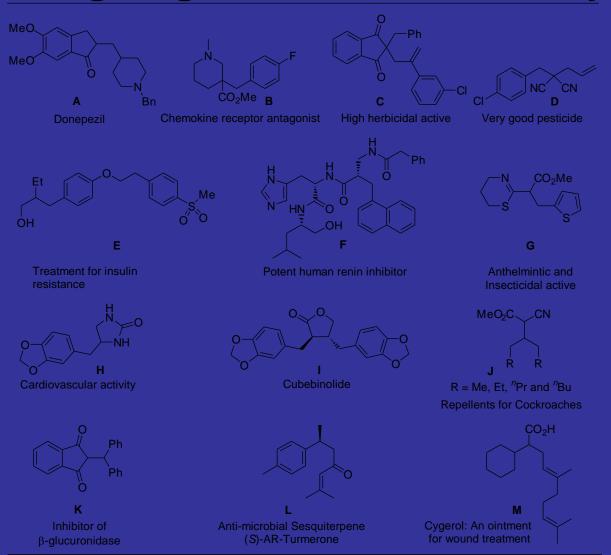


 $33 \ \mu M$ 



Courtesy Prof SCN

#### Development of Drug Synthesis Using Organo-Click Chemistry







2 hits XATROA QOVXII

·H-O



IBEMAD IDEBEZ JOKROR MIYBAX01 NASQED01 VAGVIJ YOVQUW01 VETWIB XATROA

Hydrogen bond contacts O-H distance 1.4 - 2.2 Å O-H...O angle 140 - 180 deg

CSD filters 3D coordinates determined No polymer No error R factor <= 0.1 9 hits BEQJUC DASXIF GEHKIO IBEMAD IDEBEZ CUNVUD01 QUFDAX QOVXII LUWFAK

O–H donor environment around 48 maleate ions in the CSD. The Refcode for O– $H_{donor}$ ···O<sub>maleate</sub> hydrogen bond from one donor (black, 14 hits), two donors (red, 3 hits), and three donors (blue, 1 hit) are shown

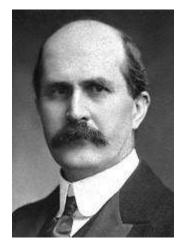


#### Crystalin Research TBI@UoH innovation venture

## The History of X-ray Diffraction



Max von Laue MVL German 1879-1960 1914 Physics Laue diffraction of X-rays by crystals

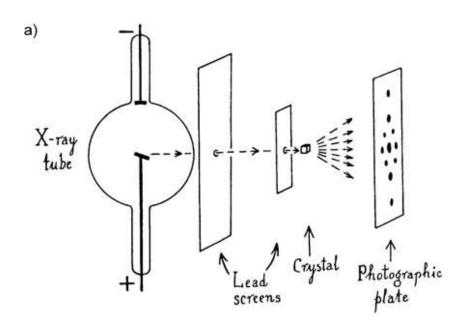


```
William Henry
Bragg
WHB
England
1862-1942
1915 Physics
Design of X-ray
spectrometer
```



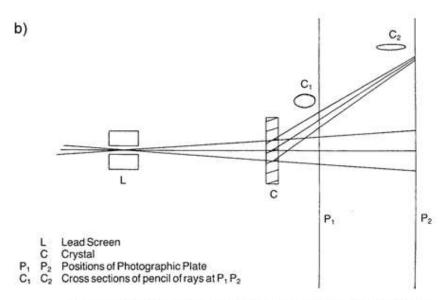
William Lawrence Bragg WLB Australia-England 1890-1971 1915 Physics Famous Bragg's Law  $n\lambda = 2d \sin\theta$ 

#### Laue's experiment



Laue's experiment.

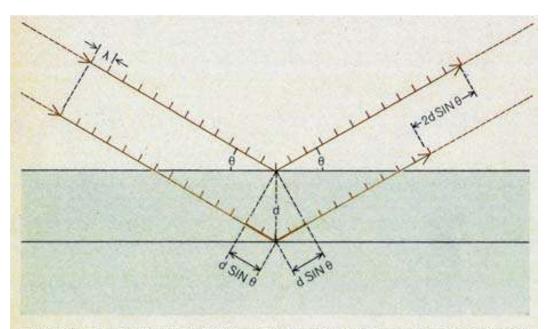
Note the elliptical spots on Laue's diffraction experiment



Change of shape of the X-ray reflexions as the photographic plate was moved away from the crystal. Reflexions that were round when the plate was near the crystal became drawn out in the horizontal direction further away. Bragg pointed out that reflexion by the lattice planes of an incident cone of X-rays of continuously varying wavelength would come to a focus in the vertical direction, but would spread out in the horizontal direction

Bragg realized that the <u>diffraction</u> of X-rays (in Laue experiment) was nothing but the <u>reflection</u> of the rays from the atomic planes in the crystal

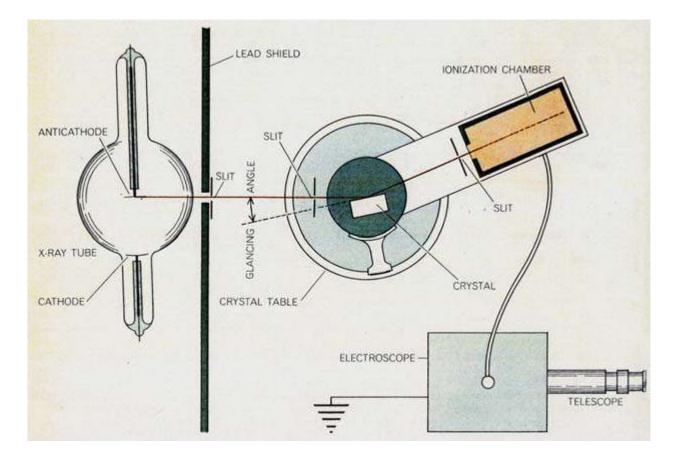
#### WLB – Bragg's Law $n\lambda = 2d \sin \theta$



BRAGC'S LAW, first formulated by the author in 1912, states the condition for diffraction of an incident beam of monochromatic X rays by the successive sheets of atoms in a crystal. In general terms the law states that if the path difference for waves reflected by successive sheets of atoms is a whole number of wavelengths, the wave trains will combine to produce a strong reflected beam. In more formal geometric terms, if the spacing between the reflecting planes of atoms is d and the glancing angle of the incident X-ray beam is  $\theta$ , the path difference for waves reflected by successive planes is  $2d \sin \theta$ . In this diagram the extra path followed by the lower ray (heavy colored line at bottom) is four wavelengths long, which is exactly equal to the path difference of  $2d \sin \theta$  between the two diffracted rays (upper right).

Original equation was  $n\lambda = 2d \cos \theta$ 

#### WHB – Designed the spectrometer



X-ray diffractometer was designed by WHB and used by WLB to record the reflections of chemical compounds NaCl, KCl, ZnS, CaF2, CaCO3, FeS2 and Diamond!

