WHY STUDY THE FATTY ALCOHOL COMPONENT?

- FATTY ALCOHOLS SUCH AS CETOSTEARYL ALCOHOL ARE OFTEN UTILIZED IN MANUFACTURING SUSTAINED RELEASE MATRICES.

- CETOSTEARYL ALCOHOL IS COMPOSED PRIMARILY OF THE LONG CHAIN FATTY ALCOHOLS HEXADECANOL AND OCTADECANOL. MINUTE VARIATIONS IN THE RATIOS OF THESE ALCOHOLS ALTER THE PHYSICAL PROPERTIES OF THE CETOSTEARYL ALCOHOL.

- DURING COMPACTION OF A SUSTAINED RELEASE PRODUCT VARIATION IN COMPACT TENSILE STRENGTH WAS NOTED. THIS VARIATION WAS LINKED TO THE CETOSTEARYL ALCOHOL USED IN THE FORMATION OF THE MATRIX.

WHY ESTABLISH A THERMAL ANALYSIS CRITERIA?

- TO RESOLVE THE VARIATIONS IN THE FINISHED DOSAGE FORM SEVERAL LOTS OF CETOSTEARYL ALCOHOL, HEXADECANOL, OCTADECANOL AND MIXTURES OF HEXADECANOL AND OCTADECANOL WERE COMPRESSED WITHOUT DRUG AND EVALUATED WITH RESPECT TO TENSILE STRENGTH.

- SINCE COMMERCIAL QUALITY ALCOHOLS ARE PURCHASED IN LARGE QUANTITIES A SEMI-QUANTITATIVE TEST WAS REQUIRED WHICH WOULD PERMIT RAPID SCREENING OF THESE MATERIALS AS TO THEIR ABILITY TO FORM SUITABLE COMPACTS.

- A TREND WAS NOTED WHEREIN THE COMPACT STRENGTH OF THE SUBJECT ALCOHOL INCREASED AS A FUNCTION OF INITIAL HEAT OF FREEZING.

- THERMAL ANALYSIS PROVIDED A FAST, DISCRIMINATING AND REPRODUCIBLE PROBE FOR COMPACT STRENGTH.

THERMAL ANALYSIS

- A DUPONT 990 THERMAL ANALYZER IN CONJUNCTION WITH A DUPONT 910 DIFFERENTIAL SCANNING COLORIMETER WAS EMPLOYED.

- ALL SAMPLES TESTED WERE ACCURATELY WEIGHED INTO ALUMINUM PANS DESIGNED FOR USE IN THE 910 DSC SYSTEM. THE PANS WERE NONHERMETIC SEALING.

- ALL THERMAL SCANS WERE CARRIED OUT USING A METAL COOLING CAN IN PLACE OVER THE CELL. THIS METHOD PERMITTED DSC MEASUREMENTS BELOW AMBIENT TEMPERATURE. THE COOLANT WAS SOLID CARBON DIOXIDE IN A SLURRY WITH ACETONE. DRIED NITROGEN WAS PURGED THROUGH THE SAMPLE CHAMBER ($10cm^3$/min).

- ALL THERMAL MEASUREMENTS WERE CALIBRATED USING INDIUM AS A REFERENCE SAMPLE. LOW TEMPERATURE VERIFICATION WAS CARRIED OUT USING COMMERCIAL CALIBRATORS TRACEABLE TO NBS.

- TO DETERMINE HEATS OF RECRYSTALLIZATION, THE x-y RECORDER WAS SET USING A TIME BASE (min/cm) ON THE x AXIS WITH THE y AXIS SENSITIVITY IN mv/cm. THE HEATING RATE (5°C/min) WAS KEPT CONSTANT FOR ALL ANALYSES.

- FREEZING PEAK AREAS (cm^2) WERE MEASURED USING A PLANIMETER. A BASELINE WAS DRAWN AND BOUNDARIES OF THE PEAK WERE DEFINED AS THE BEGINNING OF DEVIATION FROM THE HORIZONTAL.

- HEAT OF FREEZING WAS MEASURED ON FIVE SAMPLES OF THE SUBJECT ALCOHOL. THE RESULTING PEAK AREA WAS USED TO CALCULATE ENERGY WITH THE FOLLOWING:

$$E = \frac{\Delta Hm}{60 \text{ sec/min } AB \text{ } \Delta qs}$$

WHERE E IS THE CALIBRATION COEFFICIENT (μw/mv) FOR THE INSTRUMENT, A IS PEAK AREA (cm^2), B IS THE TIME BASE (min/cm), m IS MASS OF THE SAMPLE (mg), Δqs IS y AXIS SENSITIVITY (mv/cm).

