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THERMOANALYTICAL DETECTION AND DETERMINATION OF PRECURSORS AND SIDE PRODUCTS IN PHARMACEUTICALS

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ABSTRACT

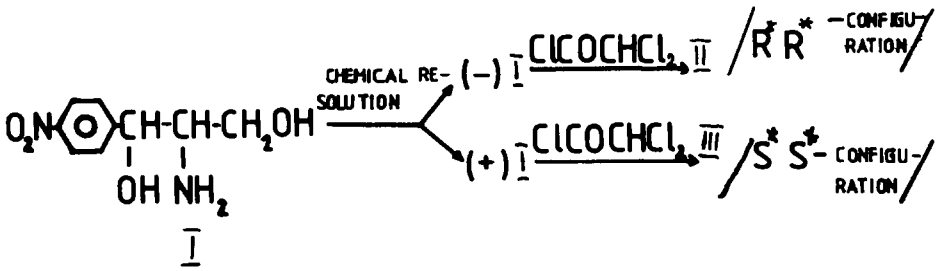
Some selected pharmaceuticals /CHLORAMPHENICOL, TAMOXIFEN CITRATE, GRANDAXIN/, produced by large scale multistep synthetic methods have been studied by DSC and TG to detect and determine low level of precursors and side products possibly present.

MEASURING METHODS

DSC measurements are made with Du Pont 990 Thermal Analyzer supplied with a DSC module and PERKIN-ELMER DSC 2C Calorimeter coupled with TADS DATA SYSTEM. TG experiments is carried out with MOM Derivatograph /System Paulik-Paulik-Erdey/ without flushing gas.

RESULTS AND DISCUSSION

1./ Optically active CHLORAMPHENICOL /II/ manufactured by chemical resolution of racemic p-nitro Aminodiol /I/ and N-dichloroacetylation of its levorotatory form / (-) I/ usually contains more or less biologically inactive "enantiomeric" impurity /III/due to the parallel dichloroacetylation of the residual dextrorotatory p-nitro Aminodiol / (+) I/ in - I



By the analytical methods commonly used for quality control of Chloramphenicol low level of III / 1% or less/ can not be detected

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directly. We found, however, that by DSC this problem can easily be solved.

From DSC-traces of Chloramphenicol, that of its racemic form and their binary mixtures of known composition the binary /melting point/ phase diagram was constructed. It has been found, that

/i/ the racemate is a true racemic compound,

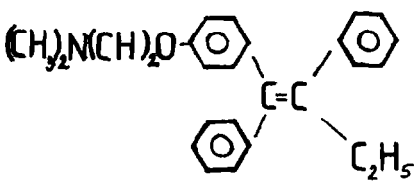
/ii/ the composition of the eutectic is about 30 % of racemic compound and 70 % of pure enantiomer II,

/iii/ the melting profile of the eutectic and that of II in the presence of each other are well separated if the enantiomeric purity is high /above 95 %/,

/iiii/ from the experimentally determined heat flows the concentration of III in II can easily be calculated by calibration,

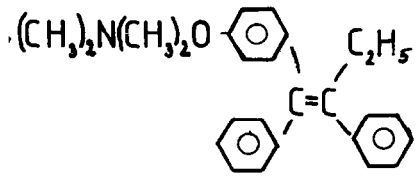
/iiiii/ detection limit of III in II is about 0,1 %.

2./ The citrate salt of TAMOXIFEN base /IV/ is a widely used pharmaceutical as antioestrogene. When manufactured by industrial-scale synthetic methods E-isomer /V/ /as impurity/ can also be formed, which shows non-desired side effects. The admissible amount of V in IV is 1 per cent /1/.



IV /Z-isomer/

m.p. 369-371 K



V /E-isomer/

mp 345-347 K

The great difference in the melting points of IV and V prompted us to elaborate a DSC-method for determining E-isomer content in Tamoxifen base, a method which can be used as in-process control procedure for the large-scale manufacture.

It has been found, that

/a/ IV forms with V an eutectic /m.p. is about 338 K/

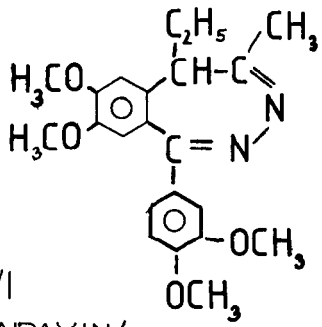
/b/ above 2 per cent of V the eutectic gives a well-defined endothermic peak whose area is proportional to the concent-

ration of V,

/c/ with increasing concentration of V the melting profile of IV is more and more deformed and the peak-wide/peak height ratio varies proportionally with the concentration of V,

/d/ below 1 % the van't Hoff method /"DSC-purity"/ can be used for the determination of V in IV.

3./ Thermal behaviour of GRANDAXIN*/VI/, a well-known minor tranquillant/ have been studied by DSC and TG



VI

/GRANDAXIN/

/*: commercialised also as TOPHISOPHAM/

It has been found, that the single endothermic peak /about 428 K/ of VI /melting/ is preceeded by an other one /about 420 K/ if the compound is crystallized from solvents containing of methanol. Applying different and systematically raising temperature scan rates, we have stated that

/i/ the first endothermic peak corresponds to the melting of the methanol solvate of VI,

/ii/ VI recrystallizes from the melt of the methanol solvate, giving a well-defined exothermic peak between the mentioned two endothermic ones;

/iii/ with increasing temperature scan rate the time interval available for the recrystallization becomes shorter and shorter and for this reason the second endothermic peak area/ /first endothermic peak area ratio and the exothermic peak area are decreased ;

/iiii/ TG-curves taken in the temperature range of the first melting endotherm show a weight loss which corresponds to the evaporation of one mole of methanol/one mole of methanol solvate;

/iiiii/ DSC can be a method of choice to detect and determine methanol solvate as impurity in VI.

CONCLUSIONS

Foreign substances found and determined in /1./Chloramphenicol: $S^{*}S^{*}$ /L/+/threo/form/ enantiomeric impurity/ /2./Tamoxifen citrate: E /"cis"/-isomer /3./ Grandaxin /Tophisopham/: methanol solvate, with the detection limit of 0,1 to 1 per cent.

REFERENCES

1 British Pharmacopeia 1980 Addendum 1982 page 111