#### 2014 – IYCr In celebration of Bragg Centenary







## Salt or Cocrystal?

Molecule	рК <sub>а</sub>	Molecular component	∆ <b>pK</b> <sub>a</sub>
Olanzapine	7.37, 4.69	Olanzapine and maleic acid 1:1	5.45
Maleic acid	1.92, 6.27	Olanzapine and maleic acid 1:2	5.45, 2.77
Malonic acid	2.83, 5.69	Olanzapine malonic acid 1:1	4.54
Fumaric acid	3.03, 4.44	Olanzapine and fumaric acid	4.34
Salicylic acid	2.97	Olanzapine and salicylic acid	4.4
PABA	4.65	Olanzapine and PABA	2.72

#### Solid-state From Innovation The Way Forward

- The number of blockbuster NCEs launched worldwide is dropping
- And costs continue to rise
- Where will next generation of drugs come from?

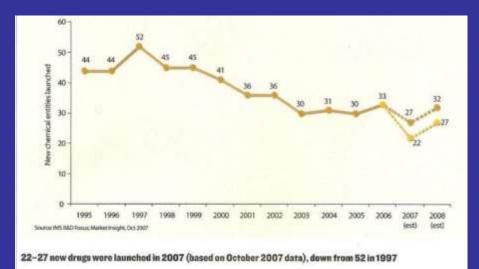


Table 1   Big pharma R&D output has dropped measurably since the early 1990s*							
Output measure	1991-1995	1996-2000	Percent change				
NCE output (product per company)	12.3	7.2	41%				
R&D spend (US \$ billion per company)	5.9	8.5	44%				
NCE sales (US \$ billion per product)	536	786	46%				
Number of new blockbuster launches <sup>‡</sup>	15	12	20%				

\*Average company statistics. #Blockbuster defined as sales greater than US \$2 billion. Sources: PJB Publications Pharmaprojects; Food and Drug Administration/Center for Drug Evaluation and Research; company reports; analyst reports; IMS Health.

#### Crystal Structure Organization and Stabilization



New Scientist 1991, 13 July



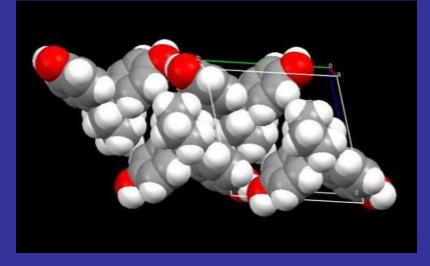
A hydrogen bond is like the attraction of a hummingbird to a flower...

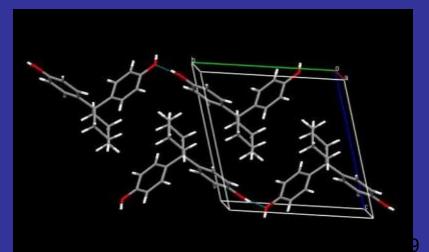


dire

...strong and directional, and also, lovely --Margaret C. Elter

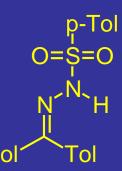
Chem. Mater. 1994, August





# **Organization and Stabilization**

Polymorph	Ulatt v	vanderWaals	Electrostatic	∆Ulatt	ΔEconf	ΔEtotal
form 1	-41.13	-39.74	-1.39	3.39	0.00	3.39
form 2	-42.10	-41.33	-0.77	2.42	6.29	8.71
form 3	-44.52	-42.32	-2.20	0.00	0.85	0.85



- Crystal structure total energy = Ulatt is make up of electrostatics, H bonding and van der Waals
- H bonding typical contributes 15-20% of energy
- Balance 80% is van der Waals and packing
- 20% energy controls 80% of the structure motif
- Therefore justified to use a H bonding model

COMMUNICATION

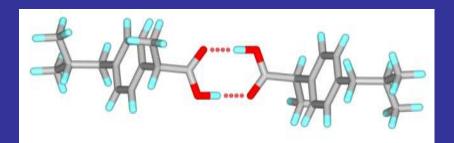
#### 186

#### Crystal engineering of the composition of pharmaceutical phases

R. D. Bailey Walsh,<sup>a</sup> M. W. Bradner,<sup>a</sup> S. Fleischman,<sup>a</sup> L. A. Morales,<sup>a</sup> B. Moulton,<sup>a</sup> N. Rodríguez-Hornedo<sup>b</sup> and M. J. Zaworotko<sup>\*a</sup>

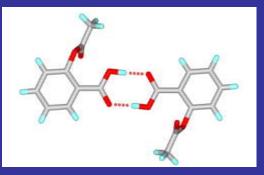
<sup>a</sup> Department of Chemistry, University of South Florida, 4202 E Fowler Ave (SCA 400), Tampa, FL 33620-5250, USA. E-mail: xtal@usf.edu; Fax: +1 813-974-3203; Tel: 813-974-4129

<sup>b</sup> Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109-1065, USA

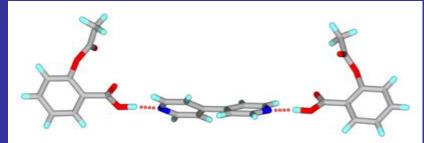


### Ibuprofen and its cocrystal





#### Aspirin and its cocrystal



## Structure of a 1:1 complex between the anthelmintic drug mebendazole and propionic acid

J Chem Cryst 1998, 11

Mino R. Caira,<sup>(1)</sup>\* Theo G. Dekker,<sup>(2)</sup> and Wilna Liebenberg<sup>(2)</sup>

# Molecular complexes of sulfonamides. 3. Structure of 5-methoxysulfadiazine (Form II) and its 1:1 complex with acetylsalicylic acid

J Chem Cryst 1994, 695

Mino R. Caira<sup>(1)</sup>

Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid state

Mino R. Caira,\* Luigi R. Nassimbeni and Alexander F. Wildervanck Department of Chemistry, University of Cape Town, Rondebosch 7700, South Africa

J Chem Soc Perkin 2 1995, 2213

## Temozolomide – birth of a blockbuster

The history of anticancer drug temozolomide can be traced back over 30 years -

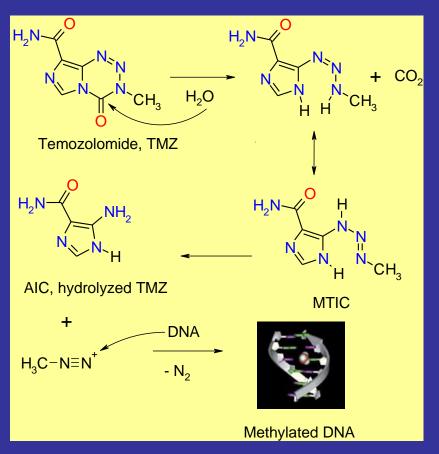
Scientists gathered from across the world in October 2008 to celebrate the 30<sup>th</sup> anniversary of the start of the research project which led to the discovery of Temodal, at Aston University, Birmingham, UK.



**Malcolm Stevens** 



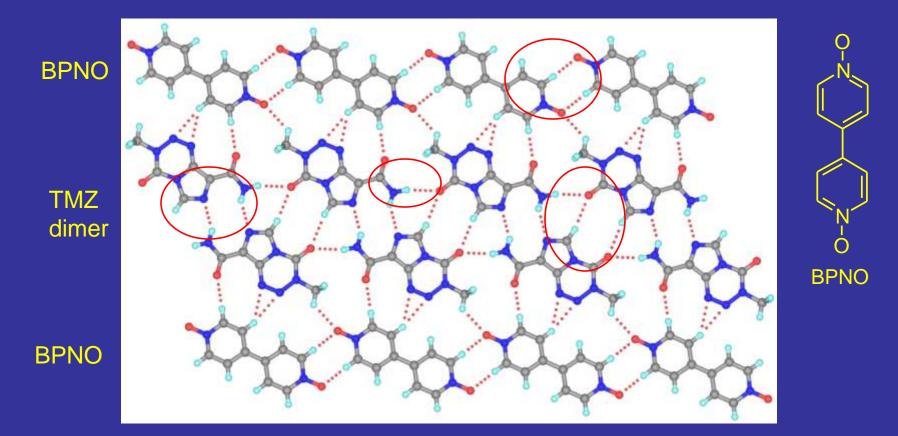
**Richard Stone** 



Chemistry World, 2009, 48.