COMPACTION

- THE INSTRON UNIVERSAL TESTING MACHINE EQUIPPED WITH FLAT FACED 12.7 MM PUNCHES WAS USED TO COMPACT THE SUBJECT SAMPLES.

- ALL SAMPLES WERE ACCURATELY WEIGHED USING A MICRO WEIGHING FUNNEL TO ASSURE COMPLETE TRANSFER OF MATERIAL INTO THE DIE CAVITY OF THE INSTRON.

- CALIBRATION OF THE TESTING MACHINE INVOLVES THE USE OF AN INTERNAL CALIBRATION CIRCUIT, WHICH SHORTED THE STRAIN GAUGE TO A KNOWN RESISTANCE EQUIVALENT TO A 200 KG FORCE LEVEL.

- TWO STRAIN RATES WERE USED TO DETERMINE IMPACT OF THIS VARIABLE ON COMPACT STRENGTH.

COMPACT STRENGTH MEASUREMENT

- A CONVENTIONAL TABLET HARDNESS TESTER WAS EMPLOYED. THE HEBERLEIN UNIT USED WAS EQUIPPED WITH FLAT PLATTENS. NO PADDING MATERIAL WAS REQUIRED ON THE PLATTENS TO ACHIEVE TENSILE FAILURE OF THE COMPACTS.

- A CALIBRATION PROCEDURE WAS ESTABLISHED USING MECHANICAL TABLETS WHICH ARE DESIGNED TO FRACTURE AT SELECTED FORCE LEVELS (5,10,15,kp). THE MECHANICAL TABLETS AS SUPPLIED BY THE MANUFACTURER WERE TESTED USING THE INSTRON TO ESTABLISH A KNOWN FORCE VALUE FOR THE TEST DEVICE IN QUESTION.

- THE CALIBRATORS WERE THEN TESTED USING THE HARDNESS TESTER TO ASCERTAIN THE EXTENT OF CORRELATION BETWEEN THE STANDARDIZED FORCE (INSTRON) AND THE HARDNESS TESTER. DUE TO VARIATION IN THE HARDNESS TESTER DATA WHEN COMPARED TO THE INSTRON A CONVERSION CHART WAS ESTABLISHED TO CORRECT THE READINGS OBTAINED FROM THE HARDNESS TESTER.

- THE CORRECTED FORCE FROM THE CONVERSION PLOT WAS USED TO CALCULATE THE TENSILE STRENGTH USING THE FOLLOWING EQUATION:

$$\sigma = \frac{2P}{\pi Dt}$$

WHERE t IS TABLET THICKNESS, D IS THE DIAMETER AND P IS THE RECORDED FORCE IN KILOPONDS. ALL TENSILE STRENGTH VALUES ARE AN AVERAGE OF A MINIMUM OF 5 SEPARATE MEASUREMENTS ON FIVE INDIVIDUAL COMPACTS. ALL FRACTURED COMPACTS WERE INSPECTED TO ASSURE THAT TENSILE FAILURE HAD OCCURRED AS SEEN BY A FRACTURE OCCURRING PARALLEL TO THE DIRECTION OF LOADING.

MATERIALS

- THIS WORK REQUIRED THE USAGE OF SAMPLES WITH A HIGH PURITY LEVEL (AT LEAST 98%) AS WELL AS SAMPLES WHOSE LEVEL OF PURITY CORRESPONDS TO COMMERCIALLY AVAILABLE FATTY ALCOHOLS (APPROXIMATELY 95%).

- ALL FATTY ALCOHOLS OBTAINED WERE UTILIZED AS SUPPLIED BY THE MANUFACTURER WITH NO FURTHER PURIFICATION BEING CARRIED OUT IN OUR LABORATORY.

- TO DETERMINE THE IMPACT OF PROCESSING SAMPLES WERE FUSED AND SUBSEQUENTLY COOLED TO MODEL THE FUSION PROCEDURE USED IN THE MANUFACTURE OF MATRIX TABLETS.

RESULTS

- TO ASSURE THE PROCEDURE WAS CAPABLE OF PRODUCING REASONABLE RESULTS, A SERIES OF HIGH PURITY FATTY ALCOHOLS WERE TESTED WITH THE RESULTING ENERGY OF FUSION DATA COMPARED TO LITERATURE VALUES. SINCE THE DATA ANALYSIS TECHNIQUE IS IDENTICAL FOR EITHER FUSION OR FREEZING AND SINCE CONSIDERABLE ENERGY OF FUSION LITERATURE DATA EXISTS THIS PARAMETER WAS SELECTED AS THE BEST TEST CRITERIA. A GOOD CORRELATION WAS OBTAINED BETWEEN THE RESULTS FROM THE PROPOSED PROCEDURE AND LITERATURE VALUES.

