

Figure 1 - Chemical structure of CDDO methyl ester

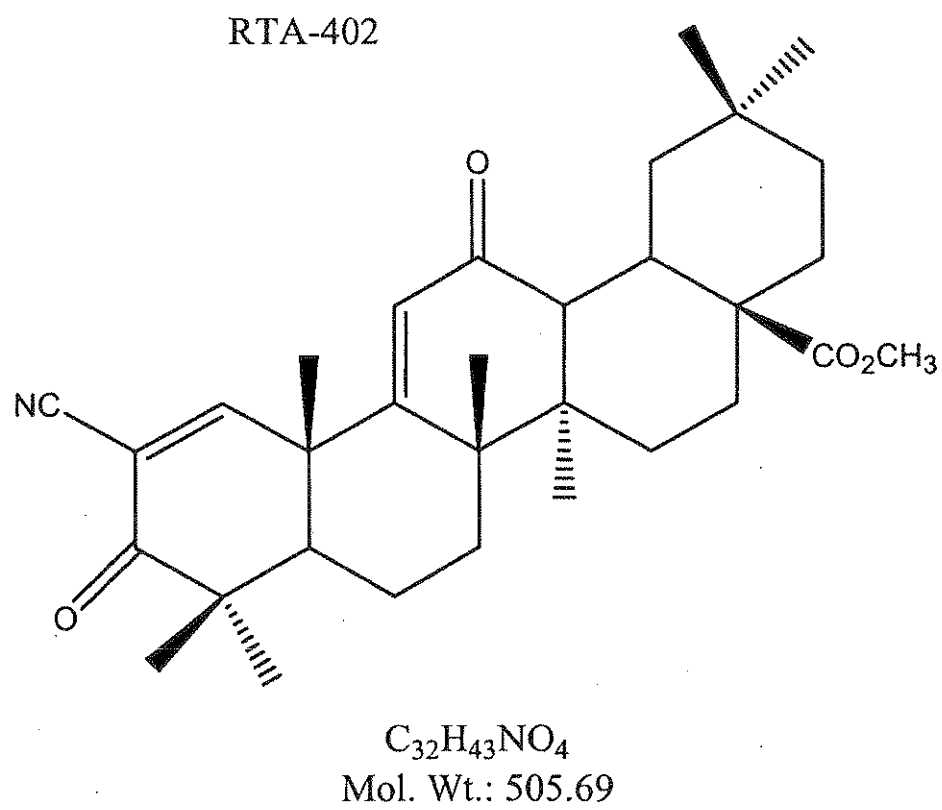


Figure 2 – XRPD pattern of Form A (top) and Form B (bottom)
From top to bottom: unmiconized Form A (2A), micronized Form A (2B), and Form B
(2C).

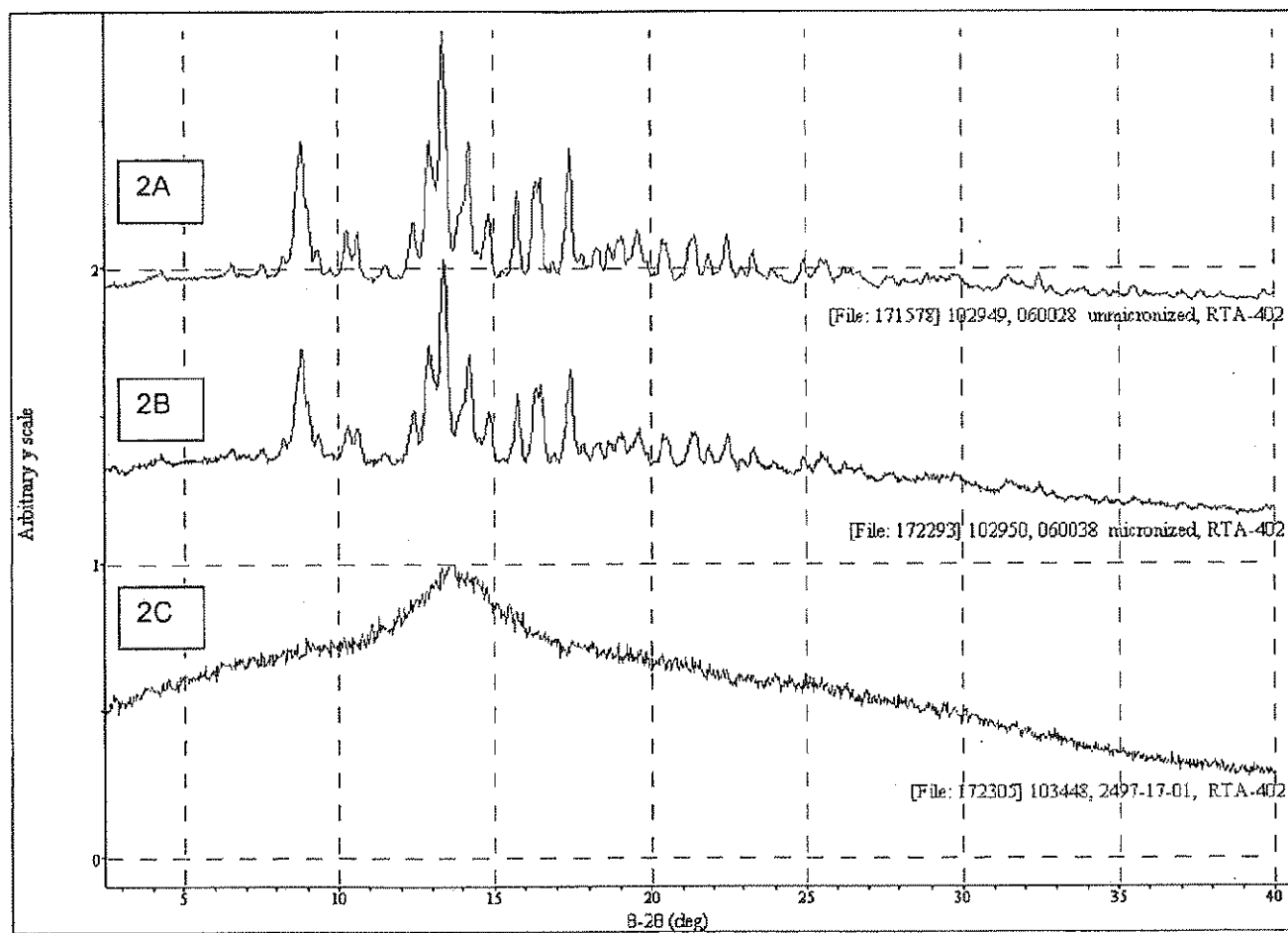
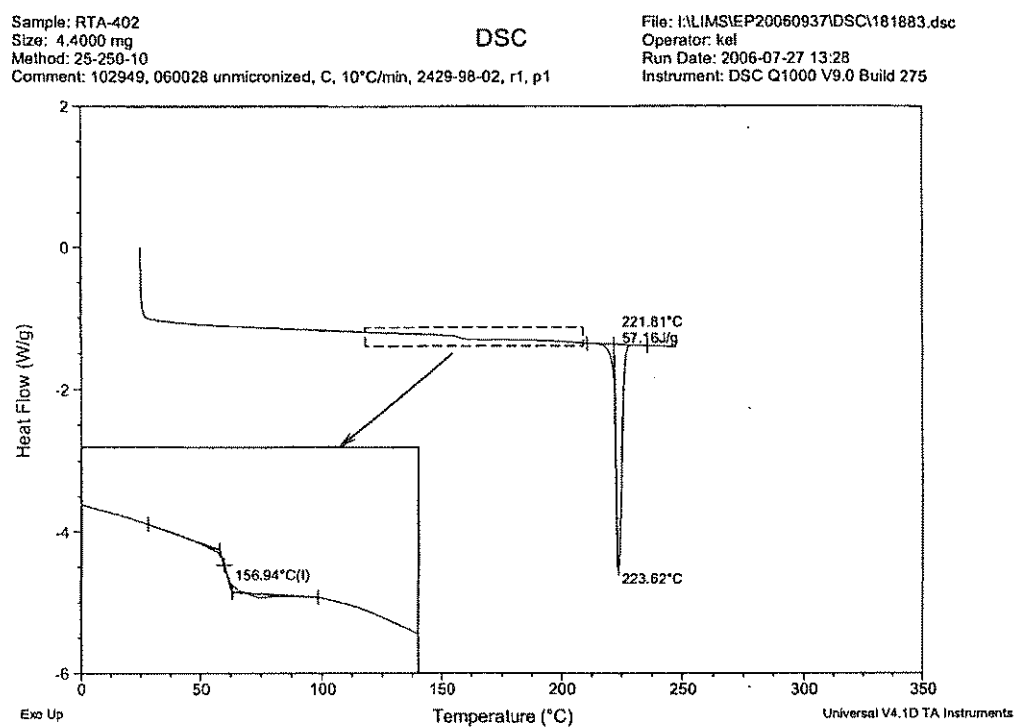


Figure 3 - DSC and TG curve of CDDO methyl ester.



Sample: RTA-402
Size: 5.5850 mg
Method: 25-350-10
Comment: 102949, 060028 unmiconized, 10°C/min, p1

TGA

File: I:\LIMS\EP20060937\TGA\172251.tga
Operator: KEL
Run Date: 27-Jul-2006 15:32
Instrument: AutoTGA 2950 V5.4A

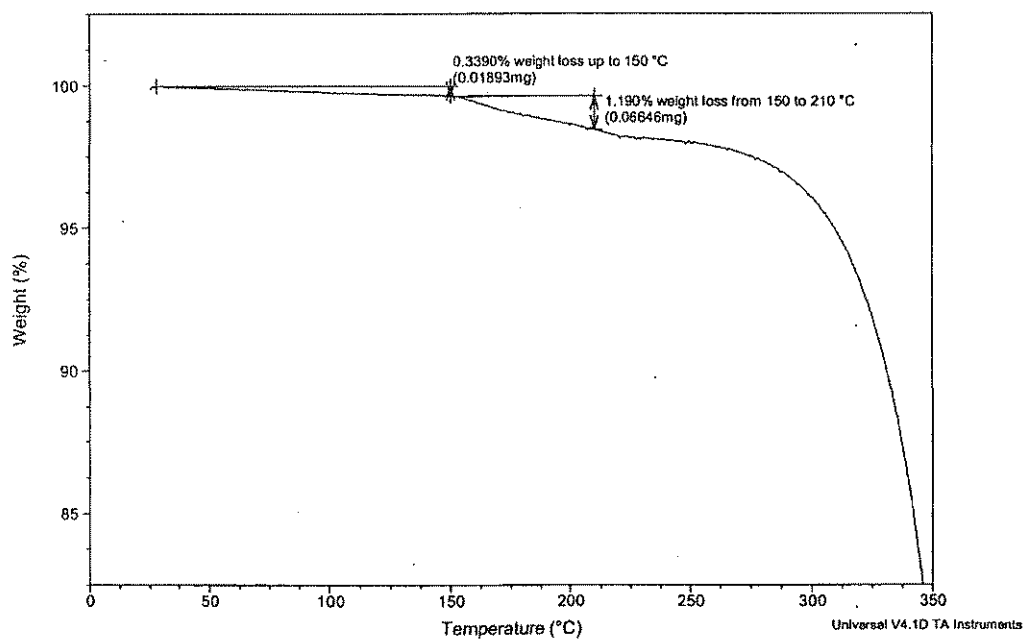


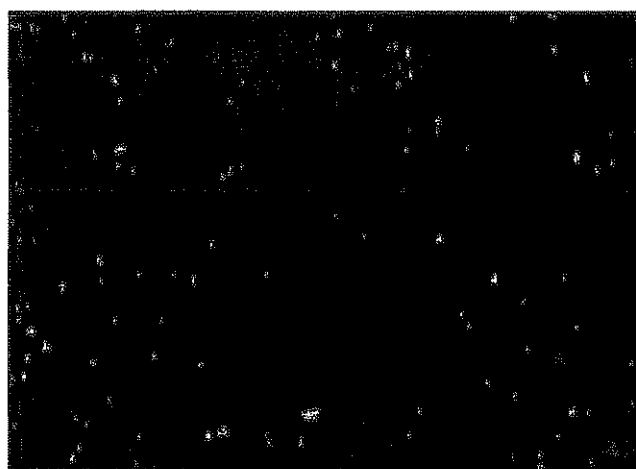
Figure 4 - Hot stage analysis of Form A - unmicronized