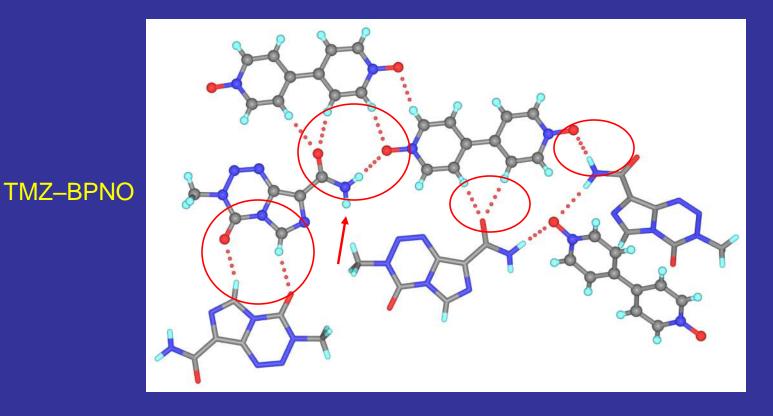
US Patent 5,260,291, 1993.

### TMZ : BPNO 1:0.5 Form I (MeCN/EtOH)



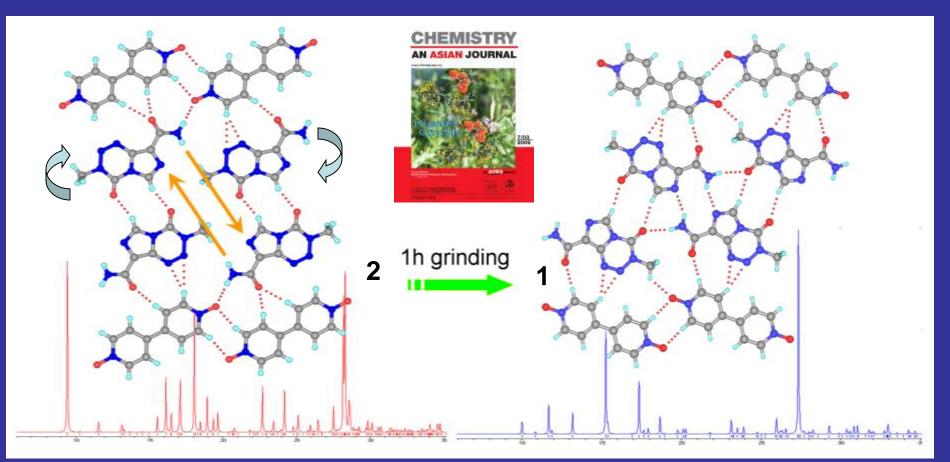
**TMZ** syn N–H···O amide, anti N–H···N dimer, C–H···O dimer **BPNO** C–H···O dimer, Weak TMZ–BPNO C–H···O interaction

### TMZ : BPNO 2:1 From II (MeOH, US or DMSO)



**TMZ** syn N–H···O N-oxide, C–H···O dimer anti N–H is not intermolecularly bonded

### **Enantiotropic system**



Non-bonded N-H (metastable) form  $2 \rightarrow N-H\cdots N$  (stable) form 1 Nangia, *Chem. Asian J.* **2008**, *3*, 1122-1133. <sup>226</sup>

## Why make TMZ cocrystals?

- Chemistry World, July 2009, 48-51. Invented by Malcolm Stevens.
- Blockbuster anticancer drug. Treatment of choice for brain tumors.
- Schering-Plough. Temodar®/ Temodal®. Sales \$1 billion in 2008.
- White color turns to light tan/pink powder, indicates degradation.
- Hydrolytic degradation in H<sub>2</sub>O, MeOH and EtOH and rate of hydrolysis is higher in water compared to pure ROHs.
- Samples with 1.8% water content decompose faster than <0.1% water.</li>
   Undergoes degradation at 45% RH.
- Stable at pH < 5 but labile at pH > 7.
- Two batches of freshly prepared TMZ.

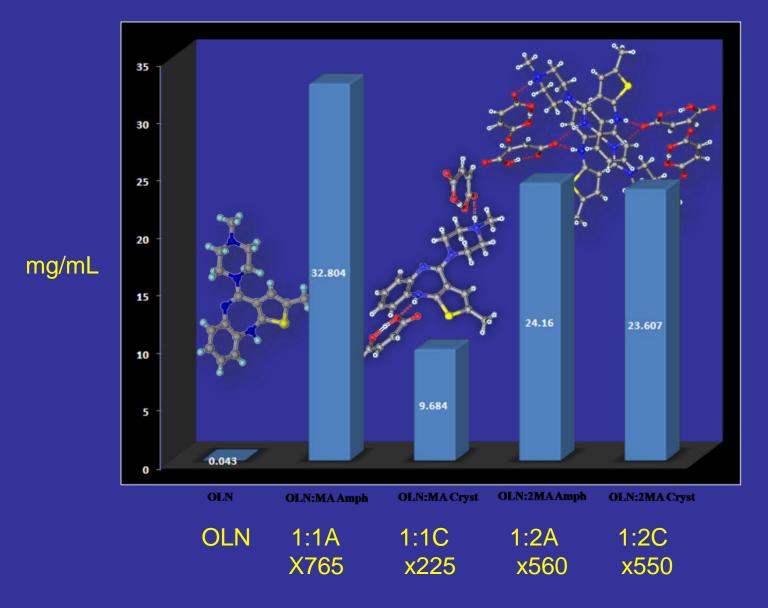




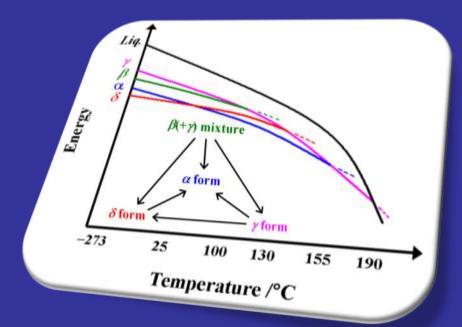
## Talk plan

- Crystal Engineering
  - Heterosynthons in cocrystal design
  - New cocrystals of Acid and Amide APIs
  - Cocrystals of Temozolomide, Fluoroquinolones, SNRI
- Modify PC and PK drug profile
  - Stability improvement in Temodar
  - Solubility enhancement in Norflox/ Ciproflox
  - Amorphous salt of Olanzapine
  - Stability and Dissolution studies
- IP and Biz Potential in Pharma formulation

### Dramatic enhancement of solubility



### Optimal polymorph Stability <u>and</u> Dissolution



Four polymorphs of pyrazinamide are characterized by X-ray diffraction, FT-IR, NIR and Raman spectroscopy, and DSC. The commercial  $\alpha$  polymorph is the thermodynamic phase at room temperature in contrast to a recent paper in the same journal which showed that the  $\delta$  form has the lowest free energy. The  $\alpha$  polymorph of pyrazinamide has both good stability and dissolution rate. Crystal Growth & Design, ASAP<sup>0</sup>

### Long term stability of cocrystal



Pure TMZ

Sample A - TMZ BP/TM/055/48/B Sample B - TMZ BP/TM/055/47/A Temozolomide– Succinic acid

TMZ–SA cocrystal remains white after prolonged storage of 1 year!



