Department of Pharmaceutics
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Product Development III
Pre-formulation Example

Pre-formulation data on a compound, SQ 20,009, are shown on the attachment "Pre-formulation Example". You should consider the data in each of the major properties headings (e.g. background, organoleptic properties, microscopic examination, physical properties, solution properties, stability (solid), drug-excipient compatability, stability in solution) and answer the following questions.

What does the data mean?
What implications are there for the design and development of a dosage form?

In addition, each student should provide an overall summary describing the strategy for dosage form selection, and design and development.

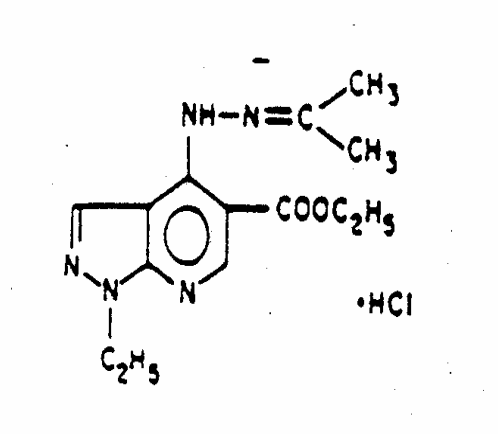
Attachment – Pre-formulation Example

I Background

1) Compound: SQ 20,009

2) Chemical name: 1-Ethyl-4[(1-methylethylidene)hydrazinol]-^{1}H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, ethyl ester, hydrochloride (1:1)

3) Chemical structure



$C_{14}H_{20}ClN_5O_2$ Molecular wt 325.80

4) Lot number: RR004RA

5) Solvent of recrystallization: Acetone and aqueous hydrochloric acid.

6) Purity: batch RR004RA contained 0.15% impurities as determined by paper chromatography.

7) Therapeutic category: Psychotropic

8) Anticipated dose: 25 to 50 mg single dose

II Organoleptic properties: SQ 20,009 is a white powder with a characteristic aromatic odour and a bitter taste.

III Microscopic examination: The crystals of SQ 20,009 are needle-like.

IV Physical characteristics

1) Density: Fluff and tap densities of SQ 20,009 were determined to be 3.0 and 3.5 g cm^{-3}, respectively.

2) Particle size (microscopic): The needle-like crystals of SQ 20,009 ranged in width from 2 to 10 μm. On grinding in a small ball-mill the average length was reduced to about 30 μm from about 80 μm.

3) Surface area: Not determined.

4) Static change: SQ 20,009 "as is" material exhibited some static change. Grinding of SQ 20,009 did not significantly alter this property.

5) Flow properties: As would be expected with materials having needle-like crystals, SQ 20,009 was not very free flowing. Grinding of SQ 20,009 significantly improved its flow.

6) Compressibility: SQ 20,009 compressed well into a hard disk which did not show any tendency to cap or chip.

7) Hygroscopicity: When exposed to 80% relative humidity at room temperature, SQ 20,009 did not pick up any moisture over a 24-hour period.

8) Polymorphism: The potential problem associated with SQ 20,009 is its instability in solutions. For this reason a less soluble material is desirable. However, high solubility of the material makes it very unlikely that a sufficiently less soluble form can be discovered. For this reason investigation of polymorphism of SQ 20,009 was not undertaken. The free base of SQ 20,009 is an oily liquid and is not considered suitable for development into a solid dosage form.

V Solution properties

1) pH of 1% Solution: 1.9

2) pK_a: 2.04

3) Solubility: SQ 20,009 is exceedingly soluble in water and lower alcohols. In aqueous systems it dissolved in excess of 400 mg ml^{-1}, and in lower alcohols it dissolved in excess of 100 mg ml^{-1}. Because of the very high solubility, an exact solubility determination was not attempted.

4) Partition coefficient: Not determined.

5) Dissolution (particulate): Capsules containing 50 mg of SQ 20,009 showed 100% dissolution in 15 min. The dissolution was studied in 1 L of water at 37°C at a stirring rate of 100 rpm using the rotating basket.

VI Stability (solid)

1) Heat: SQ 20,009 was found to be stable after 12 months at 50°C and ambient humidity.

2) Humidity: Exposure of SQ 20,009 to a high humidity of 80% relative humidity showed a visible discolouration after 8 weeks. The samples were not assayed.

3) Light: Upon exposure to 900 fc of illumination at 33°C and ambient humidity, SQ 20,009 showed signs of yellowing after 2 weeks.

VII Drug-excipient compatibility studies

1) Differential thermal analysis: Using weight ratios of 1:3, 1:1, and 3:1, mixtures of magnesium stearate, stearic acid, lactose, and Avicel with drug showed an interaction only with magnesium stearate.

2) Thin-layer chromatography: Mixtures of SQ 20,009 and magnesium stearate, lactose, stearic acid, and Sta-Rx 1500 starch were stable after 8 months at 50°C and 12 months at room temperature.

VIII Solution stability: Aqueous solutions of SQ 20,009 showed rapid time-dependent changes in the ultraviolet spectrum. Analysis of the data and the degraded samples showed that the Schiff base moiety of SQ 20,009 underwent reversible hydrolysis to the corresponding hydrazine compound and acetone. The hydrolysis was pH-dependent. The half-lives for hydrolysis at 37°C in media of different pH are shown in Table 18. The ester function in SQ 20,009 is also susceptible to hydrolysis. Studies with a structural analog 1-ethyl-4-butylamino-^{1}H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, ethly ester showed that the ester function underwent significant hydrolysis only under alkaline conditions.

Table 18 Example B: Half-Lives for the Hydrolysis of SQ 20,009 under Various pH Conditions at 37ºC

pH Condition	$^{T}1/2$ (min)
0.1 N HC1	5
0.01 N HC1	50
pH 3.0	70
pH 4.0	150