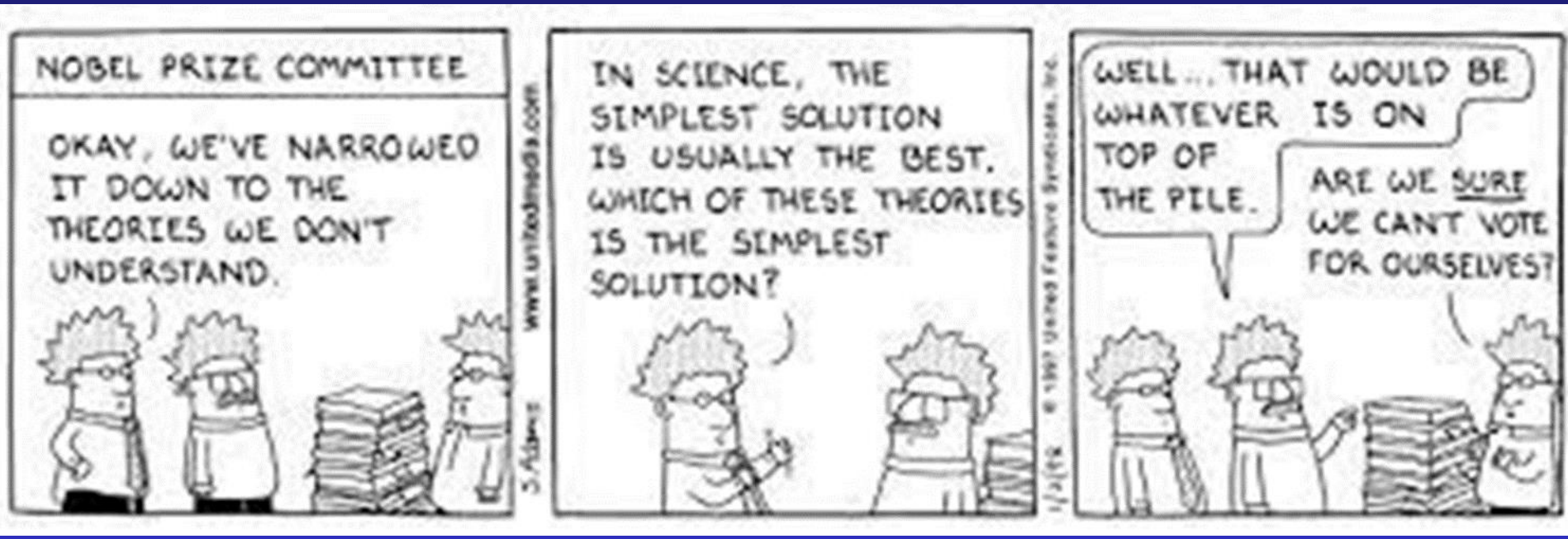
The Role of Occam's Razor in Formulation Design

S. Esmail Tabibi


NOBEL PRIZE COMMITTEE
OKAY, WE'VE NARROWED IT DOWN TO THE THEORIES WE DON'T UNDERSTAND.
IN SCIENCE, THE SIMPLEST SOLUTION IS USUALLY THE BEST. WHICH OF THESE THEORIES IS THE SIMPLEST SOLUTION?
WELL... THAT WOULD BE WHATEVER IS ON TOP OF THE PILE.
ARE WE SURE WE CAN'T VOTE FOR OURSELVES?

Occom's razor

Fewest ingredients

Most acceptable ingredients

Fewest preparation steps

Simplest physiological model, and/or

Simplest increased activity

Solubility equation of Yalkowsky and Banerjee

- A demonstration of the effect of lipophilicity and crystal lattice energy on solubility