### Crystal in Research

Crystalin Research is a new scientific enterprise evolved from the academic activities of Prof. Ashwini Nangia at University of Hyderabad. Crystal in will leverage Scientific Inventions and Innovations through Pharmaceutical R&D and transform into commercial technologies and products. We provide reliable solutions to polymorphism and crystallization problems through in-depth knowledge and expertise of the solid-state for over a decade. Our motto is to create Intellectual Property through R&D.



Ashwini Nangia PhD, Yale University Professor of Chemistry University of Hyderabad

Author of 165 research publications and 10 patents covering synthesis, crystal engineering, polymorphism, cocrystals and pharmaceutical salts.

Fellow of National Science Academies, FNA, FASc, FNASc

#### Contact

E-mail <u>ashwini.nangia@gmail.com</u> Phone +91 40 2301 1338 Mobile +91 98481 55416 URL <u>www.crystalin.co.in</u>



**Crystalin** offers the expertise and experience of academics to industry for innovative solutions to pharmaceutical solid-state issues. Over 80% drugs and 95% of top-selling drugs are administered as tablets/ capsules. All drugs coming through development in the last 5 years have many polymorphs and pseudopolymorphs.

The focus in crystal engineering is to understand hydrogen bonding and crystal packing, develop novel design strategies for cocrystals, and study polymorphism and pseudopolymorphism. Several analytical techniques - XRPD, DSC, TGA, thermomicroscopy, and NMR, IR, NIR, Raman spectroscopy - are used to characterize new solid-state forms and monitor phase transitions. Now our knowledge and experience will be applied to solve polymorphism, solvates, hydrates, stability, filterability, cocrystal, salt, dissolution, stability and tableting issues in drugs, discover novel API polymorphs, and develop robust crystallization protocols.

### Crystal in Activities

**API** analysis

DSC, TGA, HSM, IR, NIR, Raman, microscopy, XRPD, SC XRD.

#### Form screen

Polymorphs, solvates, cocrystals and salts of APIs. New crystallization methods. Green technologies.

#### PC/PK profile improvement

Soluble and stable cocrystals and salts of APIs with GRAS coformers. Synergistic pharma cocrystals.

#### Phase behavior

Kinetic & thermodynamic forms, anhydrous and hydrate/ solvate, amorphous and crystalline phases.

#### Data file

Quantification and validation of the solid form by analytical methods.

#### Structure computations

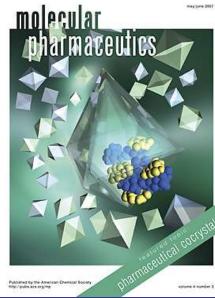
Crystal structures of new molecules, lattice energy, density, stability and morphology of polymorphs.

#### Training workshops

Diffraction, spectroscopy, thermal analysis. Pharmaceutical solid forms.

### **Cocrystals – The Current Decade**

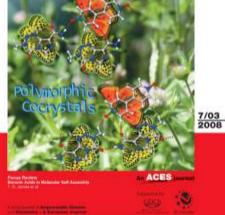




2007



CHEMISTRY AN ASIAN JOURNAL www.chemasiani.org



2008

#### 2004

e cap be used to fidericane complex corrin, a key map to developing electronic UM- attractor



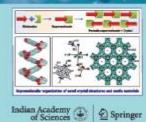
and show will be trace for a lister walless. That's because crystals of ranalgenic don't easily conspress into a tables without the addition of hinds nts that increase the pill's girth. A proof principle study suggests one possible eight loss program for the berty tablet talling the action ingredient with in matecular, thus producing a ompressible crystal. William Jones ridge University and colleagues statlisting anreastmentheti (pars d) with vertices small involves the rally incognizes as safe, including fore force ultane, serioscende force unist, and showed that the latter to of the mechanical properties of the eryntul (Adv. Mater, DOI: source na moderata). Althungh corroratais are process the application and differolution rate of active ingreductu accenty projection for intercenting mechanism d properties of an active ingredience using processing tory. The next this signal

occeptualitation is a recent study on oal. Intime (Cryst. Generali Dat. acade, 6, 1923). This new work is "elegant," new Nair Rodrigues Rornedo, a pharmaceutical acientist at the University of blichtgan. But the primits out that soluting one definity problem may comat a cost file offset insportant properties much in blowvallability and solubility. Also, any bitantinity of the controlalization indepenwould have to be complementary to the ar

lass ingratilized's - 10 BETTER BIOSYNTHESIS BUILDING BLOCKS

**C&ENews** pair of bicoroldbetic studies may provide information that makes it many to assess analogs of the sulfaceprimanides, a promiing class of anticamour agents. Bradley % July 27 '09 Macro of flerippi Diattitution of Ocrassign raphy and the University of California, Sar Deges trained with Revie A. Reynolds of Portland State University and a diregour t analyse the genome of Salinimont musica. deep-sea-diretting bactorium that makes callenoperantides. They found that not inception mides are hitry other level by an unusual polyfeetide synthase (PKN; encym