- THE ABILITY OF THE PROCEDURE TO DIFFERENTIATE FATTY ALCOHOL COMBINATIONS (C16/C18) NORMALLY ENCOUNTERED AS COMMERCIAL CETOSTEARYL ALCOHOL WAS DETERMINED USING HIGH PURITY BLENDS. THE SAMPLES EXHIBITED A TWO PEAK FREEZING CURVE WITH A DEEP TROUGH BETWEEN EACH EVENT. THE DATA SHOWS INITIAL FREEZING (ΔH_1) ENERGY INCREASES AS THE CONCENTRATION OF C18 INCREASES. IT APPEARS THAT A VARIATION OF 6% IN FATTY ALCOHOL RATIO CAN BE MAPPED WITH REASONABLE ACCURACY USING THIS SEMI-QUANTITATIVE TECHNIQUE.

- COMPACTS OF THE FATTY ALCOHOLS WERE PREPARED, TETRADECANOL WAS NOT CAPABLE OF FORMING A COHESIVE COMPACT AND IS NOT SHOWN IN THESE RESULTS. THE DIFFERENCE IN THE TWO FORCE LEVELS SUGGESTS LITTLE VARIATION OF THE FATTY ALCOHOLS AS A FUNCTION OF APPLIED FORCE. NO MEASURABLE DIFFERENCE WAS SEEN WITH RESPECT TO RATE OF STRAIN. SAMPLES WERE COMPACTED DIRECTLY FROM THE SAMPLE CONTAINER AND AFTER FUSION AS DESCRIBED PREVIOUSLY. VARIATION AMONG SAMPLES OF VARIOUS PURITIES AND BETWEEN SOURCES OF SUPPLY WAS APPARENT. IT WAS NOTED THAT SAMPLES OF EQUIVALENT COMMERCIAL PURITY VARIED WITH RESPECT TO COMPACT STRENGTH.

- EACH SAMPLE WAS CHARACTERIZED WITH THEIR INITIAL ENERGY OF FREEZING (ΔH_1) BEING COMPARED TO THEIR CORRESPONDING COMPACT STRENGTH. THERE APPEARS TO BE A TREND OF INCREASING COMPACT STRENGTH WITH INCREASING ENERGY OF FREEZING FOR THE SAMPLES STUDIED. A FATTY ALCOHOL WHICH RELEASES A LARGE DEGREE OF ENERGY UPON INITIAL FREEZING PRODUCES A STRONGER COMPACT THAN A FATTY ALCOHOL WHICH RETAINS A HIGHER DEGREE OF THERMAL ENERGY.

- SAMPLES OF OCTADECANOL WERE SELECTED FOR MICROSCOPIC EXAMINATION BY SEM. THE COMPACTS WERE SCANNED ALONG THE FRACTURED EDGE. THE MICROGRAPHS CLEARLY SHOW THAT THE STRONGER COMPACT FORMING LOT M488, IS MORE CRYSTALLINE WHILE L020A IS "WAXY" IN APPEARANCE. IT IS REASONABLE TO EXPECT M488 TO GENERATE MORE COHESIVE COMPACTS IF THE CLEARLY DEFINED CRYSTAL SURFACES ARE CONSIDERED AS THE LOCI FOR COMPACT BOND FORMATION. WHILE THE AMORPHOUS L020A SHOWS LITTLE PHYSICAL STRUCTURE WHICH ONE WOULD INTUITIVELY EXPECT TO CONTRIBUTE TO STRONG COMPACT FORMATION.

- THE EFFECT OF INCREASING LEVELS OF A THIRD FATTY ALCOHOL COMPONENT ON COMPACT STRENGTH WAS CHARACTERIZED. OF THE TWO SAMPLES OF CETOSTEARYL ALCOHOL ONLY LOT K4991 FORMED STRONG COMPACTS. THE PRIMARY DIFFERENCE BETWEEN THE TWO LOTS (K4991, L4593) WAS THE CONCENTRATION OF TETRADECANOL.
BY ADDITION OF TETRADECANOL TO LOT L4593 A CORRESPONDING INCREASE IN THE RESULTING COMPACT STRENGTH WAS NOTED.

CONCLUSIONS

- A RELATIONSHIP BETWEEN INITIAL ENERGY OF FREEZING (ΔH_1) AND THE TENSILE STRENGTH OF FATTY ALCOHOL COMPACTS HAS BEEN DEMONSTRATED.

- SCANNING ELECTRON MICROGRAPHS SUPPORT THIS OBSERVATION SINCE THE MORE CRYSTALLINE SAMPLES ALSO EXHIBITED HIGHER ΔH_1 VALUES AS WELL AS HIGHER COMPACT STRENGTHS.