28.9 °C



150.1 °C

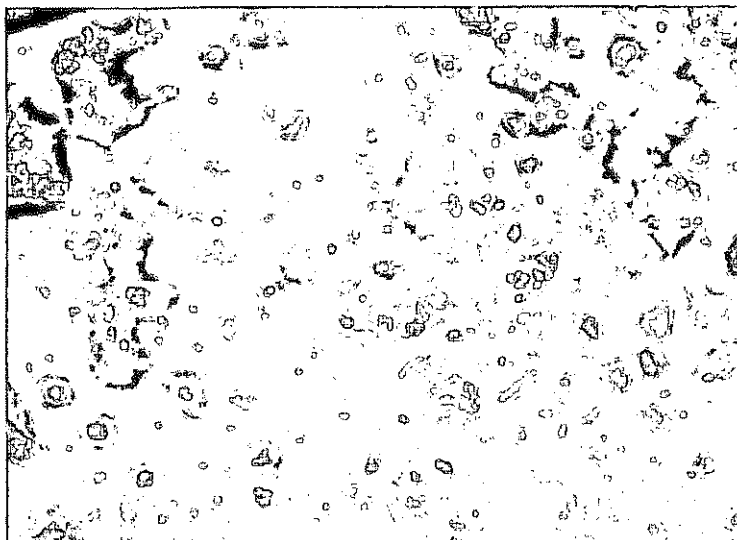


176.4 °C



200.2 °C

Figure 4 (continued) Hot stage analysis of Form A - unmicronized,



225.9 °C

Figure 5 - Dynamic vapor sorption isotherm of Form A - unmicronized

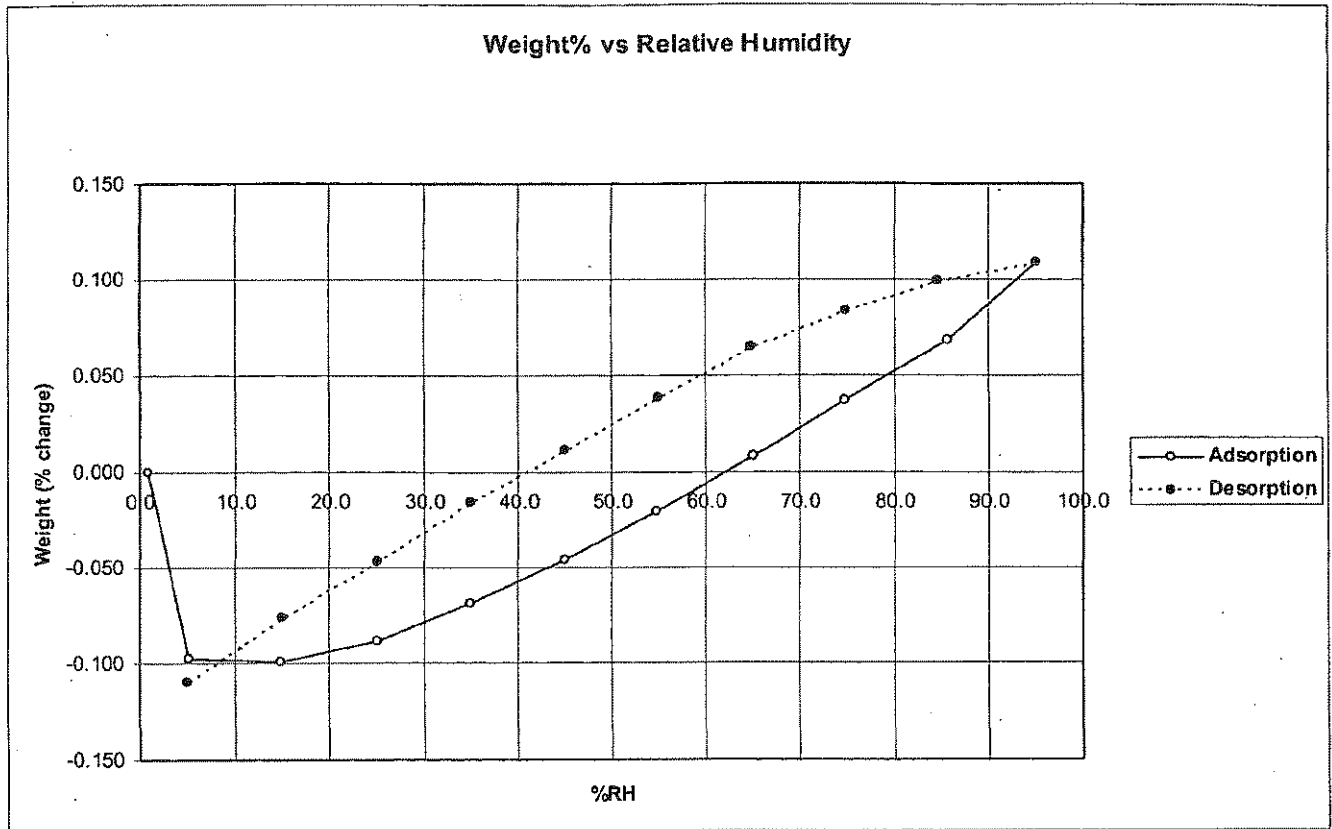


Figure 6- SEM images of Form A - unmicronized

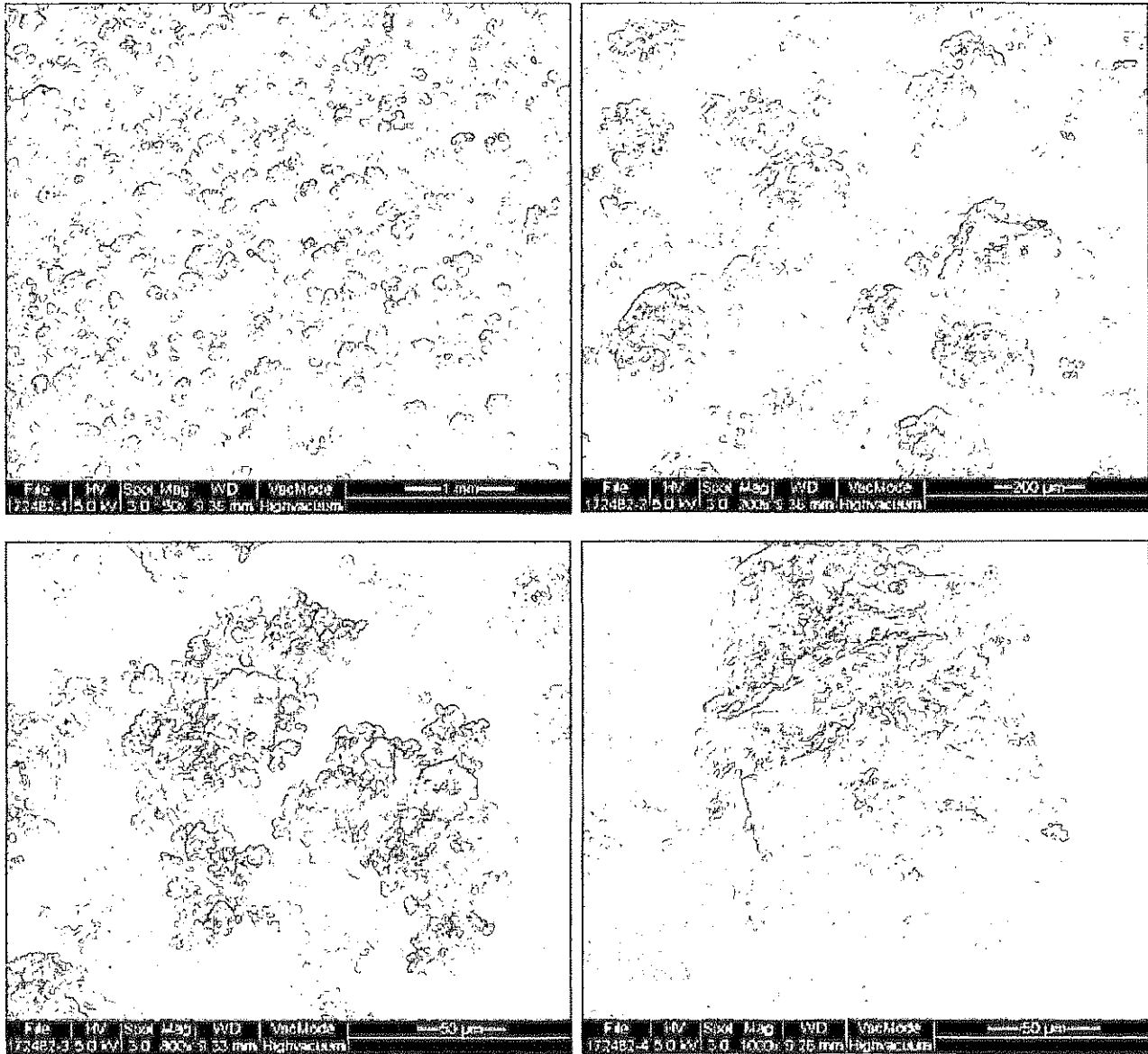


Figure 6 (continued) SEM IMAGES of Form A - unmicronized

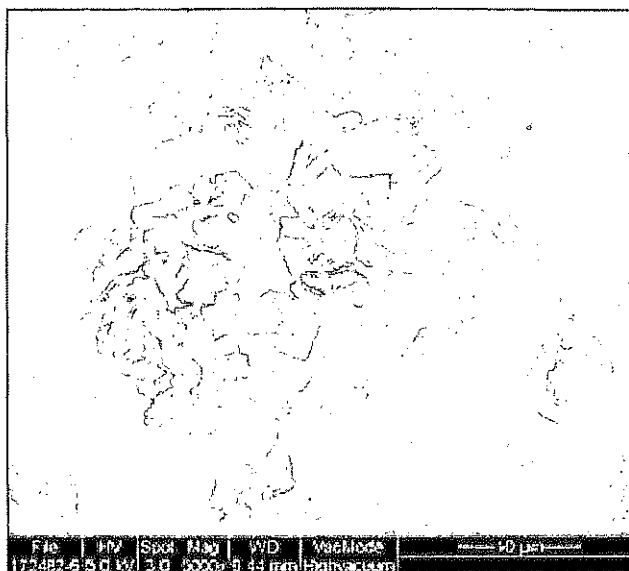
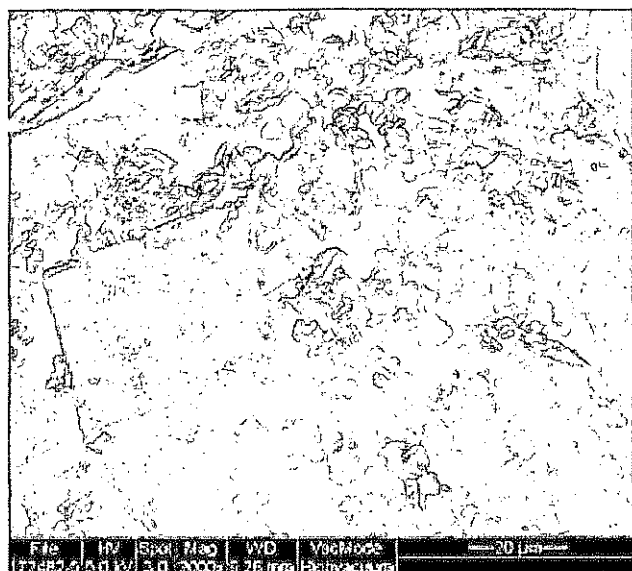


Figure 7 - Form A before (top) and after (bottom) stress at 195 °C.

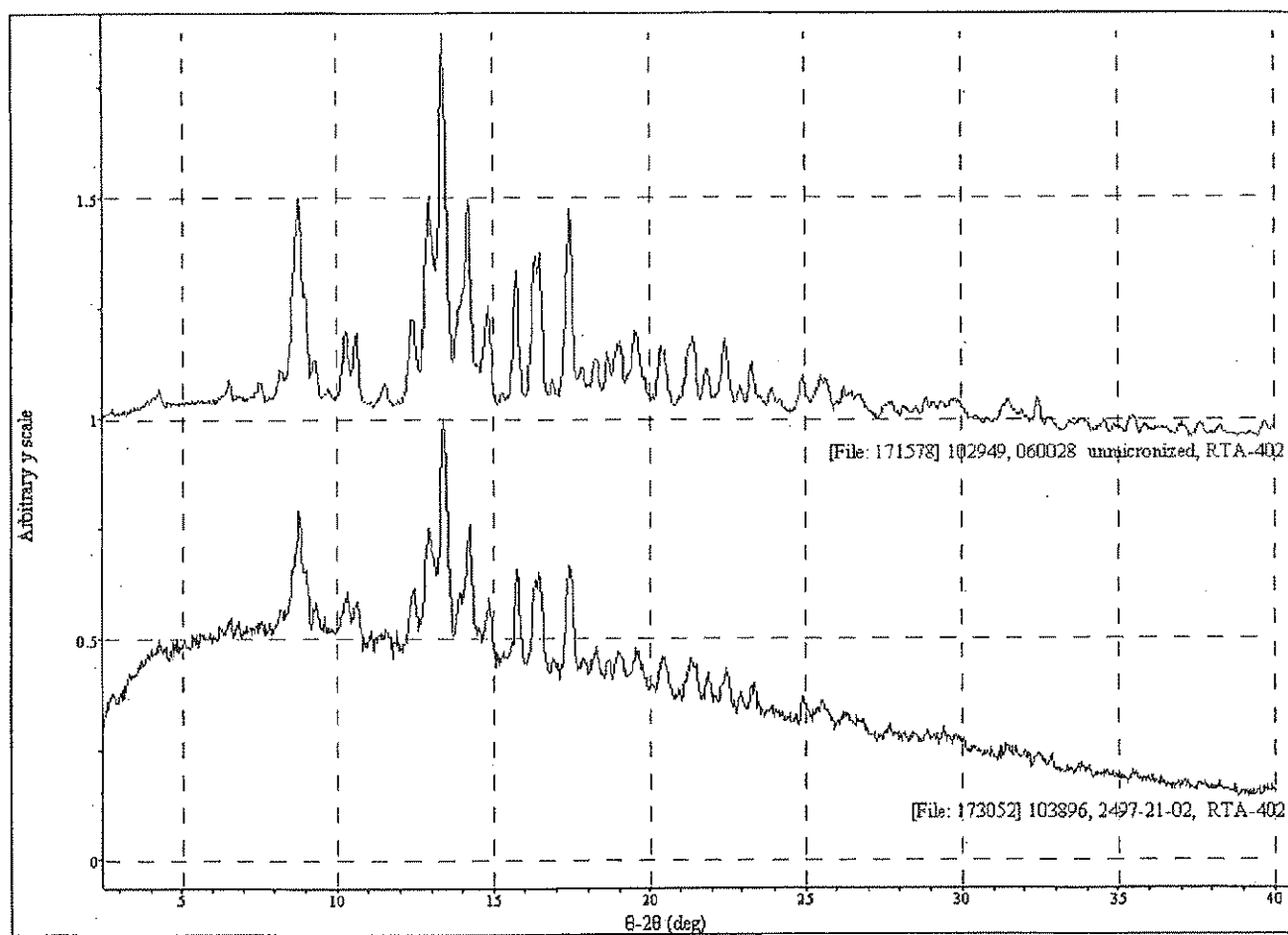


Figure 8 - NMR spectrum of Form A - unmicronized.