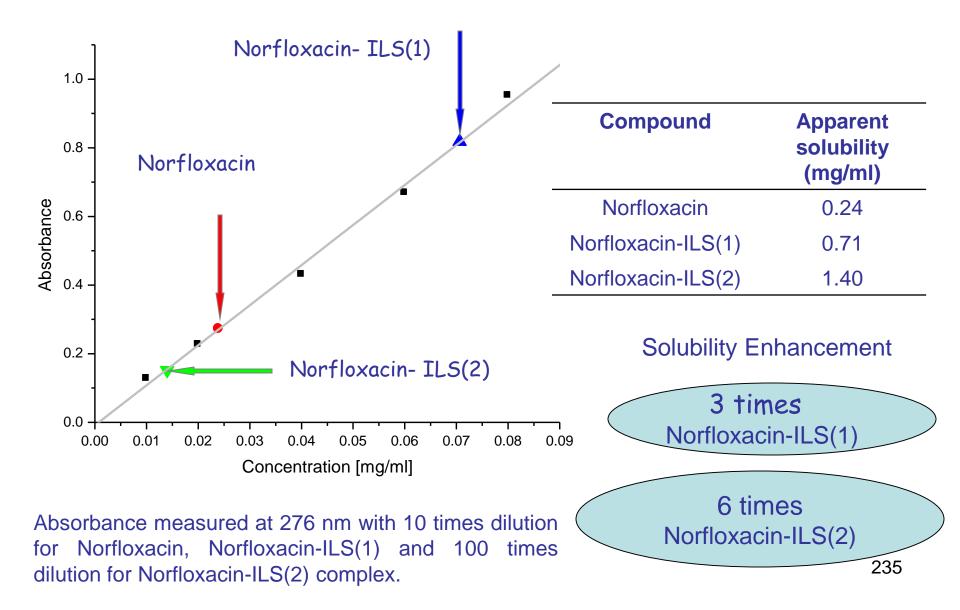




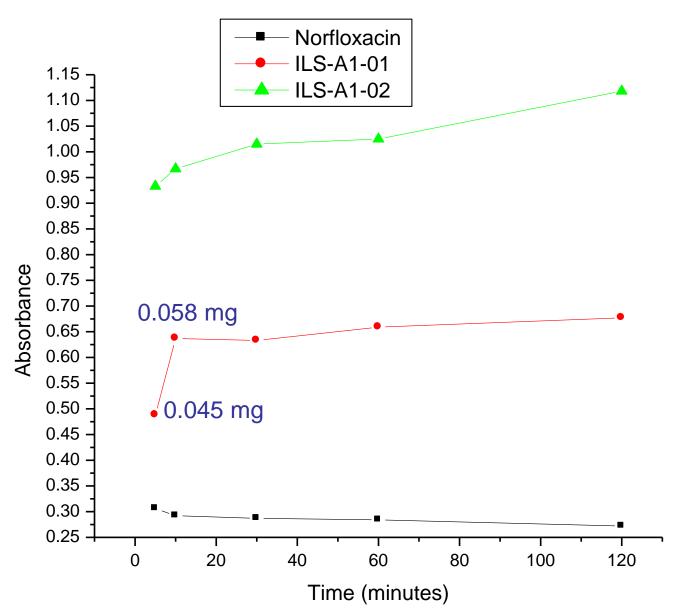
May '10



### Norfloxacin – Dissolution



### **Dissolution Profile**



## Antibiotic Activity – Synergism

Compound	Staphylococcus aureus (Gram Positive)	<i>Pseudomonas aeruginosa</i> (Gram Negative)
Norfloxacin	HighConc 쀼쀼 LowConc 쀼쀼	HighConc 쀼쀼 LowConc 쀼쀼
Norfloxacin-ILS(1)	HighConc 卝뉘뉘卝 LowConc	HighConc 뀨뀨뀨 LowConc 쀼쀼
Norfloxacin- ILS(2)	HighConc	HighConc 쀼쀼쀼쀼쀼 LowConc 쀼쀼
Ciprofloxacin	HighConc 뷰뷰 LowConc 뷰뷰	HighConc 쀼쀼 LowConc 쀼쀼
Ciprofloxacin-ILS(1)	HighConc 뷰 뷰뷰뷰 LowConc 뷰뷰	HighConc 뷰 ##### LowConc ##
Ciprofloxacin-ILS(2)	HighConc 뷰뷰뷰뷰 LowConc 뷰뷰뷰뷰	HighConc 쀼쀼쀼쀼쀼 LowConc 쀼쀼쀼쀼

Activity measured in terms of Inhibition Zone with respect to standard

#### GLOBAL HEALTH

Characteriz Decrease tl Essential D	Mebendazole can exist as polymorphs and solvates in the solid state. <sup>9–11</sup> Of particular importance is the differences in the physicochemi- cal properties of the three known polymorphs A, B, and C. <sup>10,12,13</sup> For example, the difference in solubilities of these polymorphs in physio-	
MARIUS BRITS, <sup>1</sup> WIL	logically relevant media is $B > C > A$ . However,	
<sup>1</sup> Research Institute for	· – ·	outh Africa
<sup>2</sup> Unit for Drug Resean South Africa	form B, form C is clinically preferred because its solubility is sufficient to ensure optimal	room 2520,
<sup>3</sup> School of Pharmacy,	bioavailability. <sup>14–17</sup> This is important because	
	polymorph A has no anthelminthic activity alone	
Received 2 June 200	or when present above 30% in polymorphic	
Published online 18	mixtures. <sup>15,17</sup>	2/jps.21899

Table 1.	Physicochemical	and Spectral	Properties of the	Three Mebendazole	Polymorphs
----------	-----------------	--------------	-------------------	-------------------	------------

	IR (cm <sup>-1</sup> ) XRI		RPD (°20) Solubility		at 30°C (mg/mL)	DSC		
Form	–NH	>C=0	Unique	100% $I/I_0$	0.1 M HCl	$0.1 \mathrm{M} \mathrm{HCl} + 1\% \mathrm{SLS}$	$T_{\mathrm{m}}$ (°C)	$\Delta H \; (kJ/mol)$
A B	$\begin{array}{c} 3370\\ 3340 \end{array}$	1730 1700	$7.67 \\ 5.84$	7.67 19.07	$\begin{array}{c} 0.02 \pm 0.005 \\ 0.07 \pm 0.004 \end{array}$	$\begin{array}{c} 0.11 \pm 0.006 \\ 0.14 \pm 0.007 \end{array}$	244 223 235	232 181 87
С	3410	1720	4.93	19.80	$0.04\pm0.003$	$0.12\pm0.008$	$212 \\ 240$	58 172

For IR identification the stretching frequencies of the carbonyl (carbamate) and amine N–H stretch are listed. Solubility was measured in 0.1 M HCl and the USP dissolution medium for mebendazole tablets that contains sodium lauryl sulfate (SLS).

DOI 10.1002/jps

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 99, NO. 3, MARCH 2010

transformation

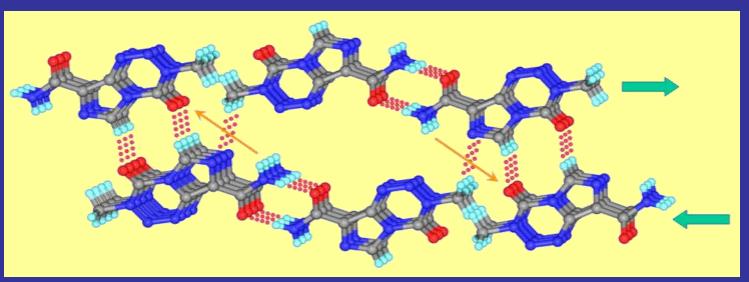
Pharmaceutical Cocrystals Past, Present & Future

- Cocrystals in their modern version are just about a decade old!
- Coincides with change in *in vitro* biology screening from manual aqueous to HT DMSO
- From conceptual model studies (1990s to early 2000s) to pharmaceutical cocrystals (mid 2000s)
- Several API•CCF cocrystals patented with improved PK, Stability, Dissolution profiles
- Deal with drug management and repurposing in the "last mile" = solid state form stage

Cocrystals of SNRI with improved solubility

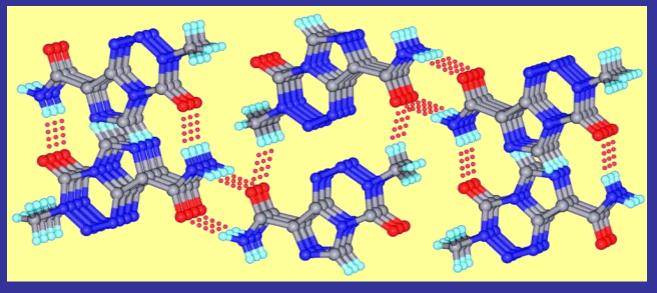
- Antipsychotic drug. Sparingly soluble in water at pH 7. Solubility 42.93 mg/L.
- Basic groups on drug molecule. Made cocrystals with acidic coformers.
- API : Coformer 1:1, 1:2 stoichiometry. Both crystalline and amorphous forms.
- Measured solubility of pure API and CCs by UV-Vis spectroscopy.