- THE PRESENCE OF C14 (TETRADECANOL) IN MIXTURES OF C16 AND C18 WAS FOUND TO INCREASE THE AMOUNT OF ENERGY LIBERATED DURING INITIAL FREEZING AND SUBSEQUENTLY CAUSE THE SAMPLE TO PRODUCE COMPACTS HAVING A HIGHER TENSILE STRENGTH.

- THESE DATA SUGGEST THAT MEASUREMENT OF THE HEAT OF FREEZING (SOLIDIFICATION) PROVIDES A USEFUL PROBE IN PREDICTING SUBSEQUENT COMPACT PROPERTIES.
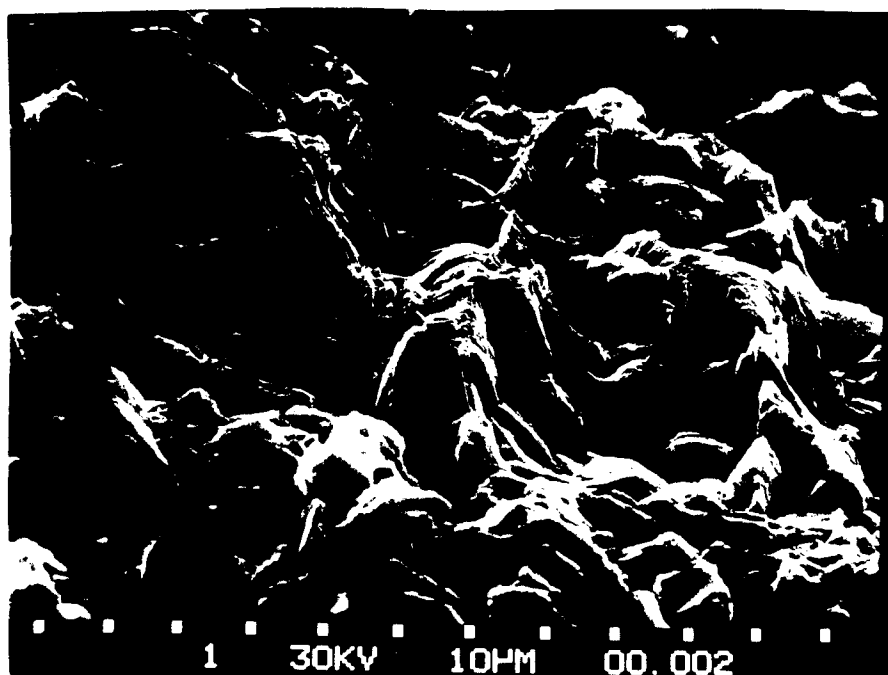
C_{18} M488   1000X Magnification
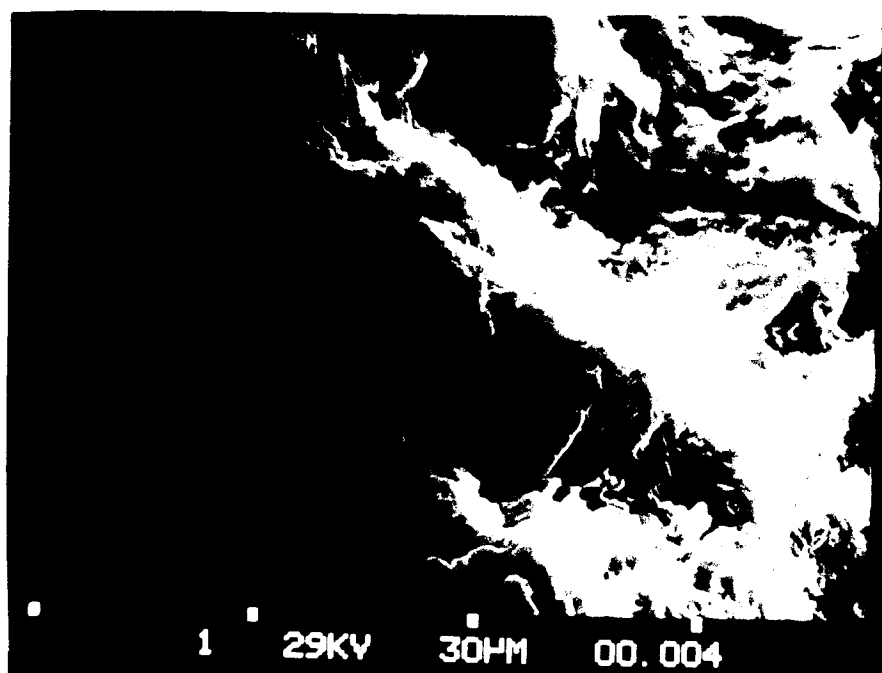
C_{18} L020A   1000X Magnification