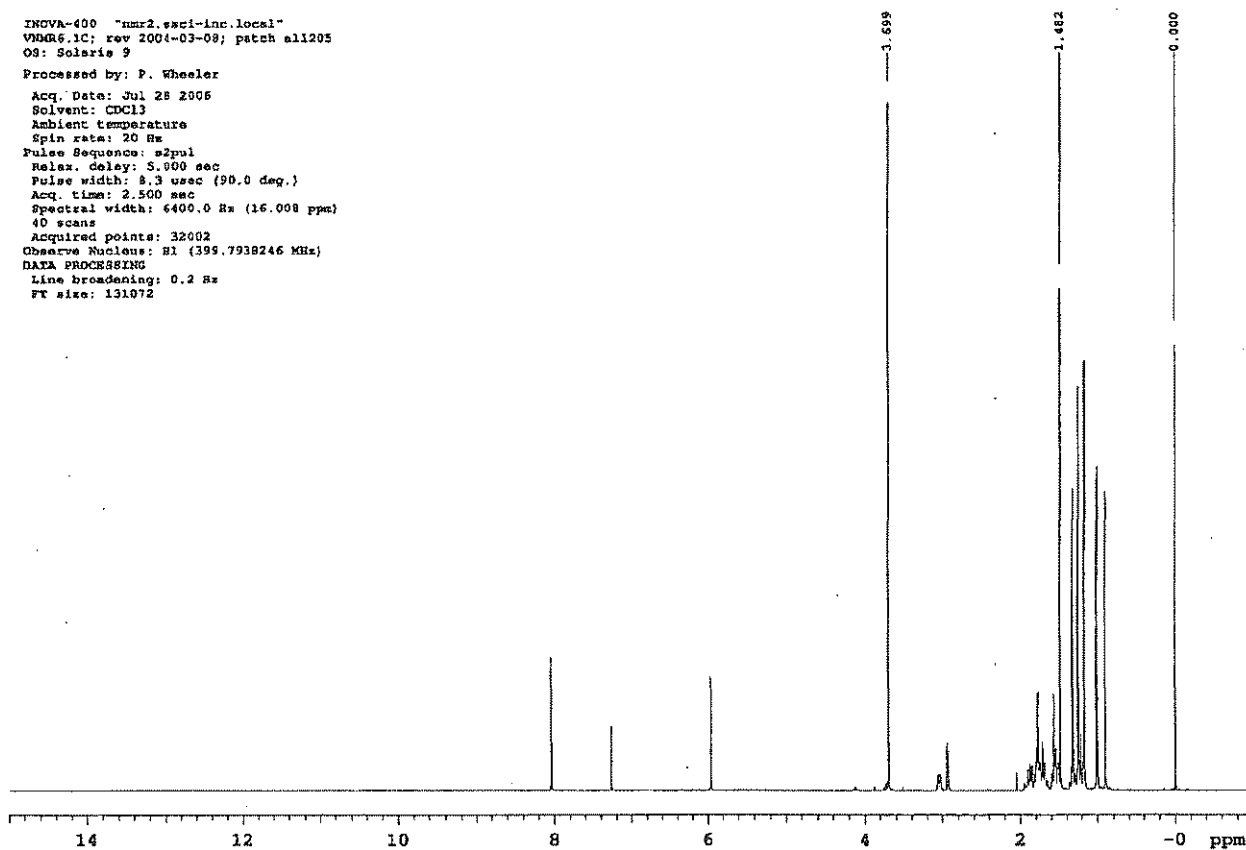
102949, RTA-402, Lot 060028 unmicronized, in CDCl₃ w/ TMS, 1H NMR, referenced to TMS at 0.0 ppm

File: 172444

INOVA-400 "nmr2.exe-inc.local"
VMDR6.1C; rev 2004-03-08; patch all205
OS: Solaris 9

Processed by: P. Wheeler

Acq. Date: Jul 25 2005
Solvent: CDCl₃
Ambient temperature
Spin rate: 20 Hz
Pulse Sequence: zgpg30
Relax. delay: 5.000 sec
Pulse width: 8.3 usec (90.0 deg.)
Acq. time: 2.500 sec
Spectral width: 6400.0 Hz (16.000 ppm)
40 scans
Acquired points: 32002
Observe Nucleus: H1 (399.7938246 MHz)
DATA PROCESSING
Line broadening: 0.2 Hz
FT size: 131072



Plot file: 172444-1

Figure 9 - MDSC curve of Form B CDDO methyl ester.

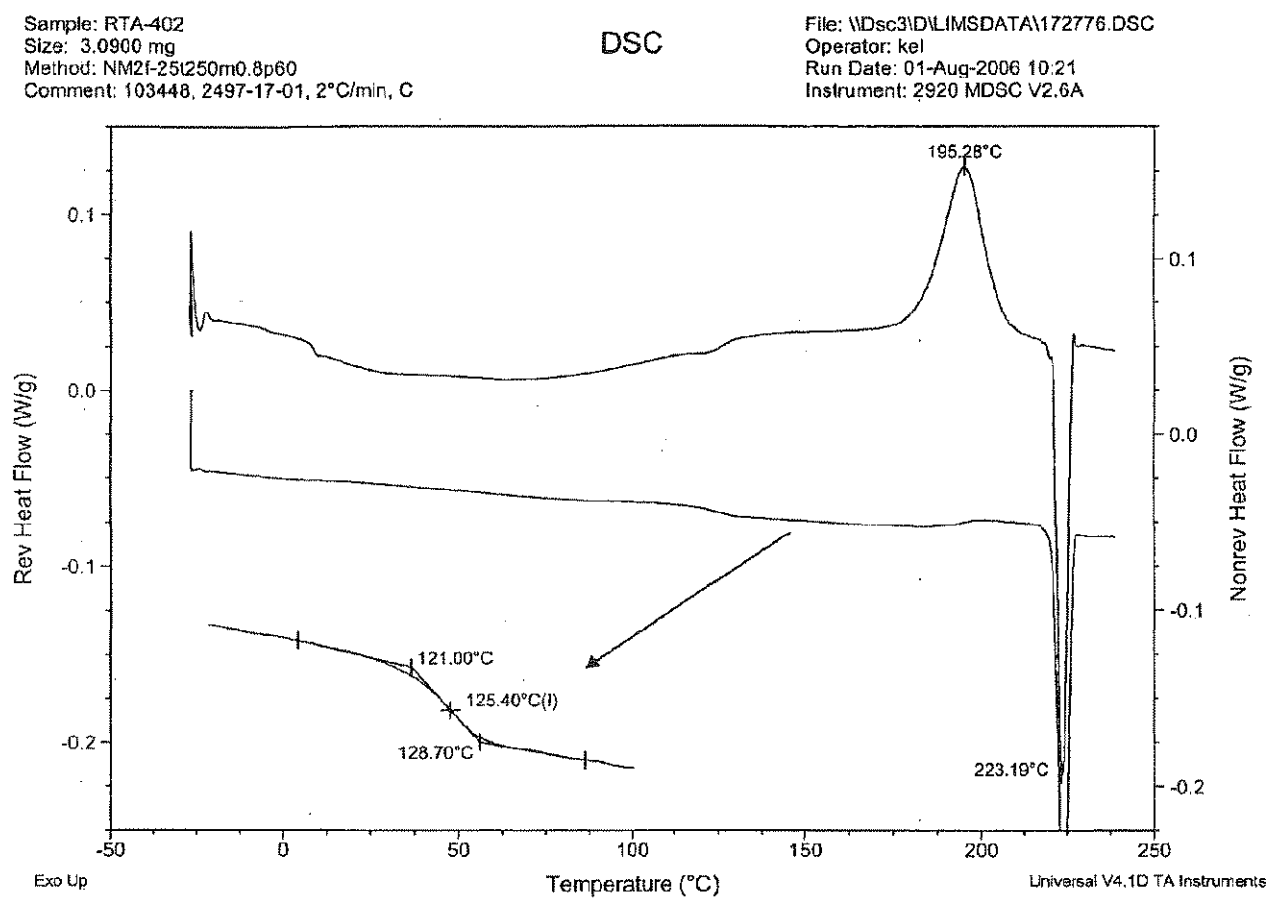


Figure 10 – Form B CDDO methyl ester before (top) and after (bottom) stress.

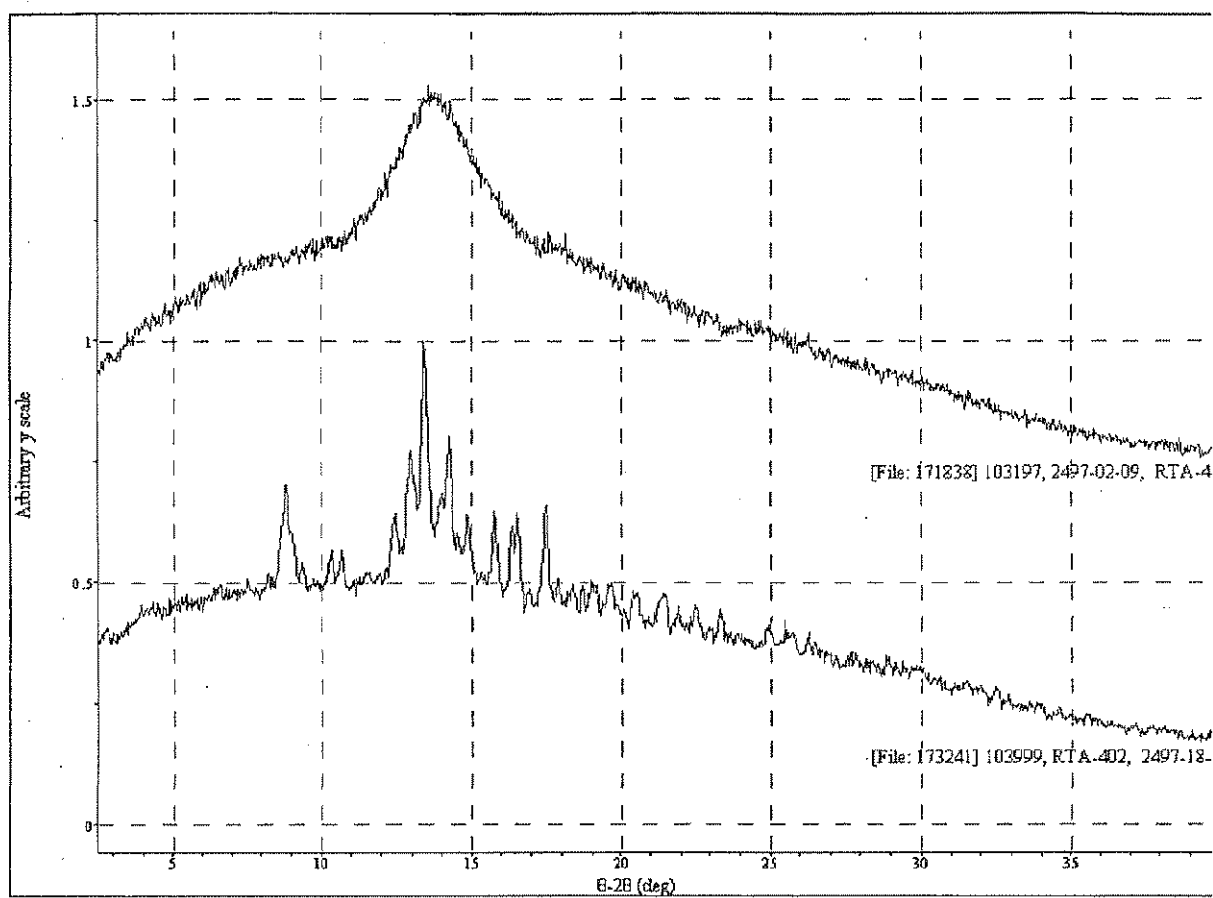


Figure 11 - NMR spectrum of Form B CDDO methyl ester.

103448, 2497-17-01, RTA-402, in CDCl₃ w/ TMS, 1H NMR, referenced to TMS at 0.0 ppm

file: 172792

INOVA-400 "nmr2.escl-inc.local"
VNMRS6.1C; rev 2004-03-08; patch all205
OS: Solaris 9

Processed by: P. Wheeler

Acq. Date: Aug 1 2006

Solvent: CDCl₃

Ambient temperature

Spin rate: 20 Hz

Pulse Sequence: zgpg30

Relax. delay: 5.000 sec

Pulse width: 8.3 usec (90.0 deg.)