### Polymorphs of TMZ



### Polymorph 2 Metastable

### Polymorph 1 Stable





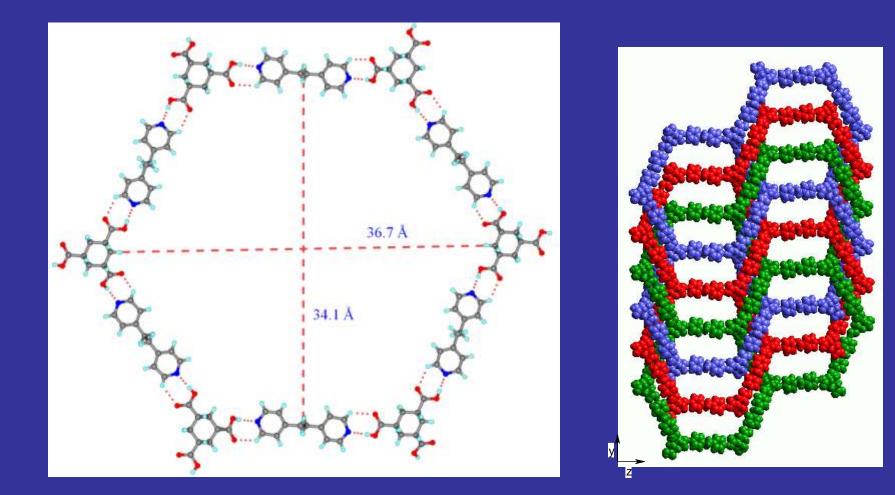


### Pharmaceutical Cocrystals to Modify Physico-Chemical and Dissolution Profile of APIs

Ashwini Nangia School of Chemistry University of Hyderabad ashwini.nangia@gmail.com

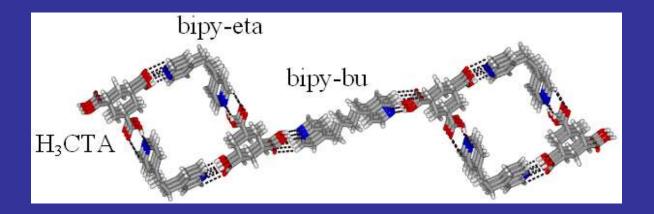


### Cis,cis-1,3,5-CTA – Bipy-ethyl

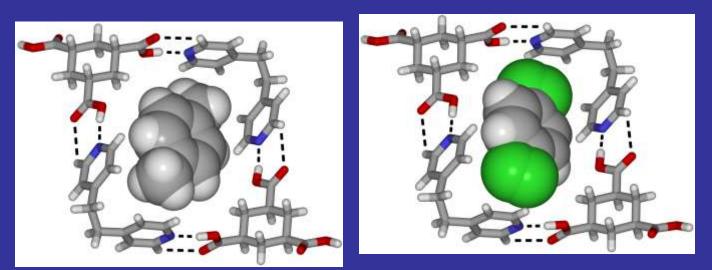


### **Two-component cocrystal**

## [CTA-Bipy-bu-Bipy-et]-Guest



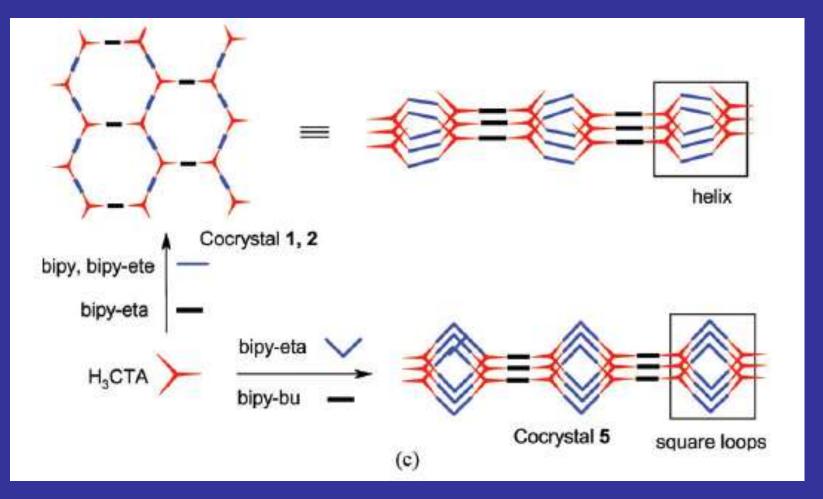
## 3 component host lattice



4 component cocrystal

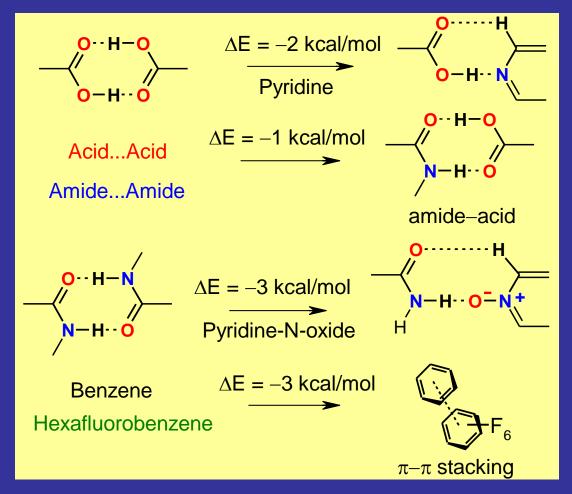
Cryst. Growth Des. 2003 3 547; 2005 5 1683; New J. Chem. 2008, 32, 800. 244

### Self-assembly model Hexagonal and Square nets



New J. Chem. 2008, 32, 800-807; CrystEngComm 2008, 10, 1735-1738. 245

### Co-crystallization by Design The Role of Enthalpy



Nangia, *Mol. Pharmaceutics* **2007** *4* 417-434 Nangia, J. Org. Chem. **2002** 67 556-565 *Chem. Commun.* **2006** 1369-1371

## H bonding vs. Close packing





### **Polymorphs & Cocrystals**

Advanced

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Available online at www.sciencedirect.com

Advanced Drug Delivery Reviews 59 (2007) 617-630

Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates<sup>☆</sup>

N. Blagden, M. de Matas, P.T. Gavan, P. York\*

Institute of Pharmaceutical Inversition, University of Bradford, Richmond Rd, Bradford, BD7 1DP, UK

Received 16 April 2007; accepted 10 May 2007 Available online 29 May 2007

### The Emerging Utility of Co-Crystals in Drug Discovery and Development

Annual Reports in Medicinal Chemistry, Volume 43 Nicholas A. Meanwell ISSN 0065-7743, DOI 10.1016/S0065-7743(08)00022-5

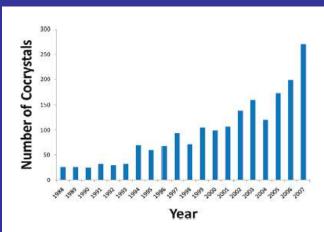


Figure 1. Frequency of occurrence of organic molecular cocrystals in the Cambridge Structural Database from 1988 to 2007. For the purposes of this graph, cocrystals are distinct from solvates, hydrates, and simple salts.