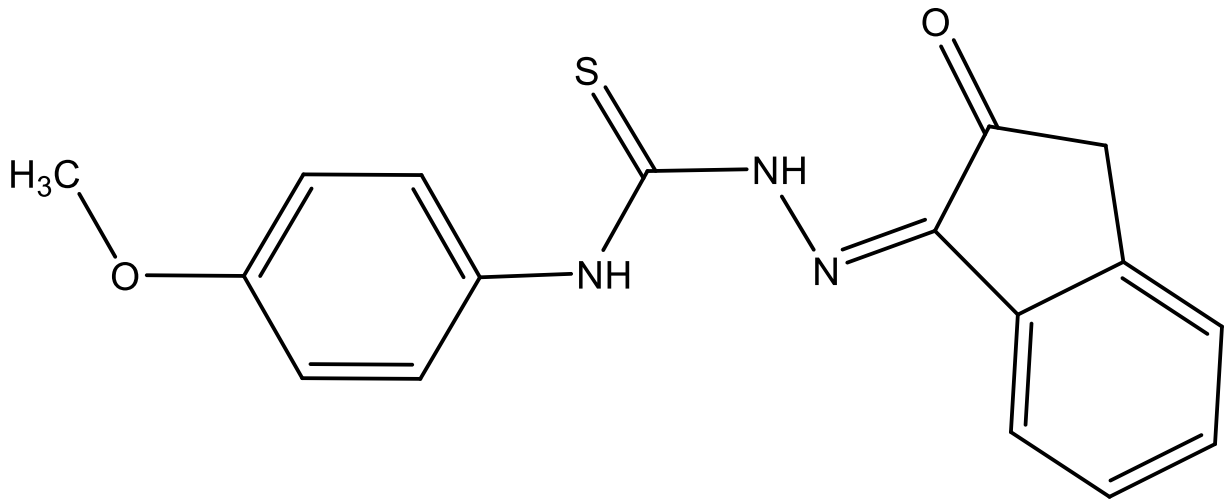
$$\text{Log } S = 0.8 - \text{Log } P_{ow} - 0.01(MP - 25)$$

S; solubility
Log P_{ow}; octanol/water partition coefficient
MP; melting point

Log P 1 unit ↑
MP 100°C ↑

Solubility 10-fold ↓

NSC-73306



MW :	**326**
MP	**245°C**
$logK_{ow}$:	**2.02**
S_{int}	**< 1 mcg/ml**
pK_a :	**9.02**

NSC-73306

NSC73306 could specifically kill cancer cells that overexpressed an ABC transporter responsible for MDR.

73306-Solubility

Most solvents	poor
N-Methylpyrrolidone (NMP)	> 50 mg/ml

1 mg/ml solution in NMP
precipitates on dilution

1 mg/ml solution in NMP + PVP-K12
does not precipitate on dilution

73306-Dispersion

NSC-73306 Dispersion Formulations*

Component	Formulation 1#	Formulation 2#
NSC-73306	20-40 mg/ml	20-40 mg/ml
Egg phospholipid	4-5% w/w	4-5% w/w
Dextrose	10% w/w	10% w/w
Tween 80	0.2% w/w	--
Pluronic F68	--	0.2% w/w

\# deflocculated nanodispersions

* microfluidized

Chemical Stability of 73306

Solution

- T-90% < 60 hours @ pH 3.5 & RT
- T-90% < 3 hours @ pH 7.4 & RT

Suspension

- T-90% > 300 days @ pH 7.4 & RT

73306-Suspensionl Physical Stability

Suspension

T-90% > 1 year @ 2-8°C

Small needles observed @ 17 months

Clusters observed @ 24 months

Dilution Stability of 5% Formulations of NSC 73306

Formulated in Solvent System	Relative Enhancement (1:10 dilution)	Average Diameter (nm)	Suspension Quality
NMP	1.00	100	poor
NMP, PVP-K12 (1:1)	2.06	184	good
NMP, PVP-K12 (1:1)	2.10	246	good
NMP, PVP-K12, SDS (1:1:0.05)	4.71	537	good