MEASURED VARIABLE _____

Du Pont Instruments

PART NO. 990525

RUN NO. _____ DATE 9/20/83

OPERATOR AB

SAMPLE Cu L2425

ATM N₂ @ 1485Z

FLOW RATE 1000/min

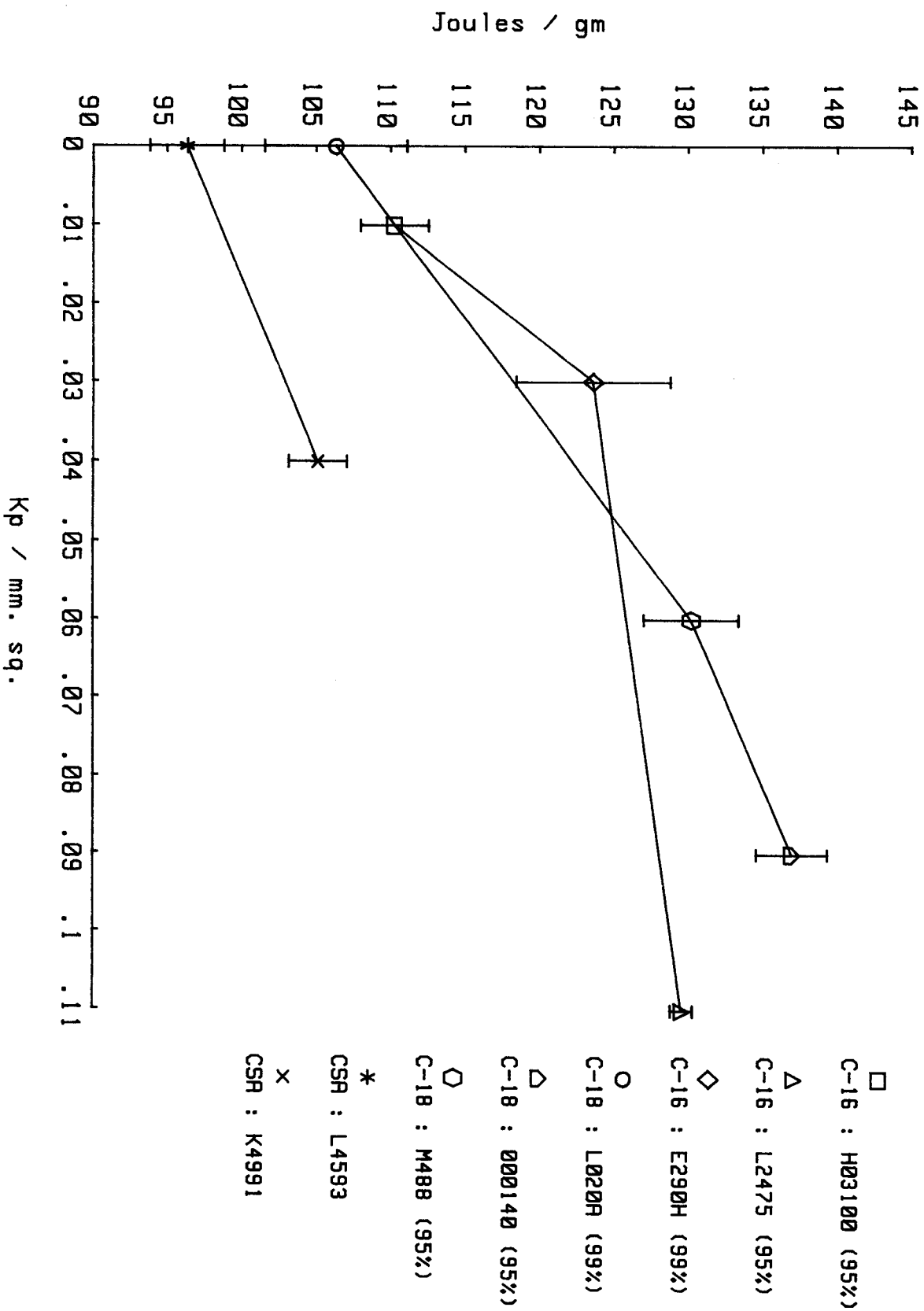| T-AXIS	DSC	TMA	DMA
PROG RATE, °C/min 5	RANGE, 200 µW/mV	1 µm/mV	0.05 Hz/mV
	DTA	DTM	FREQ, mV/cm 0.005 dB/mV
RANGE, mV/cm Time	50 mK/mV	DTM 0.1 µm/(min mV)	
HEAT COOL ISO	RANGE, mV/cm 5/10	MODE	DAMPING, mV/cm
SHIFT, cm — 0 —	WEIGHT, mg 5.38mg	RANGE, mV/cm	OSC AMP, mm
TIME, min/cm 0.6	REFERENCE M.T. Pan	SAMPLE SIZE	A/Z GAIN, %
	LOAD, g	LOAD, g	SAMPLE SIZE