Acq. time: 2.500 sec

Spectral width: 6400.0 Hz (16.000 ppm)

40 scans

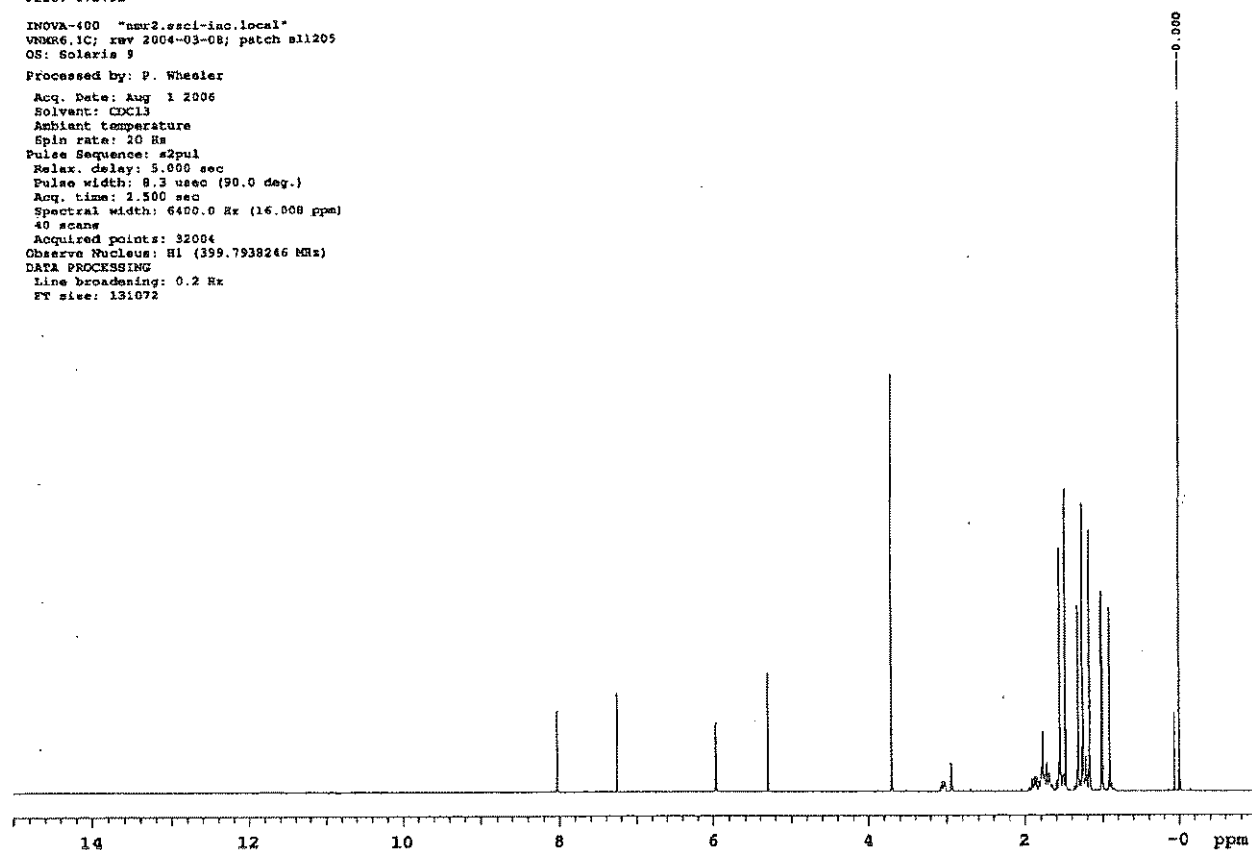
Acquired points: 32004

Observe Nucleus: H1 (399.7938246 MHz)

DATA PROCESSING

Line broadening: 0.2 Hz

FT size: 131072



Plot file: 172792-1

Figure 12 - ORTEP drawing of a single CDDO methyl ester molecule with labeling. Atoms are represented by 50% probability anisotropic thermal ellipsoids.

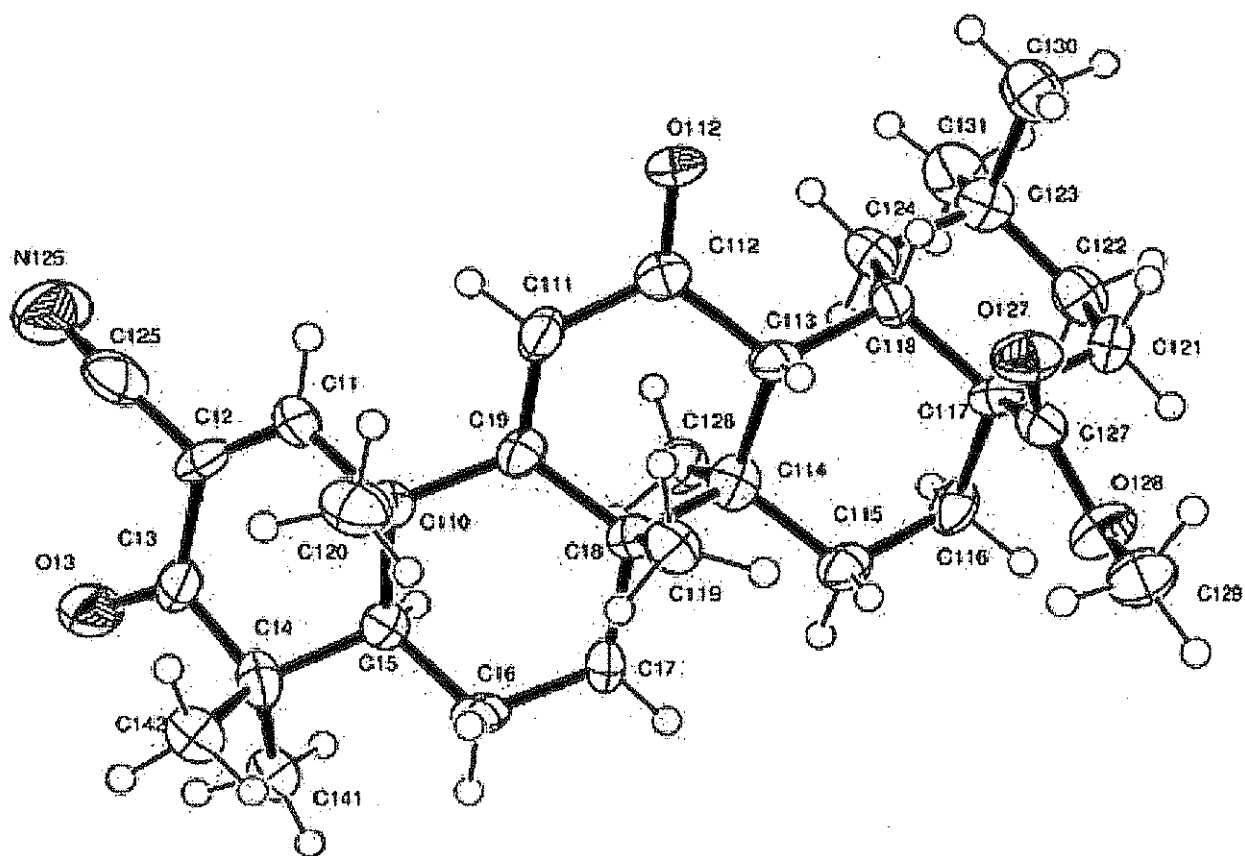


Figure 13 - ORTEP drawing of the contents of the asymmetric unit of Form A crystals. Atoms are represented by 50% probability anisotropic thermal ellipsoids.

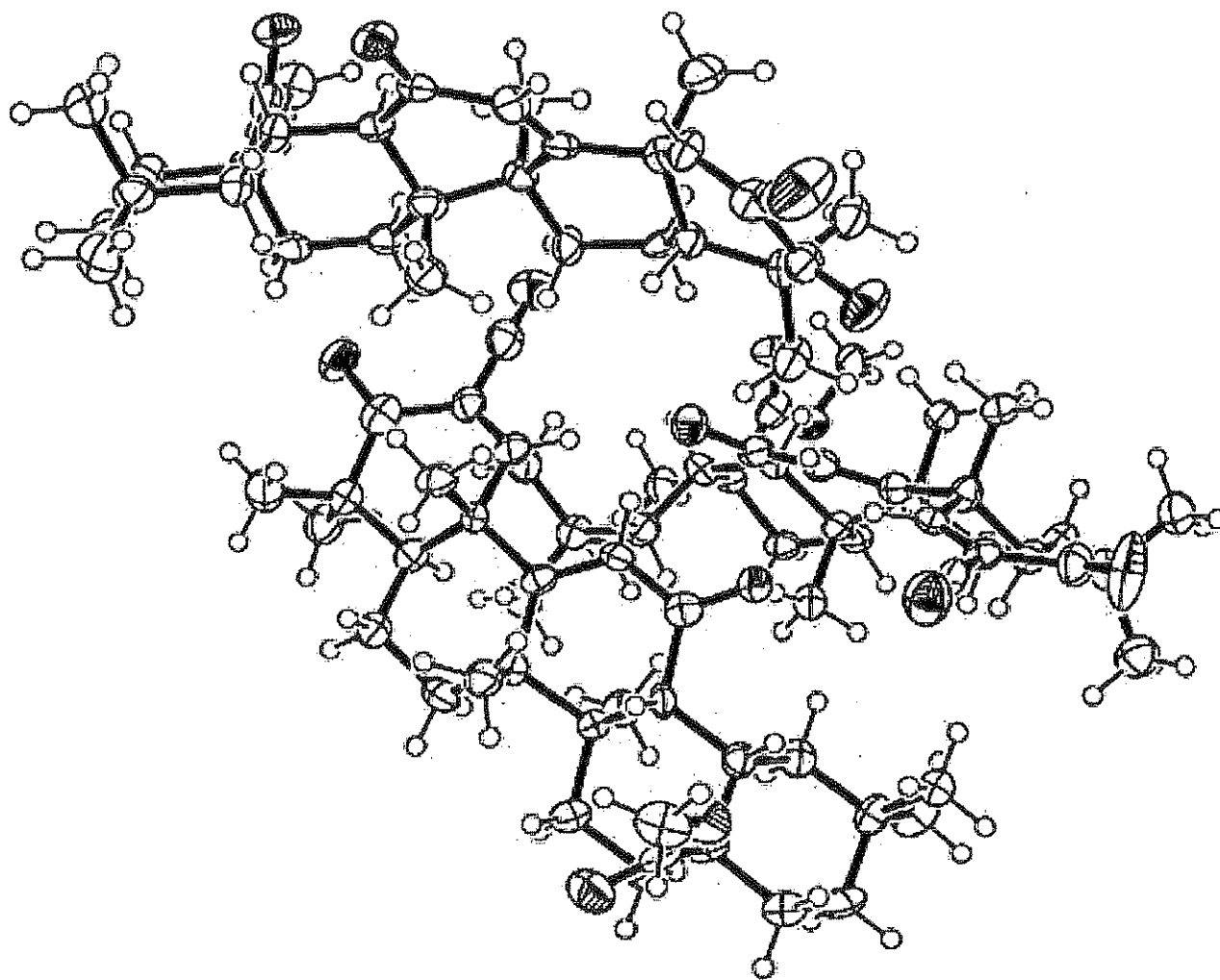


Figure 14 - Packing diagram of Form A crystals viewed down the crystallographic a axis.

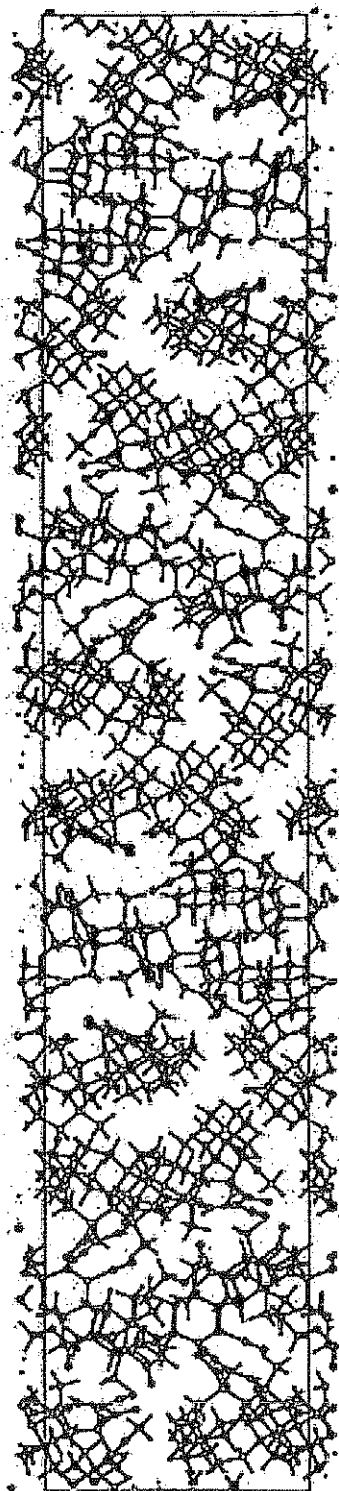


Figure 15 - Packing diagram of Form A crystals viewed down the crystallographic b axis.