73306-Summary

Solution is not feasible because of

very low solubility and poor stability

Suspension (refrigerated) is

stable for at least one year

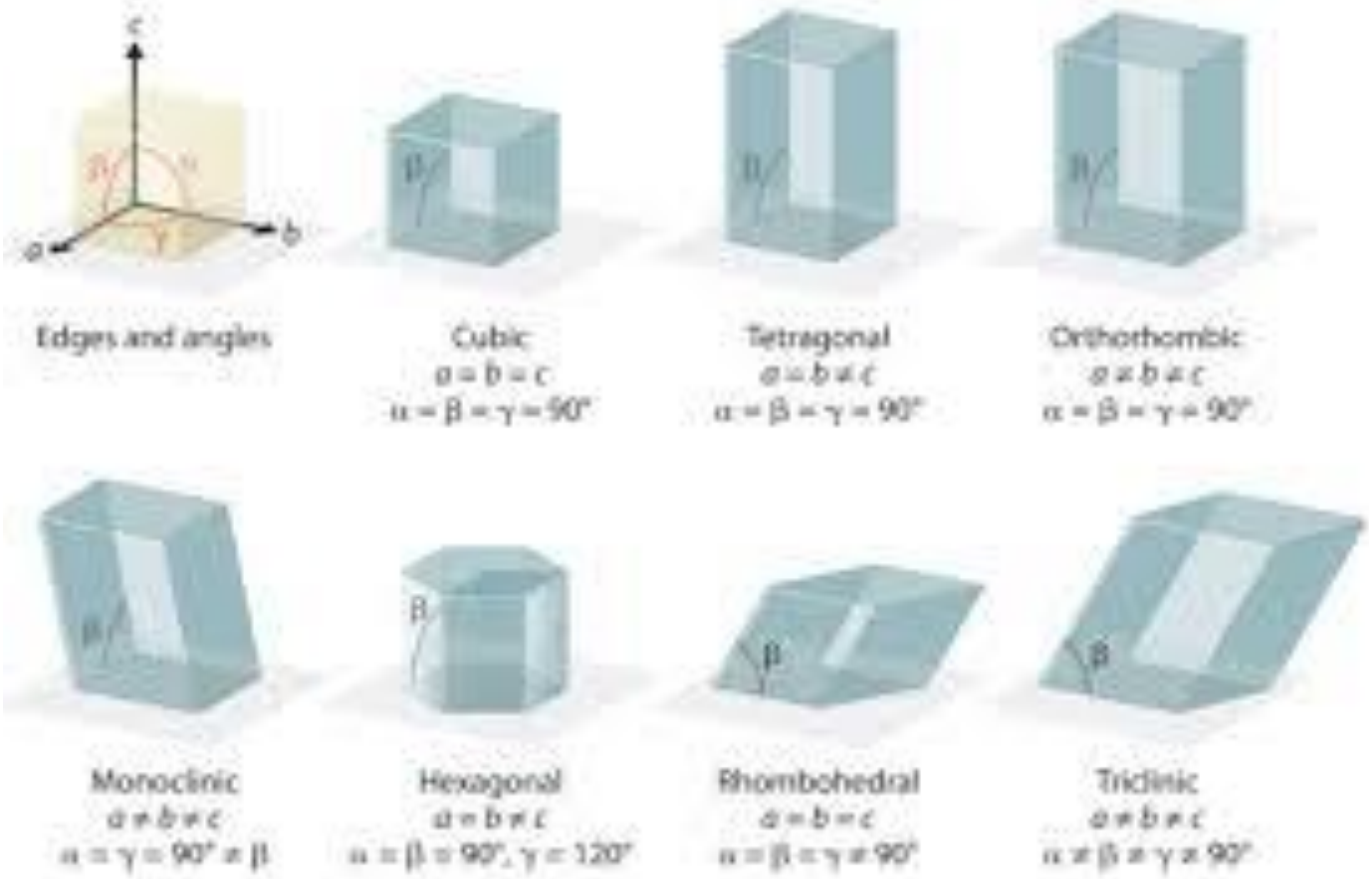
Self suspending formulation is also possible


READY? HERE IT COMES!
CARWASH
EXIT

Polymorphism is an especially influential phenomenon in pharmaceutical sciences, **significantly influences various properties of API** including but not limited to:

Physical Property	Biological Performance
• **Flowability,** • **Tableting,** • **Dissolution Rate,** • **Solubility, and** • **Stability**	• **Efficacy, and** • **Toxicity**

Various Crystal Shapes



SQ-109
NSC 722041

- Compatibility Study
- Preliminary Formulation
- The production

Compatibility Study

Compatibility of SQ-109 with the following excipients* was evaluated individually

- Stearic Acid, Mg Stearate
- Colloidal Silicon Dioxide, Corn Starch
- PVP, Lactose Monohydrate, Avicel 101, diCaP
- Na Starch Glycolate, Na Croscarmellose
- Capsule shell

* All excipients used were U.S.P., NF or appropriate formulary grade.

Compatibility Study

Compatibility of SQ-109 with the following excipients* was evaluated in combination

Avicel 101, Na Starch Glycolate,
Mg Stearate, and Capsule Shell

*All excipients used were U.S.P., NF or appropriate formulary grade.

Experimental design

- Each excipients/SQ-109 mixture was mixed well by hand-rotating in an 8-mL clear glass vial and placed in the following conditions:
  - At 50°C study: The vial was tightly covered with a screw cap (black phenolic closure with white rubber liner) and placed in the chamber.
  - At 40°C/ 75 % R.H. study: The vials with loose caps were placed in the chamber for environmental exchange.
- All vials were labeled with the weights of the individual components in the container.