ΔH₁ = 125.95/2

ΔH₂ = 81.33%
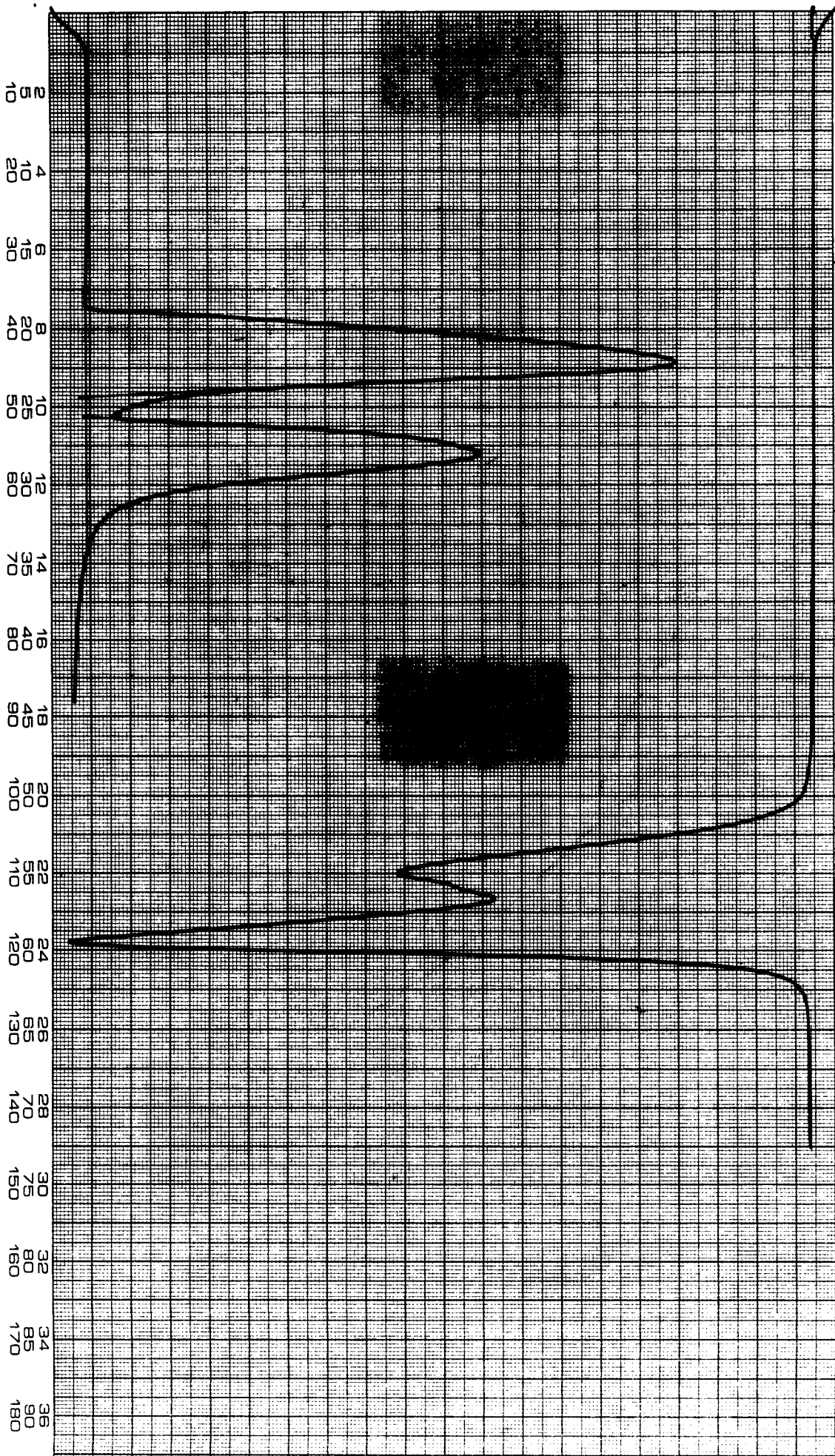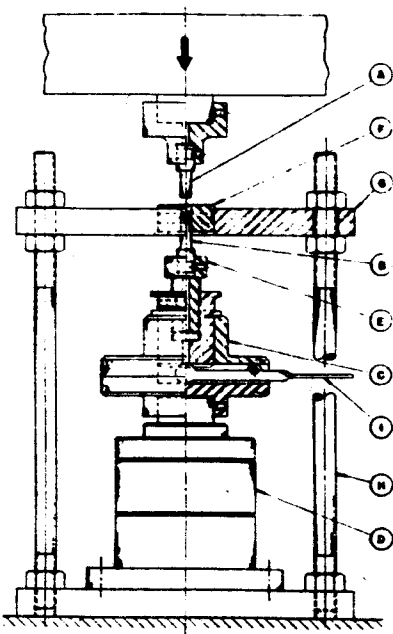
Fixture for compressing particulate solids.
Key: A, upper punch; F, die; G, metal plate; B, lower punch; E, threaded bushing; C, flange holding lower punch; I, lifting lever; H, steel rods; D, compression cell.