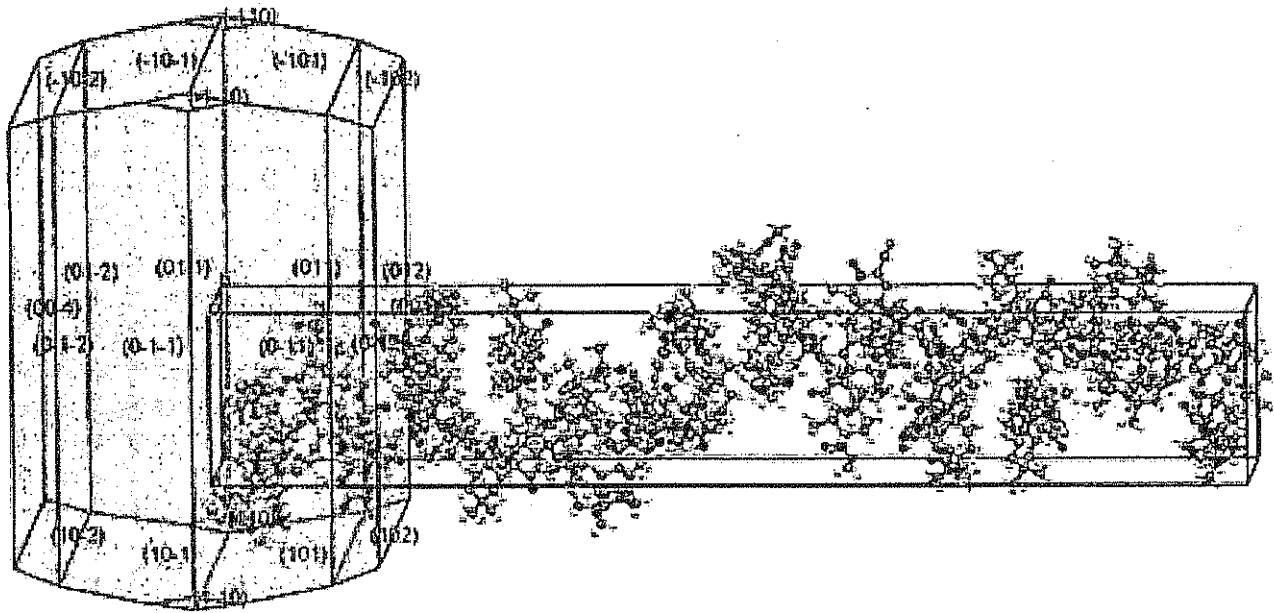


Figure 16 - Packing diagram of Form A crystals viewed down the crystallographic *c* axis.

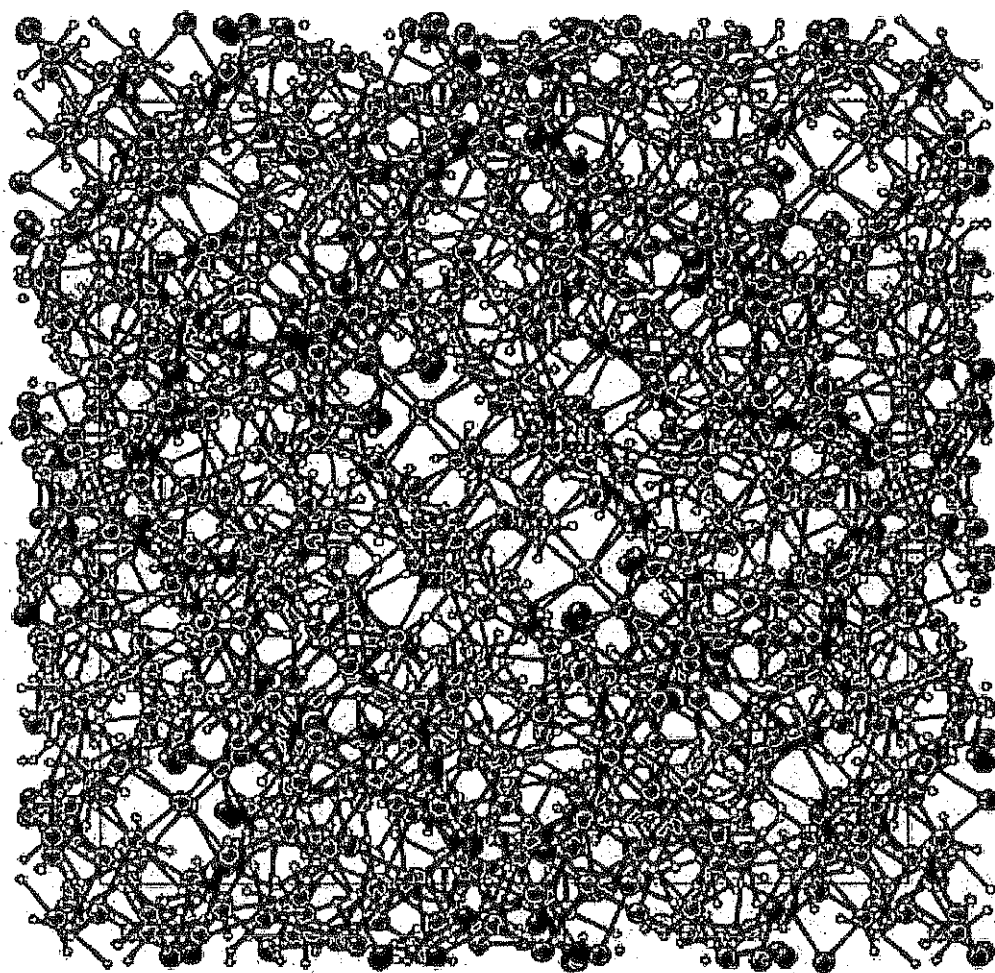


Figure 17 - Calculated X-ray powder pattern of Form A

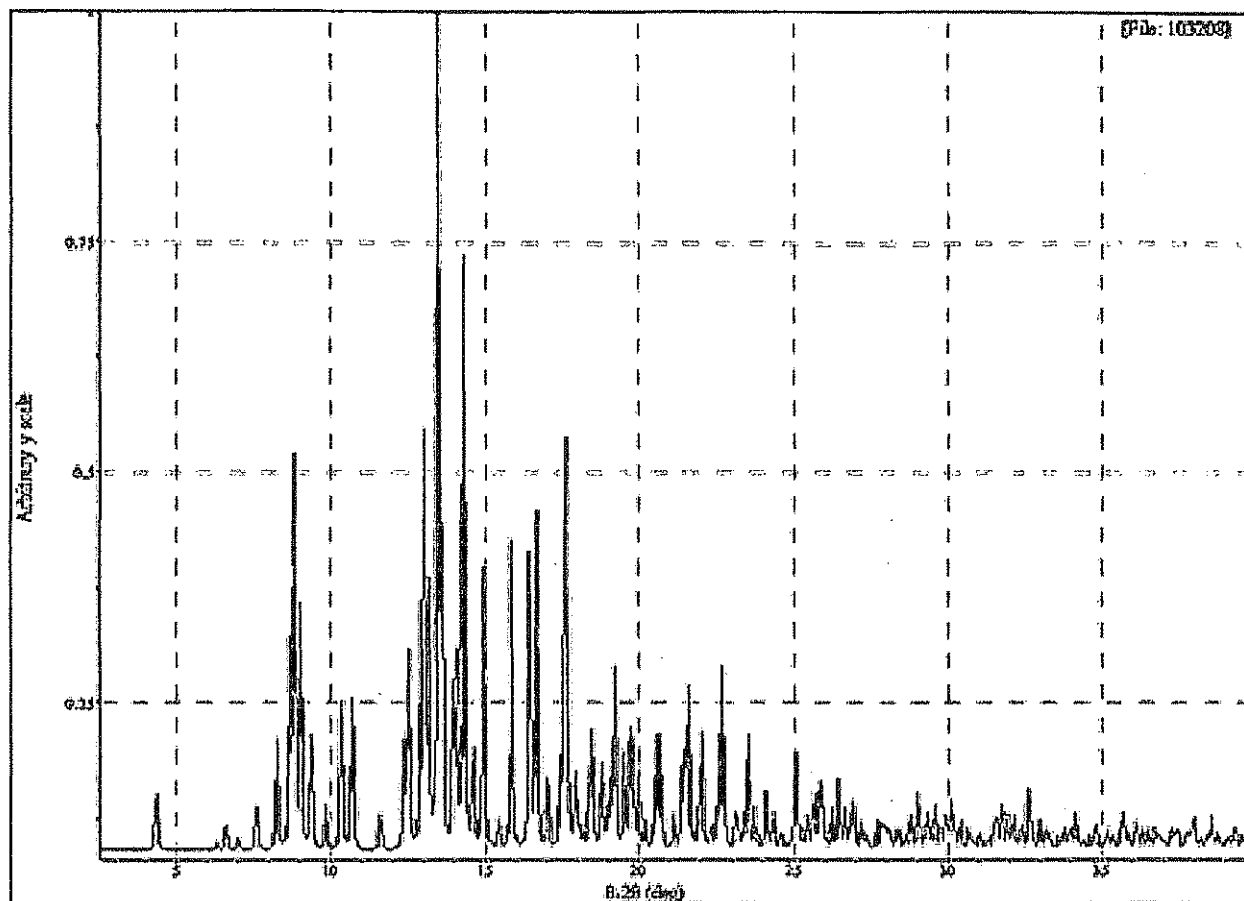


Figure 18 - Experimental XRPD of Form A

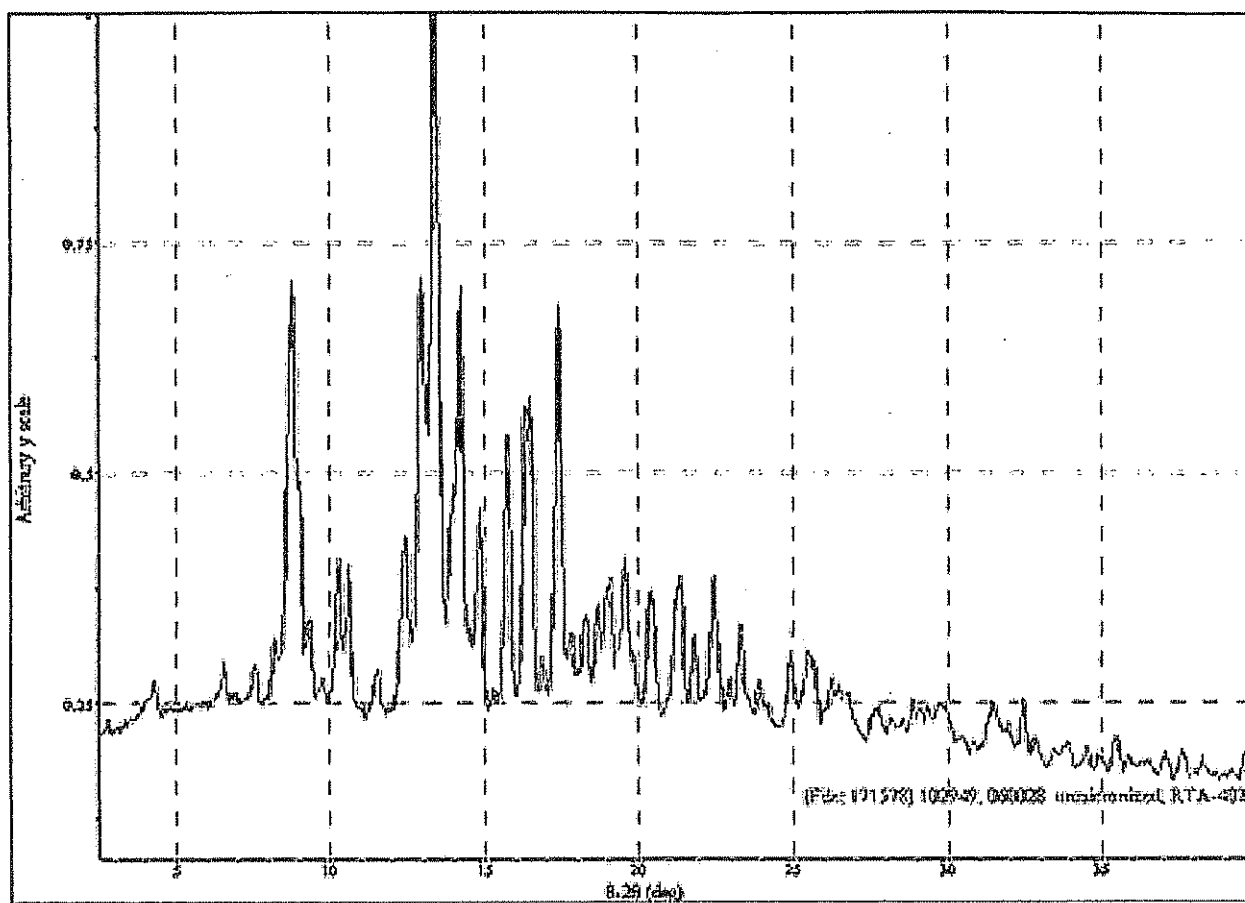


Figure 19 - Comparison of the calculated and experimental XRPD patterns of CDDO methyl ester to the XRPD pattern of CDDO methyl ester