#### Diversity in Single- and Multiple-Component Crystals. The Search for and Prevalence of Polymorphs and Cocrystals

G. Patrick Stahly\*

SSCI, an Aptuit Company, 3065 Kent Avenue, West Lafayette, Indiana 47906

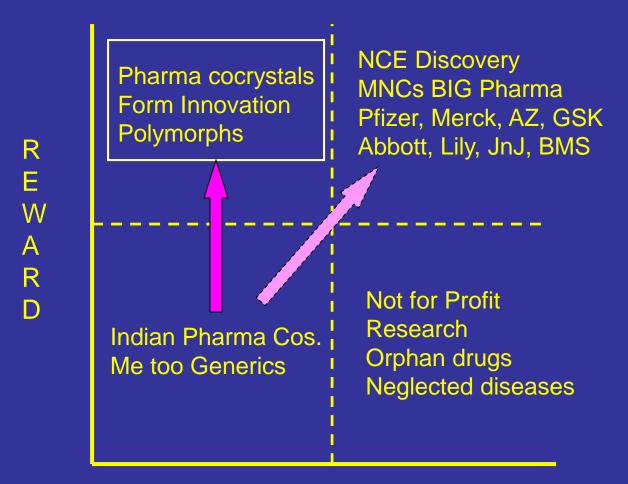
Received November 25, 2006; Revised Manuscript Received March 18, 2007

### The role of cocrystals in pharmaceutical science

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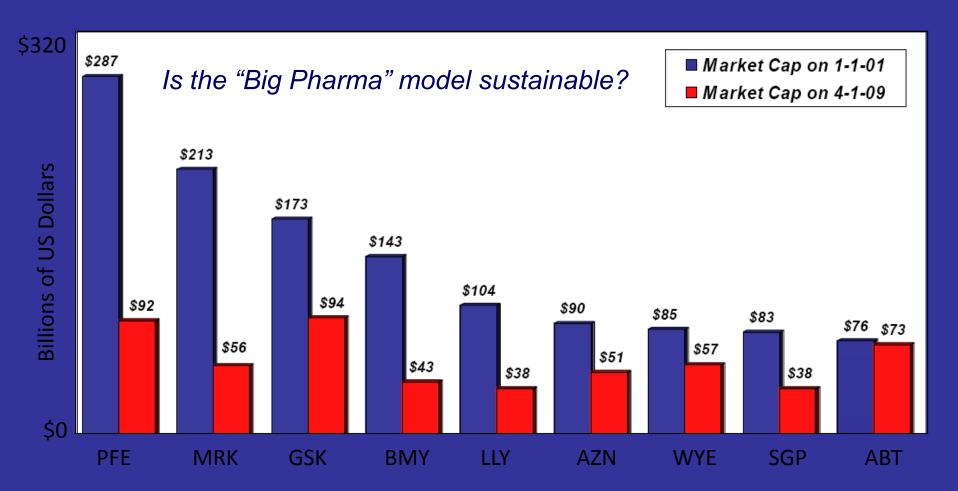
Ning Shan<sup>1</sup> and Michael J. Zaworotko<sup>2</sup>

### Cocrystals & Polymorphs Golden Quadrant



### **RISK / COST**

### **Big Pharma Performance**



Big pharma is "spending more money than ever [on R&D], yet the number of new chemical entities continues to decline," said Advanced Cancer Therapeutics President and CEO Randall Riggs. www.valueline.com, Tufts CSDD analysis, 2699

## Cocrystal 101 (Co-crystal)

• ... the term cocrystal should encompass all multicomponent solid-state assemblies of two or more molecules held together by any type or combination of intermolecular interactions. Nangia, *Mol. Pharma.* **2007** 417.

• ... a (pharmaceutical) co-crystal is a multi-component crystal in which two or more molecules that are solids under ambient conditions coexist through a hydrogen bond. Almarsson, Zaworotko, *Chem. Commun.* **2004** 1889.

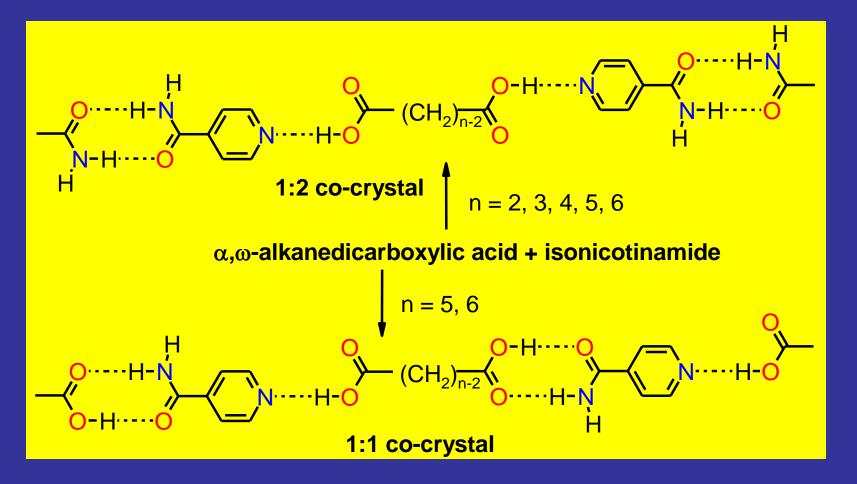
## **Organization and Stabilization**

Table 4. Lattice energies $[U_{\text{latt}}, \text{kcal mol}^{-1}]$ of forms A–D computed in Cerius <sup>2</sup> , corrected to per molecule of <b>1</b> .								
	Form A		Form B		Form C		Form D	
$U_{\rm latt}$	COMPASS	DREIDING 2.21						
total	-32.69	-42.12	-31.66	-39.66	-31.63	-39.71	-31.87	-42.42
van der Waals	-28.01	-27.78	-28.19	-27.22	-28.18	-27.23	-27.80	-27.19
coulombic	-4.68	-12.50	-3.47	-10.43	-3.45	-10.49	-4.07	-12.49
hydrogen bond <sup>[a]</sup>	_	-1.84	_	-2.01	_	-1.99	_	-2.74

[a] The hydrogen bond energy is partitioned in the DREIDING 2.21 force field but it is part of the coulombic component in the COMPASS force field.

- Crystal structure total energy = Ulatt is make up of electrostatics, H bonding and van der Waals
- H bonding typical contributes 15-20% of energy
- Balance 80% is van der Waals and packing
- 20% energy controls 80% of the structure motif
- Therefore justified to use a H bonding design

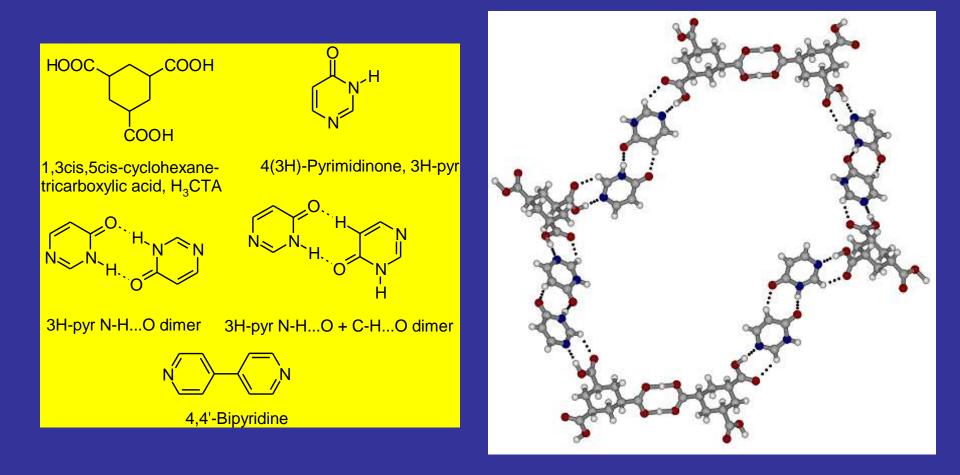
### Acid, Amide, Py synthons Supramolecular isomerism