HARDNESS DATA, CONVERSION CHART

HEBERLEIN RESULTS (kp)

INSTRON RESULTS (kp)

n=10
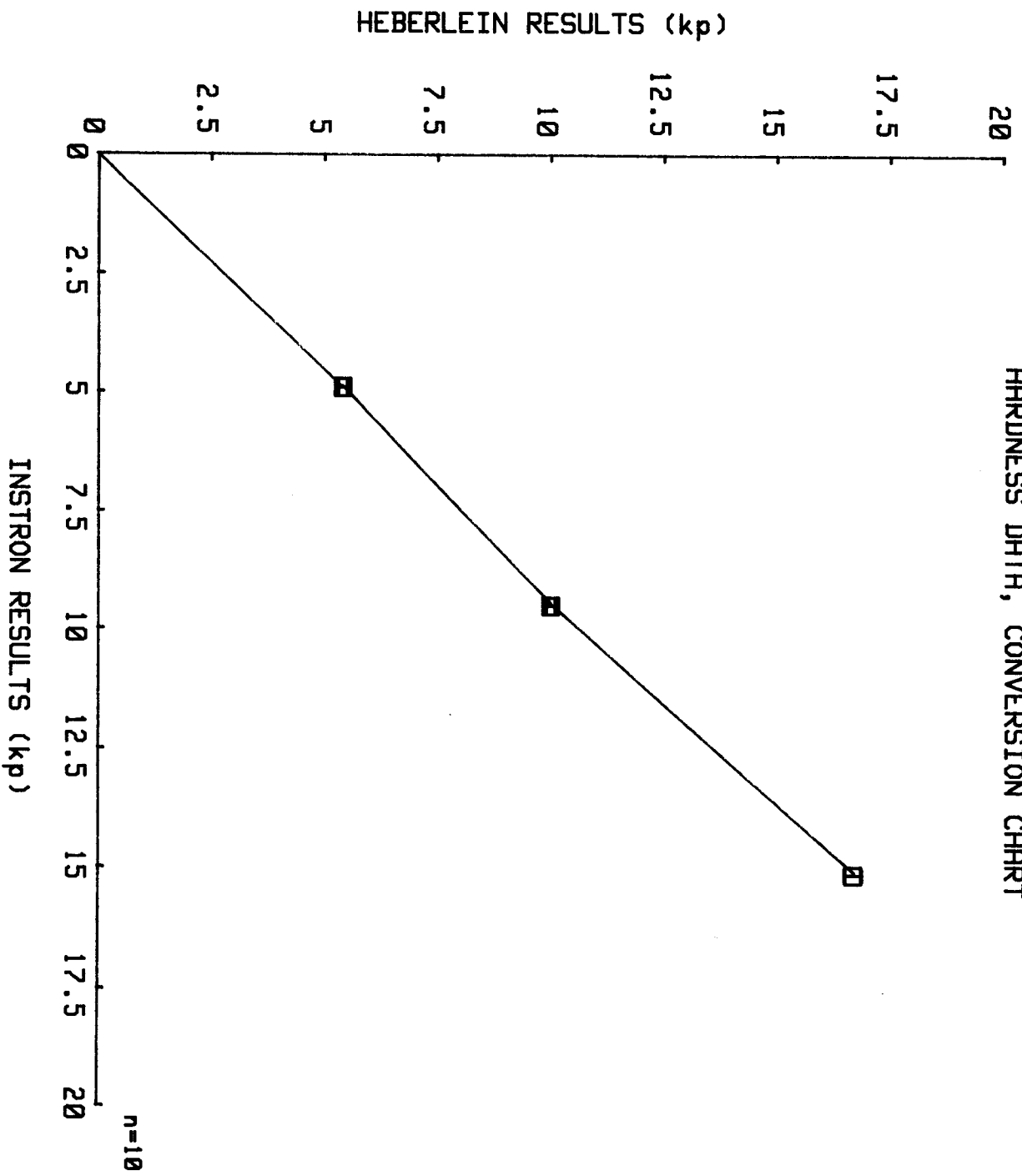
ENERGY OF FREEZING (ΔH_1)
AS A FUNCTION OF COMPACT STRENGTH

Joules / gm

Kp / mm. sq.