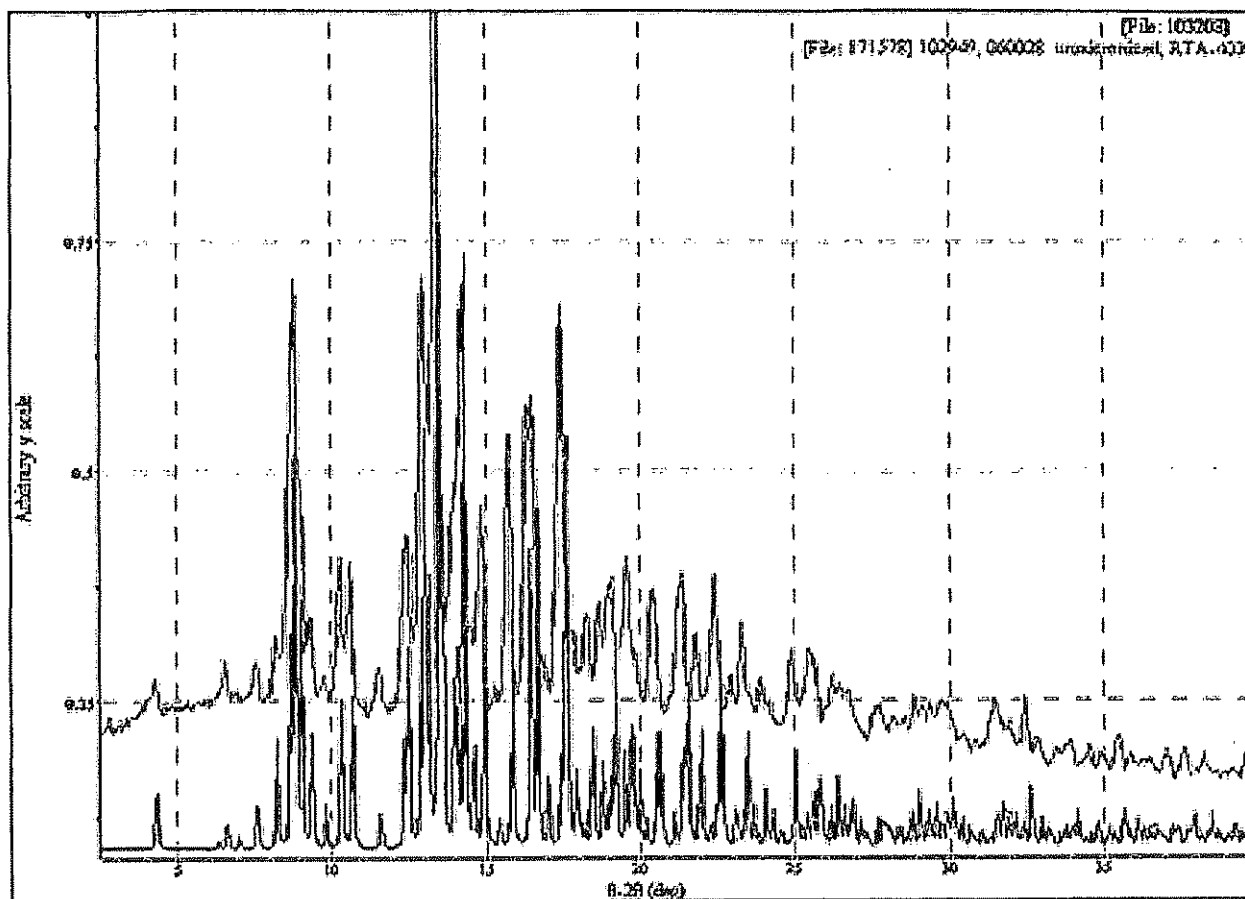


Figure 20. Representative plot of the area under the curve for Form A and Form B (amorphous), following a 4.1 mg/kg oral administration. Each data point represents the mean plasma concentration of CDDO methyl ester in 8 animals. Error bars represent the standard deviation within the sampled population.

Form A vs Amorphous in Cynomolgus Monkeys
Following a 4.1 mg/kg oral dose

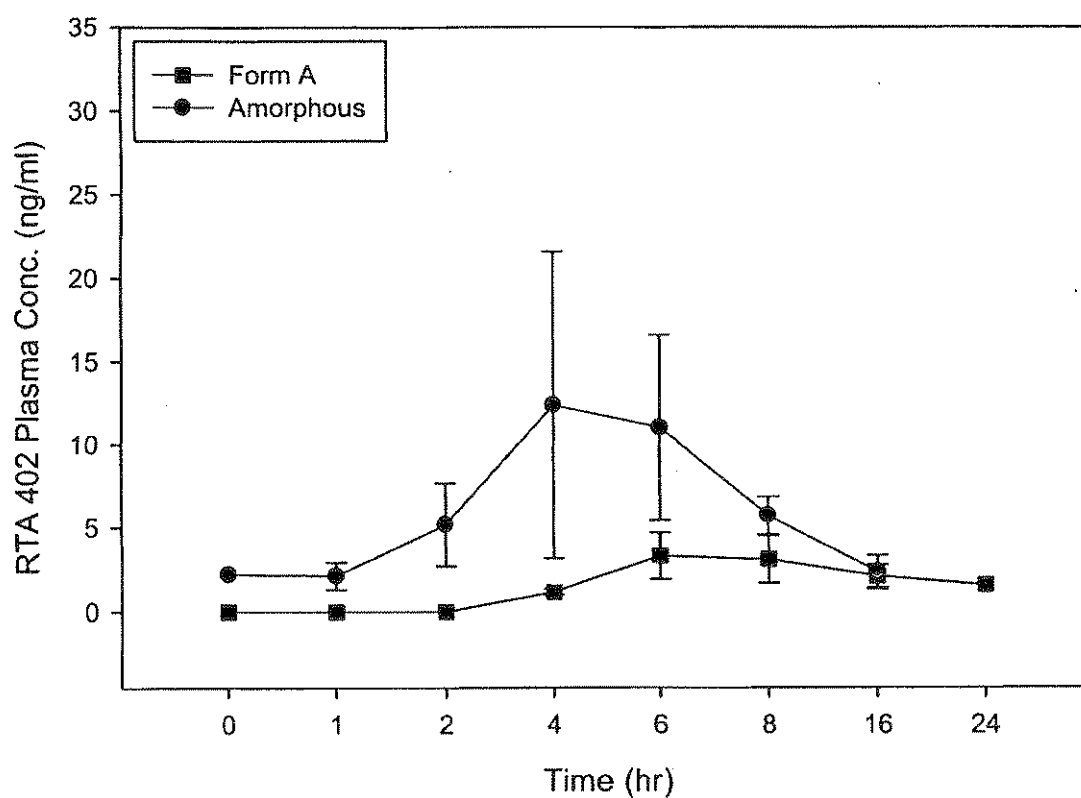
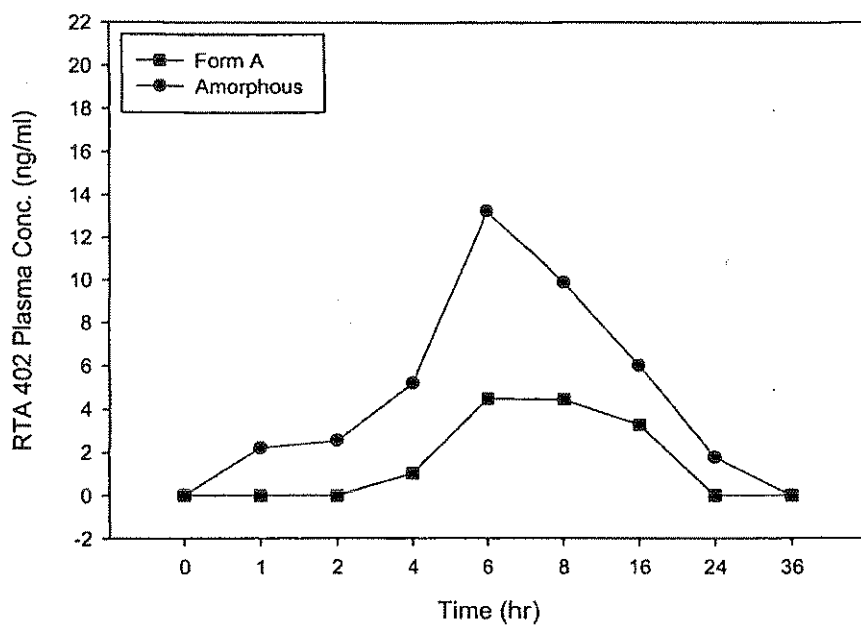


Figure 21. Animal #505M (top panel) and animal #507F (bottom panel)

Form A vs Amorphous - Monkey 505M
Following a 4.1 mg/kg Oral Dose



Form A vs Amorphous - Monkey 507F
Following a 4.1 mg/kg Oral Dose

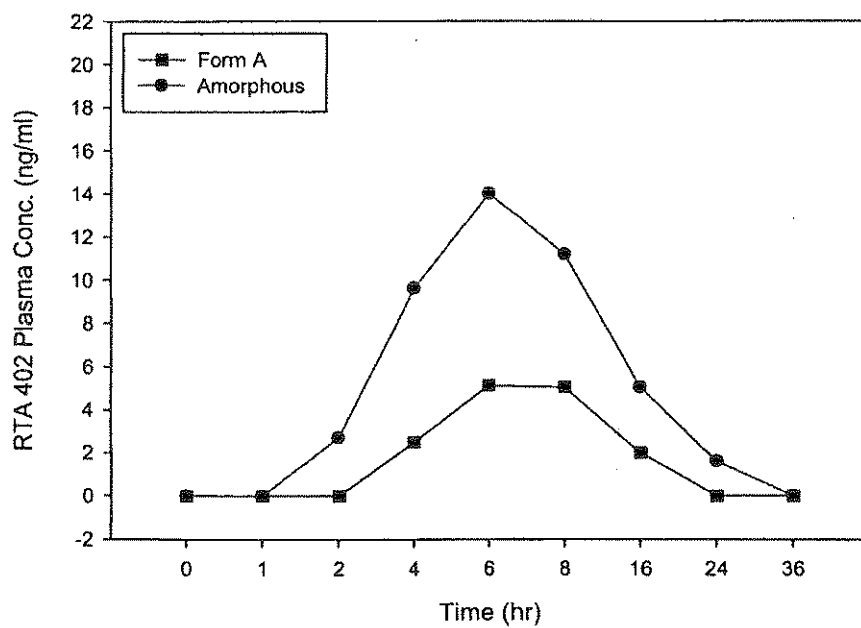


Figure 22. Animal #508F (top panel) and animal #502M (bottom panel)

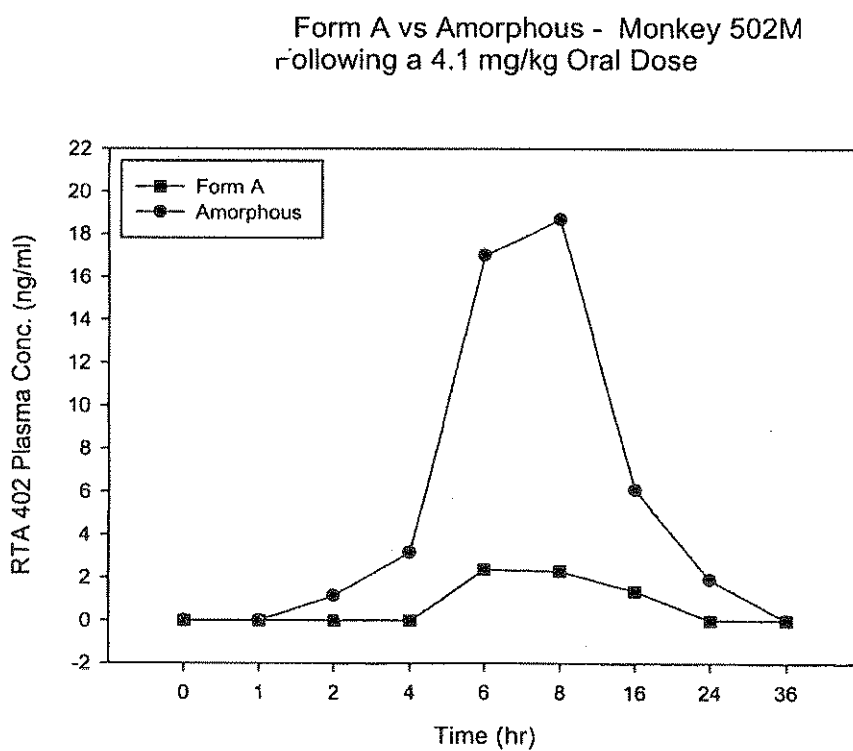
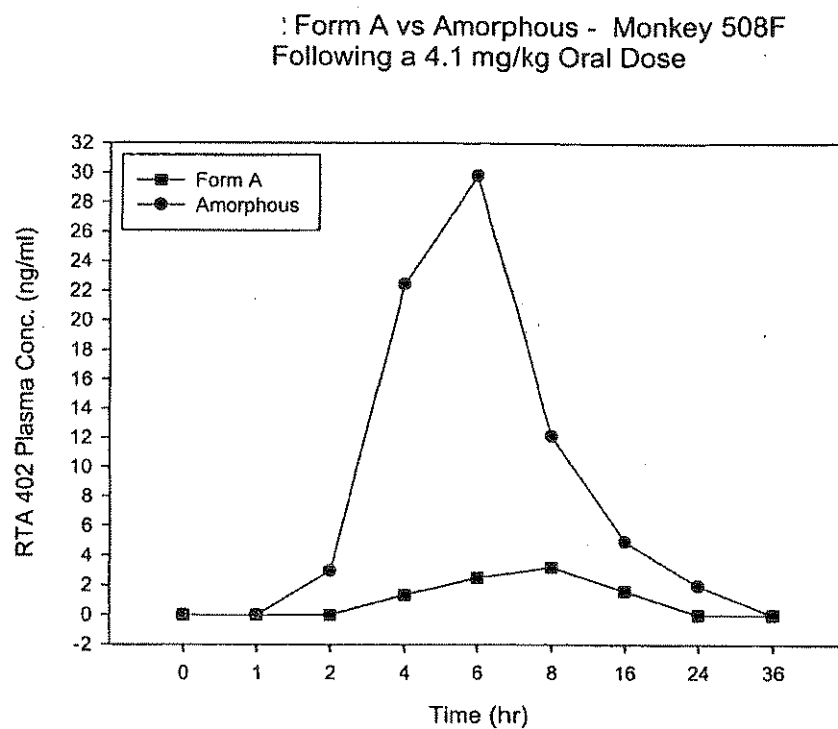