Experimental design (Continued)

- The following parameters were evaluated at each time point:
  - Appearance by visual method
  - Chemical Assay by HPLC method

Results

Percent recoveries of SQ-109 at each time point is the mean of two experiments

Storage Condition ⇒		50°C			40 °C/75 %RH		
Mixtures ⇓ Time intervals	Initial	1 Mo	2 Mos	3 Mos	1 Mo	2 Mos	3 Mos
SQ-109	98.5	93.1	102.3	92.6	93.1	101.1	99.1
Stearic acid + SQ-109	101.1	99.4	103.1	100.3	99.4	101.3	102.0
Magnesium stearate + SQ-109	101.0	103.0	102.9	100.2	103.0	101.9	101.7
Colloidal Silicon Dioxide (Cab-O-Sil) + SQ-109	100.5	102.7	103.5	101.1	102.7	101.8	101.2
Corn starch + SQ-109	100.4	101.7	102.9	98.7	101.7	103.5	100.1
Cut capsule pieces + SQ-109	100.6	104.1	104.9	100.7	104.1	106.6	100.6
Polyvinylpyrolidone (PVP) + SQ-109	100.5	100.5	103.7	100.2	100.5	96.4	103.3
Lactose + SQ-109	99.7	102.3	102.5	99.1	102.3	100.9	100.6
Avicel 101 + SQ-109	100.6	100.4	103.2	97.8	100.4	106.5	97.0
Dicalcium phosphate Anhydrous + SQ-109	100.4	103.5	103.0	99.2	103.5	101.4	88.6
Sodium starch glycolate + SQ-109	97.2	103.2	103.6	101.7	103.2	102.5	99.8
Sodium Croscarmellose (Primellose) + SQ-109	98.7	102.6	102.7	101.8	102.6	102.1	99.8
Avicel 101 + Sodium starch glycolate + Magnesium Stearate Cut capsule piece + SQ-109	100.0	93.6	102.9	105.0	93.6	103.4	101.3

Preliminary Formulation and Production of a development batch

Each Hard Gelatin Capsule contains the following ingredients:

- SQ-109
- Avicel 101
- Na Starch Glycolate
- Mg Stearate

The label copy

SQ-109
50 mg

50 Capsules NSC 722041

Store at controlled room temperature

Also contains: Microcrystalline Cellulose, NF; Sodium Starch Glycolate, NF; Magnesium Stearate, NF

CAUTION: NEW DRUG - Limited by Federal (USA) law to investigational use

NIH IIP PROGRAM

Manufactured by:
College of Pharmacy
University of Iowa
Pharmaceutical Service
Iowa City, Iowa 52242

For:
Pharmaceutical Resources Branch; DCTD, NCI, NIH
Bethesda, Maryland
20892-7446 USA

Lot #: 03-105
Date Manufactured: 8/04

Analysis of Drug Product

Lot No.: 20LM042

TEST (METHOD)	SPECIFICATION	RESULTS
Appearance (QC-19)	Clear dark red solution essentially free from visible particles of foreign matter	Conforms
Identity by HPLC (QC-202)	The retention time of sample differs by not more than ±5% from the reference standard and the sample chromatogram compares favorably with that of the reference standard	Conforms
Assay (QC-202)	90.0% - 110.0% of the labeled amount	99.0%; Pass
Volume in Container (USP<697>)	To deliver NLT 50.0 mL	51.0 mL; Pass
pH (QC-10)	Limit not yet established (approximately pH 2.75)	2.98
Total Impurities (QC-202)	NMT 4 %	1.63 %
Individual Impurities (QC-202)	List individual impurities ≥ 0.10%	RRT 1.15 = 0.25% RRT 1.39 = 0.10% RRT 1.48 < 0.10% RRT 1.74 = 0.19% RRT 2.82 = 0.15% RRT 2.91 = 0.94%
Particulate Matter (USP<788>)	NMT 6000 particles ≥ 10 µm NMT 600 particles ≥ 25 µm	≥10 µm = 147 particles/vial ≥ 25 µm = 3 particles/vial Pass
Sterility (USP<71>)	Sterile	No Growth; Sterile
Bacterial Endotoxins (USP<85>)	NMT 0.156 USP EU/mg of NSC 706744	< 0.156 EU/mg; Pass

Quality Control: _____
Printed Name/ Signature

Quality Assurance: _____
Printed Name/ Signature

Analysis of Drug Product

Product Name and Strength: Injection, 1mg/1mL, mg/vial

Lot No.: 20LM042

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Quality Control:

Printed Name/ Signature