Cryst. Growth Des. 2003 3783-790

253

### Acid–Pyrimidinone dimer



CrystEngComm 2008, 10<sup>th</sup> anniversary issue, 1735-1738 <sub>254</sub>

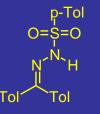
## Temozolomide



- 8-Carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (TMZ)
- Anti-tumor drug. Clinically active against malignant melanoma
- One crystal structure in the CSD
- Nine polymorphs in US Patent, 2005/0187206 A1, Aug. 25, 2005
- Structural origins of polymorphism in TMZ are not known. Polymorphic forms were characterized by PXRD and IR spectroscopy
- No cocrystals
- Co-crystallized TMZ and 4,4'-bipyridine-N,N'-dioxide (BPNO) and COOH partners

## **Organization and Stabilization**

Polymorph	Ulatt	vanderWaals	Electrostatic	∆Ulatt	ΔEconf	ΔEtotal
form 1	-41.13	-39.740	-1.394	3.39	0.00	3.39
form 2	-42.10	-41.334	-0.768	2.42	6.29	8.71
form 3	-44.52	-42.323	-2.201	0.00	0.85	0.85



- Crystal structure total energy = Ulatt is make up of electrostatics, H bonding and van der Waals
- H bonding typical contributes 15-20% of energy
- Balance 80% is van der Waals and packing
- 20% energy controls 80% of the structure motif
- Therefore justified to use a H bonding design

### age

### **A Healthier India**

#### Policy needs to resolve the conflict between drug price controls, innovation and affordable healthcare



**DAVID TAYLOR** PROFESSOR PHARMACEUTICAL& PUBLIC HEALTH POLICY. THE UCL SCHOOL OF PHARMACY. UNIVERSITY OF LONDON

The debate about essential medicines pricing and access in India illustrates the difficulties inherent in establishing policies that serve conflicting public interests in achieving goals such as caring well and ensuring safety for all, while also pursuing financially-sustainable success in scientific innovation and trade. It highlights problems facing those interested in rather than improved. continuing drug and vaccines development and ensuring that, once marketed, such products contribute effectively to improving public health. Modern pharmaceuticals played a significant role in increasing average life expectancy at birth in India from little more than 40 years in 1960 to the world average of about 67 years today. Yet because of communicable diseases is growing. Further pharmaceutical discoveries will be essential for controlling such conditions and preventing long term ill-health as India's future population ages.

largest medicines maker. Yet, It is not surprising that such

despite this many people have deeply ambiguous feelings about synthetic drugs and the companies that discover and sell them. But as social change continues legitimate public demand for science-based preventive and curative medicines will continue to rise.

Cost-based pricing?: Resolving such challenges demands economic logic and political courage, alongside worldclass science. Against this background critics of the recent draft National Pharmaceutical Pricing Policy fear an extension of the essential medicines category that will include an ever-widening range of products, coupled with a narrowly defined, costbased pricing regimen. This combination could make producing such treatments for sale in India so unattractive that their supply is curtailed

India already has among the lowest medicine prices in the world. Yet, past experience shows that low costs are in themselves no guarantee of universal access to quality healthcare. Universal access to quality care demands adequate overall investment in socially just and economically robust health systems.

The response to such conthis success the burden of non- cerns by those favouring more restrictive drug price controls is to stress that drug costs are seen by the public to be the greatest barrier to treatment access. They argue that even among the middle classes the high cost of medicines is often India is now the world's third-seen as potentially ruinous.



citizens want political action to improve their outlook. But in reality it is misleading to suggest that better healthcare will be achieved simply by for instance, cutting newer anticancer agents' prices. This is because in contexts like oncology the main costs of effective treatment lie outside the pharmaceutical sphere. What is needed is an affordable and adequate system of health care financing that assures both continuing competitive market driven investment in better therapies and community wide support for those unfortunate enough to develop conditions like cancer.

More sustainable solutions: The resolution of questions about how countries such as India can most fairly and effectively provide health care and factor costs could well mislead medicines must come from within their own unique societies. Yet, at the same time, India is so large that the entire global community will in time be affected by its policies. Giv-

en that humanity shares many common problems, there should be benefits to be gained from analysing other regions' experiences and needs.

Seen from this perspective, key points to consider in thinking about essential medicines pricing and supply in India include:

 By international standards, combined public and private spending on medicines in India is not (at around 1.5% of GDP) unexpectedly high, especially when it is remembered that private drug costs often include large markups imposed by suppliers. Yet, publicly-resourced spending on health services as a whole is exceptionally low. So, focusing too exclusively on reducing drug or any other single set of policymakers and distort public debate.

The poorest half to a third of the Indian population lacks reliable access to modern essential medicines. This appears in the world market.

part to be due to problems like the improper diversion of supplies from public services and/or inappropriate additional charging. No centrally imposed medicine pricing approach will address this issue. Global experience shows that when populations need free drug supply, simply driving down prices may benefit those able to pay, but leaves those unable to pay even worse off because it obscures their needs. Like all other advancing nations, India must earn its living in the world by contributing to technical advances and selling products based on them at fair and viable market prices. Its success to date in producing generic and branded generic medicines has been related to a particular phase in history, during which there have been special opportunities for expanding low price off-patent medicine sales. But the situation is changing fast. To build further successes by contributing more to therapeutic innovation, policymakers will need to concentrate more on permitting an adequate price base for new products while they are exclusively available, while also allowing efficient market mechanisms to minimise the cost of older medicines.

Health improvement everywhere is dependent on constructive and honest partnerships between all sections of society, including not only governments and health professionals but also the researchbased companies that succeed in bringing new treatments to

#### **Cosmic Uplink**

### Culture Vulture

#### VITHALCNADKARNI

In 1960s, the average life expectancy of the unknown Indian was 42. By that measure, your columnist's father was already on bonus time. Midlife crisis should have occurred in his 20s. But life expectancy continued to rise. By 2009, it was 64.5 years: lower than Russia (75 years) but higher than Afghanistan's 45 years, which nearly spanned the duration the parent spent in retirement.

So, this wasn't his nadir. Nor was it a period of catastrophic decline. Of course he had lucked out, better than most Indians, in the genetic lottery. But he wasn't unique. For, as David Bainbridge says in his natural history of Middle Age, the middle span is the biggest evolutionary advantage Nature has bestowed on humankind as compared to most other animals.

Ancient evidence suggests that our ancestors frequently lived well into middle age and beyond. But why did natural selection favour it? It's a silent testimonial to the power of culture over vulture; and that of life-long learning.

This has left its mark on the human brain, Bainbridge says. Middle-aged people need not necessarily think better than younger adults. headds, "but they may have to think differently Imaging studies suggest that they sometimes use different brain reasions than young poonlo

ZAHIDALI