Figure 23. Thermograms of CDDO methyl ester hemibenzene solvate

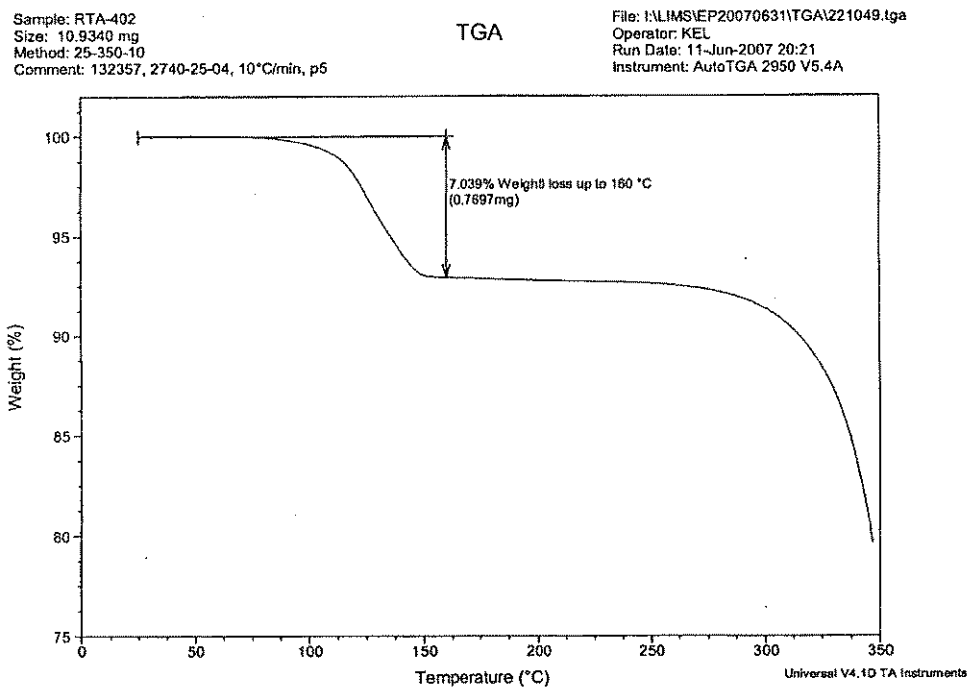
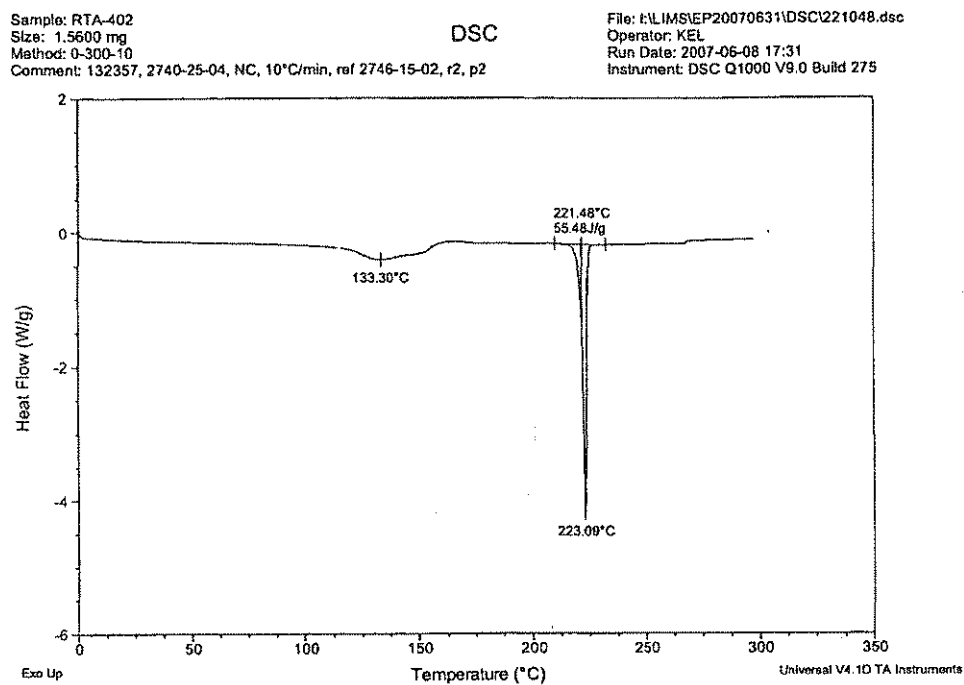


Figure 24 - Thermograms of CDDO methyl ester dimethanol solvate

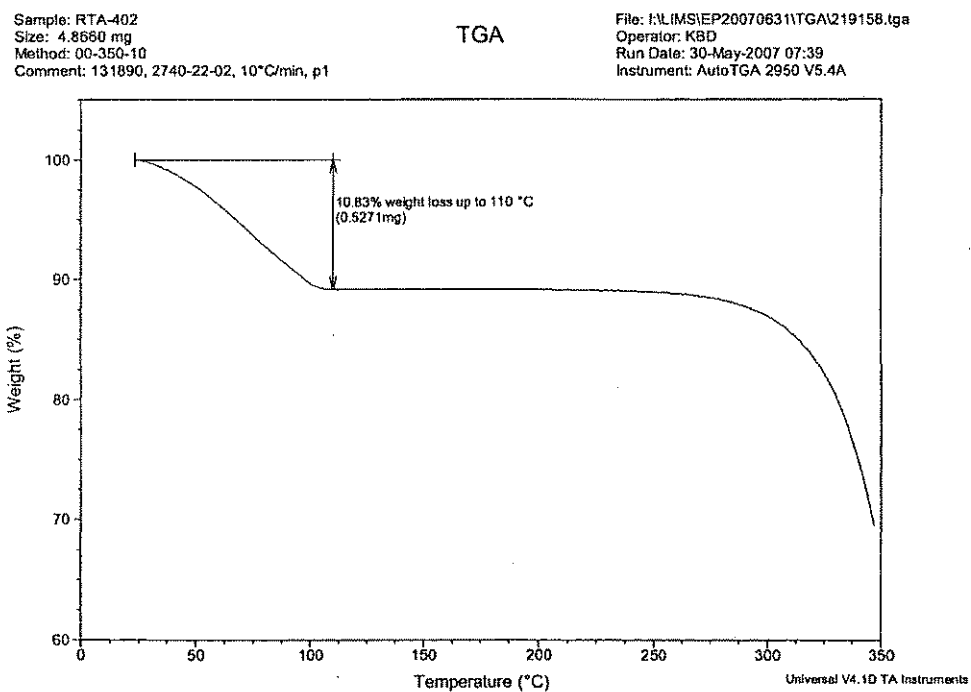
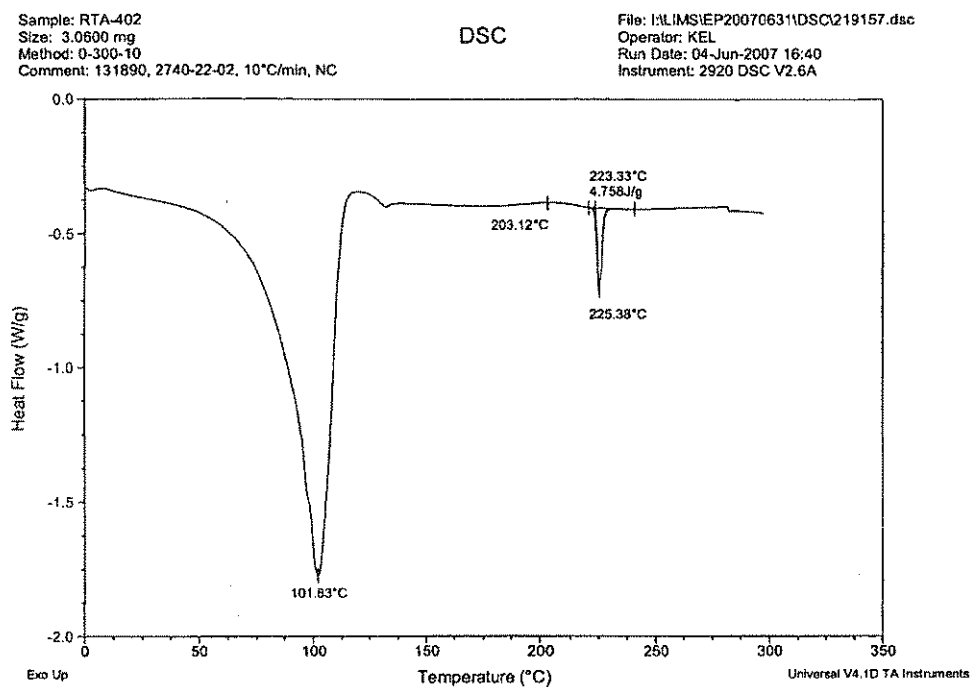


Figure 25 - TGIR data of CDDO methyl ester dimethanol solvate

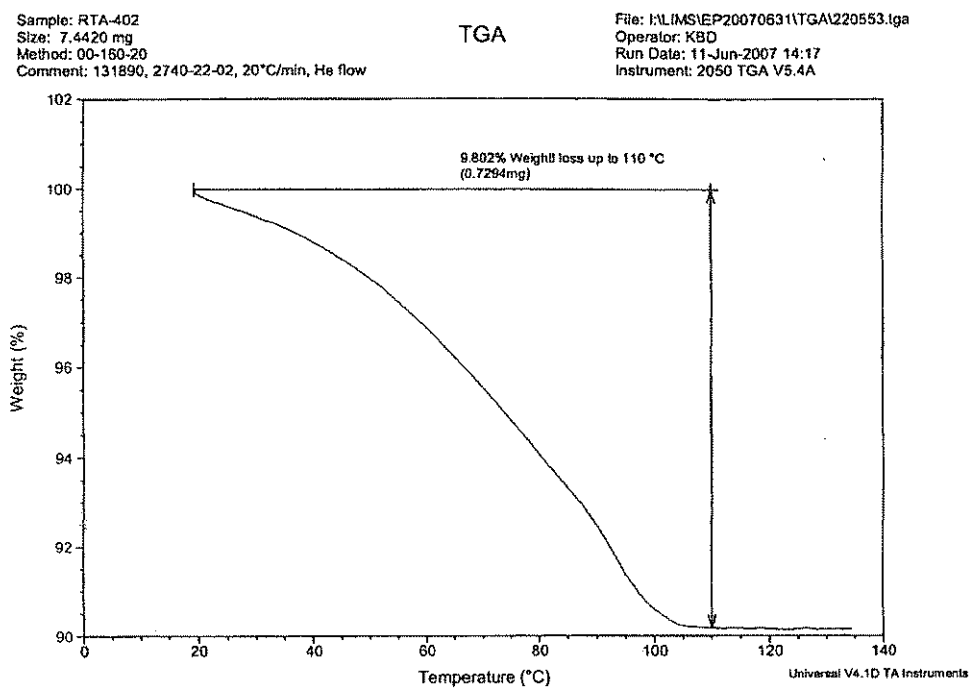


Figure 26 - XRPD patterns of CDDO methyl ester dimethanol solvate before (top) and after (bottom) TGIR analysis (up to 140 °C).

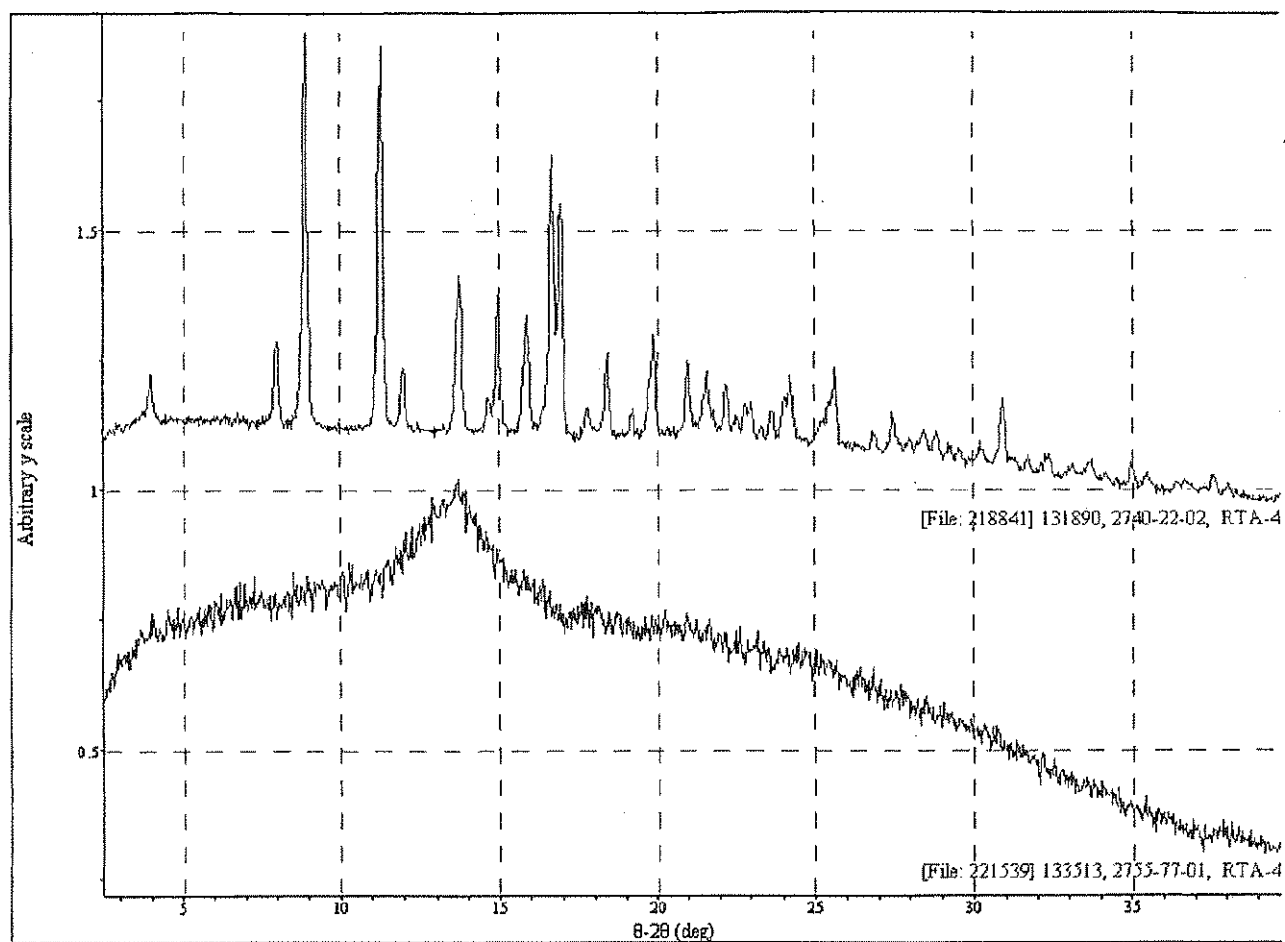


Figure 27 Overlay PDF, Form A vs. Form B. Local order similar from about 5 Å to about 20 Å.