□ C-16 : H03100 (95%)

△ C-16 : L2475 (95%)

◇ C-16 : E290H (99%)

○ C-18 : L020A (99%)

⬠ C-18 : 000140 (95%)

⬡ C-18 : M480 (95%)

* CSA : L4593

× CSA : K4991

Energy of Freezing as a Function of C_{16} Concentration[a]

% C_{16}/MOLE FRAC	% C_{18}/MOLE FRAC	ΔH_1 J/g	ΔH_2 J/g
31/.334	69/.666	117.0 (1.3)[b]	44.0 (1.1)[b]
29/.313	71/.687	118.6 (1.3)	50.5 (1.5)
27/.292	73/.708	119.6 (2.2)	53.0 (2.5)
25/.271	75/.729	120.3 (1.5)	57.2 (1.7)

[a] All energy measurements are recorded as Joules/gm (J/g), ΔH represents the first measured peak, ΔH_2 corresponds to the second peak.

[b] n = 5 (std. dev.)

Heat of Fusion, High Purity Fatty Alcohol Samples

Alcohol	Lot #	Weight[a]	Calc. ΔH[b]	Lit. Value
1-Tetradecanol	A1401	3.94 mg	227.3 J/g (0.1)	213.0[c],224.7[d] J/g
1-Hexadecanol	E290H	4.46 mg	232.7 J/g (1.2)	220.6[c],229.6[d] J/g
1-Octadecanol	L020A	4.98 mg	235.6 J/g (1.8)	236.7[e],243.7[c] J/g

[a] Represents 1.84×10^{-5} moles of each alcohol.

[b] n = 5, (std. dev.).

[c] T. Eckert and J. Müller, Arch. Pharm. (Weinheim), 311, 31 (1978)

[d] C. Mosselman and H. Dekker, J. Chem. Soc. Farraday Trans., 71, 417 (1975)

[e] G. Gioia Lobbia, G. Berchiesi, and M. A. Berchiesi, J. Thermal Anal., 10, 205 (1976)
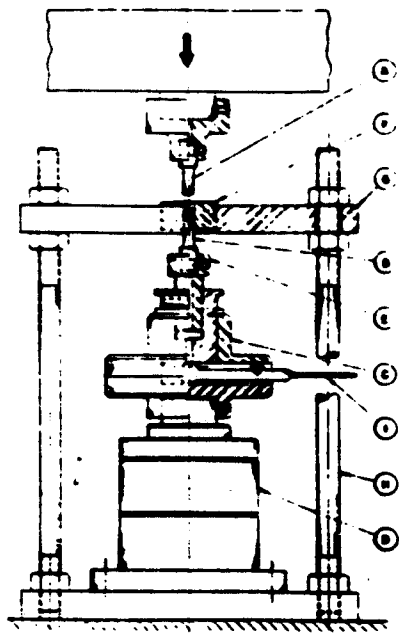
Fatty Alcohol Samples and Origins of Supply

Alcohol	Lot #	Analytical Purity[a]	Source
High Purity Material			
1-Tetradeconal	A 1401	+ 99.0%	Analabs, Div. of Foxboro North Haven, Conn.
1-Hexadeconal	E 290H	+ 99.0%	Analabs, Div. of Foxboro North Haven, Conn.
1-Octadecanol	L 020A	+ 99.0%	Analabs, Div. of Foxboro North Haven, Conn.
Commercial Material			
1-Tetradecanol	T03360	approx. 95%	Pfaltz & Bauer Inc. Stamford, Conn.
1-Hexadecanol	H03100	approx. 95%	Pfaltz & Bauer Inc. Stamford, Conn.
1-Hexadecanol	L2475	approx. 95%	M. Michel Co. New York, N.Y.
1-Octadecanol	000140	approx. 95%	Pfaltz & Bauer, Inc. Stamford, Conn.
1-Octadecanol	M488	approx. 95%	M. Michel Co. New York, N.Y.
Cetostearyl	K4991	C_{14} alcohol 3.7%[b] C_{16} alcohol 26.0% C_{18} alcohol 61.8%	Procter & Gamble Cincinnati, Ohio
Cetostearyl	L4593	C_{14} alcohol 0.8%[b] C_{16} alcohol 31.1% C_{18} alcohol 62.8%	Conoco Chem. Co. Houston, Texas

[a] Manufacturers label claim.

[b] Remaining materials are primarily long and short chain alcohols and a trace of alkanes <u>CIBA-GEIGY/PAC Data</u> 3/21/82.

Instron Punch Holding Fixture

Fixture for compressing particulate solids.
Key: A, upper punch; F, die; G, metal plate; B,
lower punch; E, threaded bushing; C, flange hold-
ing lower punch; I, lifting lever; H, steel rods; D,
compression cell.