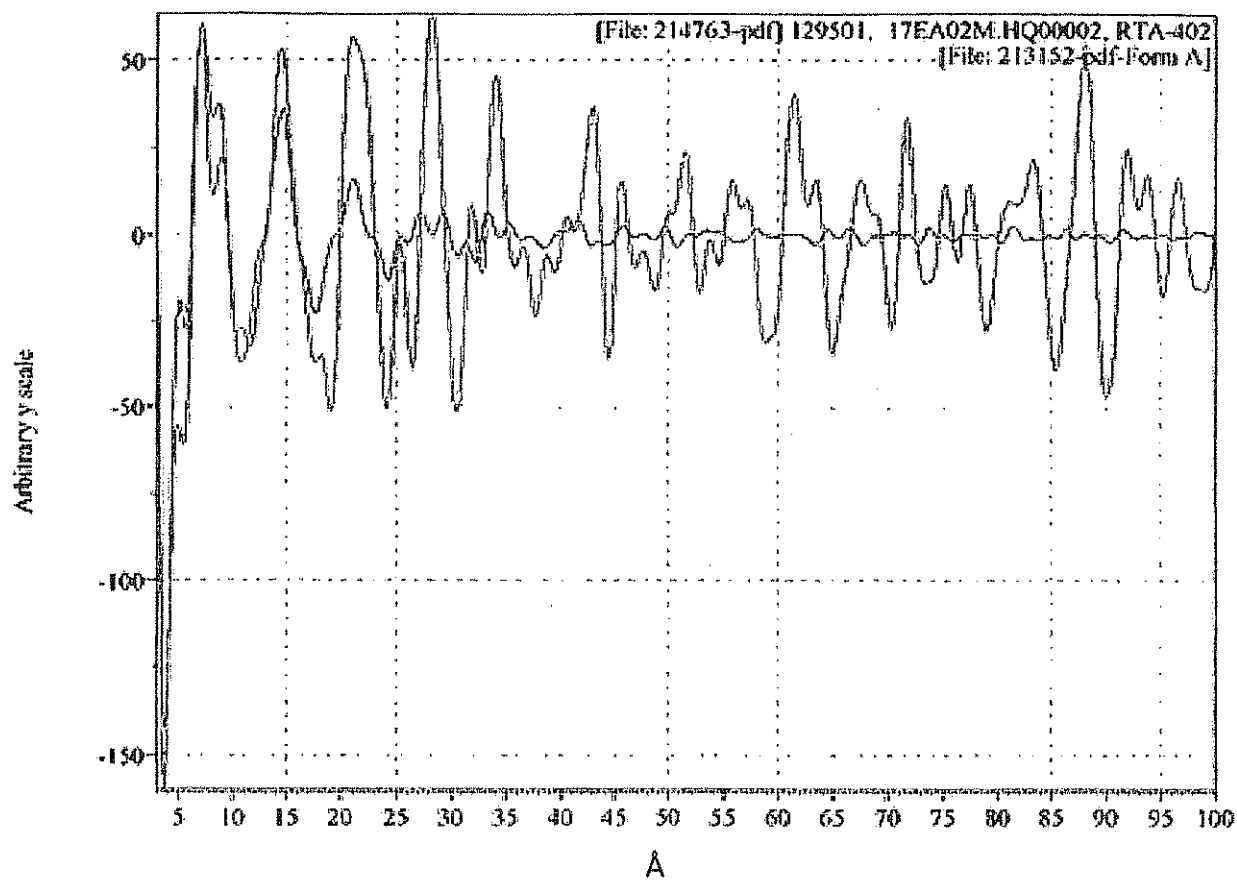


Figure 28 A PDF overlay of X-ray amorphous patterns for preparations of Form B

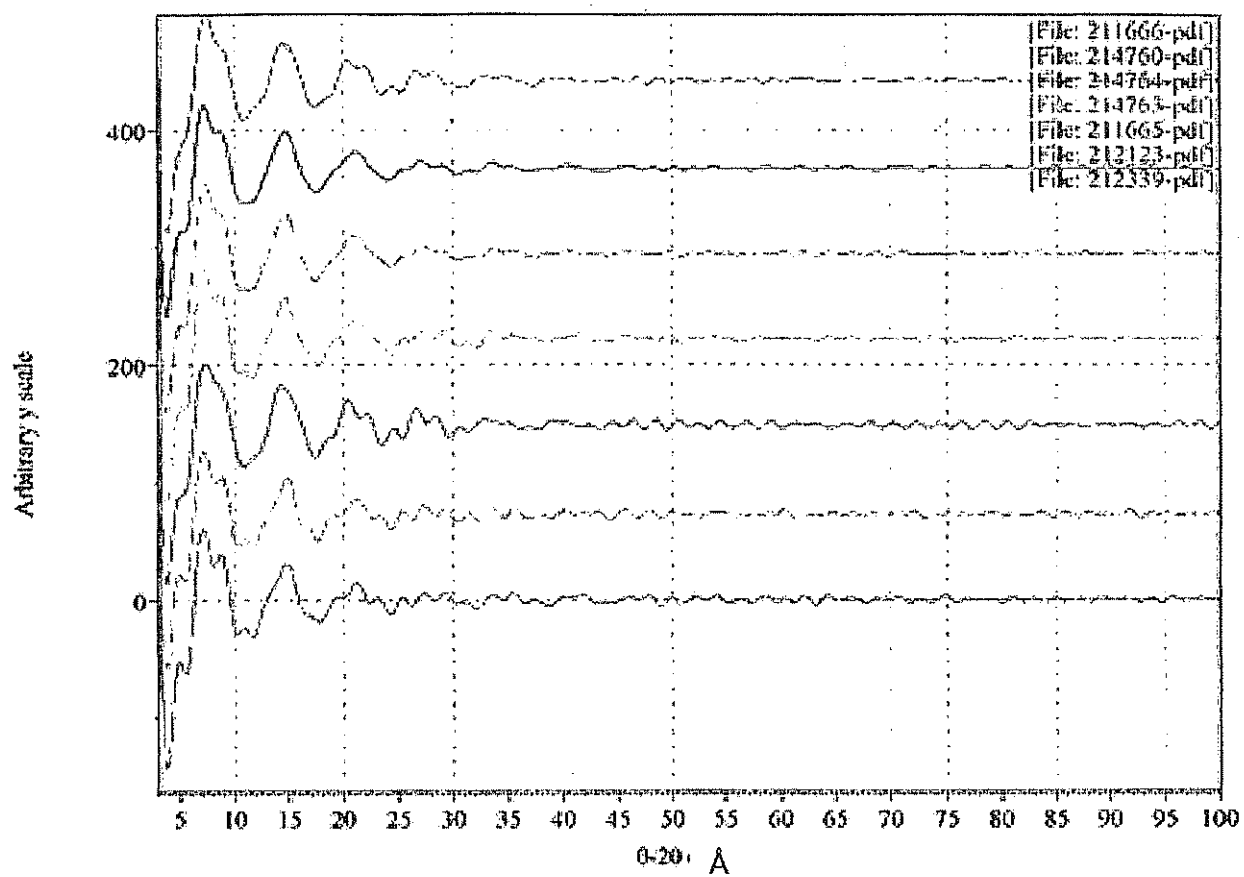


Figure 29 – A schematic representation of space group $P4_32_12$ (#96).

$P4_32_12$ (#96)

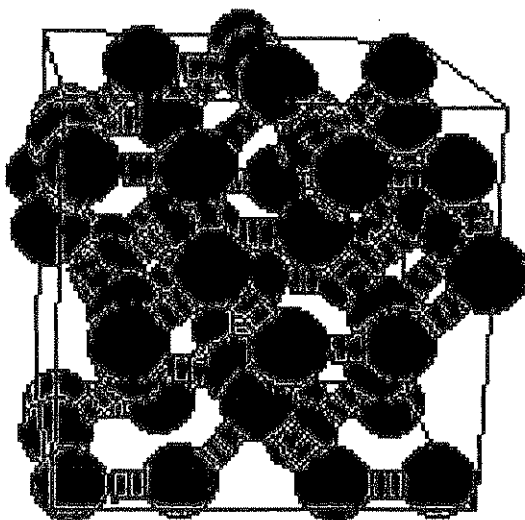
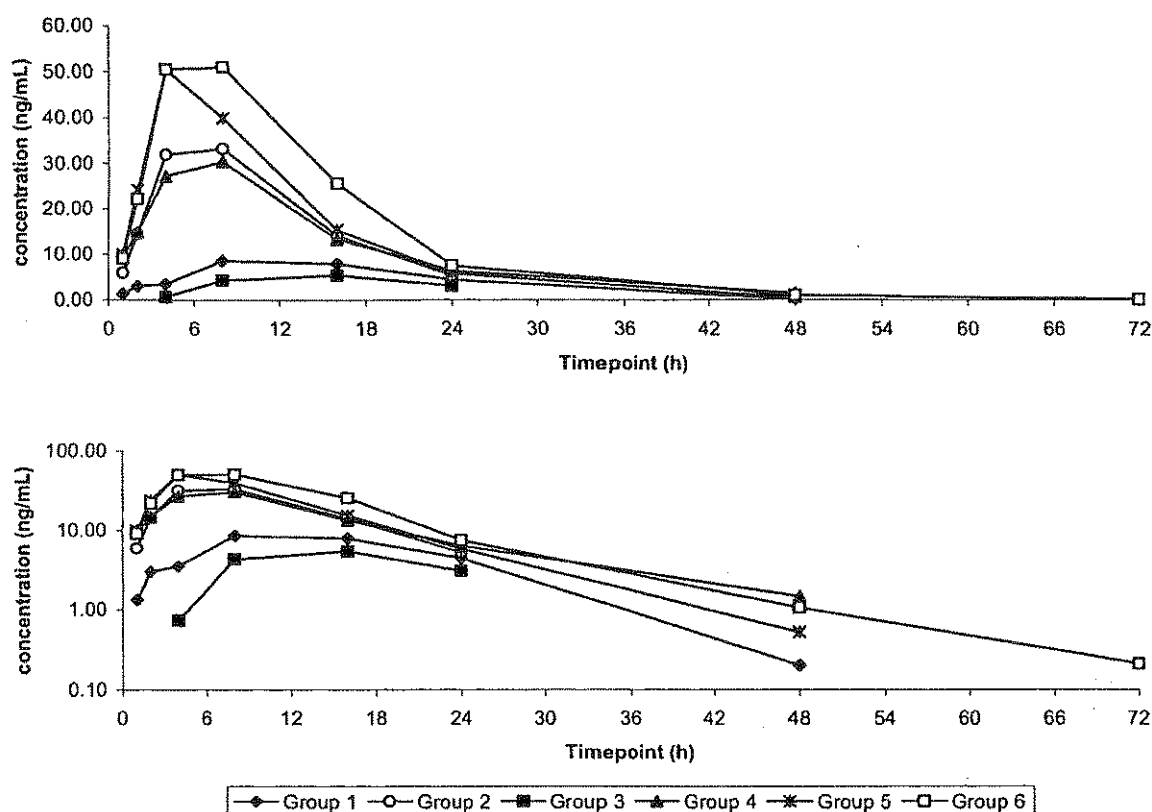


Figure 30 Mean blood concentrations of CDDO-methyl ester following single oral administrations of CDDO-methyl ester capsules to male Cynomolgus monkeys (Phases 2 and 3)



Group 1: (Phase 2), Animals received one capsule containing 30 mg of nanocrystalline Form A

Group 2: (Phase 2), animals received one capsule containing 30 mg of Form B micronized

Group 3: (Phase 2), animals received one capsule containing 30 mg of crystalline micronized Form A

Group 4: (Phase 3), animals received one capsule containing 30 mg of Form B - PVP/VA polymer matrix

Group 5: (Phase 3), animals received one capsule containing 30 mg of Form B - HPMCP polymer matrix (Hypromellose Phthalate)

Group 6: (Phase 3), animals received one capsule containing 30 mg of Form B - Eudragit L100-55 polymer matrix (methacrylic acid copolymer Type C)