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International Journal of Pharmaceutics 184 (1999) 199–206

international journal of pharmaceutics

The use of isothermal heat conduction microcalorimetry to evaluate drug stability in tablets

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Received 27 August 1998; received in revised form 5 February 1999; accepted 5 March 1999

Abstract

Isothermal heat conduction microcalorimetry was used to evaluate chemical stability of a solid drug in tablets. A variety of mixtures were compressed to flat faced tablets of 300 mg weight and 10 mm diameter. The content of drug amounted to 10%. Besides drug containing tablets, also placebo tablets as well as the non compressed mixtures were examined by microcalorimetry at 80°C. The excipient Emcompress® exhibited a substantially high exothermic heat flow that was due to a change in crystallinity. For Emcompress® containing tablets this interfering signal resulted in such a way that the calorimetric data did not reflect the drug decomposition with sufficient accuracy. In the case of the other preparations the heat flow of the excipients were low, and the calorimetric data did reflect the drug decomposition. The stability increased with increasing content of $CaHPO_4$, respectively, with decreasing content of water.

Keywords: Isothermal microcalorimetry; HPLC-assays; Drug stability; Excipient compatibility; Solid state

1. Introduction

Isothermal heat conduction microcalorimetry is an analytical method allowing determination of minute amounts of evolved or absorbed heat. The sensitivity is 10 000-fold higher than the sensitivity of conventional differential scanning calorimetry (DSC). By microcalorimetry heat flow signals in the range of μW are detectable.

The decomposition of a drug usually constitutes an exothermic process, i.e. a process which is accompanied by an evolution of heat. Since this heat evolution is very low, only microcalorimetry has the potential to detect a heat flow signal which is directly due to the chemical decomposition of a drug.

Consequently, microcalorimetry constitutes a new approach to do stability testing (Angberg et al., 1988, 1990, 1993; Hansen et al., 1989; Pikal and Dellerman, 1989; Oliyai and Lindenbaum, 1991; Tan et al., 1992; Willson et al., 1995). The applicability of microcalorimetry in excipient compatibility studies was previously reported from this laboratory (Selzer et al., 1998).

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0378-5173/99/$ - see front matter
PII: S0378-5173(99)00096-4

The objective of the present study is to examine tablets containing small amounts of drug. The question of particular interest is the ability of heat flow signals to attribute to the chemical decomposition of drug and the interference of further thermal events which are due to excipients and/or interactions between drug and excipients or excipients and excipients.

2. Materials and methods

2.1. Materials

The HMR-compound S 95 5740, (*S*)-(3-(2-(4-(*S*)-(4-(amino-imino-methyl)-phenyl)-4-methyl-2, 5dioxo - imidazolidin - 1 -yl) - acetylamino)) - 3 - phenyl-propionic acid ethylester, acetate, in the solid state was used as a model drug, which undergoes hydrolysis. As excipients potato-starch (Caesar and Loretz, Hilden, Germany), α-lactose-monohydrate (Meggle, Reitmehring, Germany), microcrystalline cellulose (MCC, Avicel PH101), (Pharma Transsanaq AG, Basel, Switzerland), talcum (Bassermann, Mannheim, Germany), calcium hydrogen phosphate anhydrous extra fine powder (E. Merck, Darmstadt, Germany), anhydrous Emcompress® (Mendell, Bodenheim, Germany), magnesium stearate (Bärlocher, München, Germany) and colloidal silica (Aerosil 200) (Degussa AG, Frankfurt, Germany) were used. For the high-performance liquid chromatography (HPLC) assays, acetonitrile (E. Merck, Darmstadt, Germany, HPLC grade) and ammonium acetate (Fluka Chemie AG, Neu-Ulm, Germany) were used.

2.2. Preparation of mixtures for direct compression

Two hundred gram batches of each mixture (see Table 1) were prepared. First, 4 g corn-starch, 1 g colloidal silica and 5 g magnesium stearate were homogenized in a mortar with a pestle. The further excipients and the drug were than added and mixed in such a way, that the ratio of the components was 1:1. Finally the powders were once more mixed in a Turbula T2C for 10 min.

2.3. Tabletting

From each mixture flat faced tablets of 300 mg weight and 10 mm diameter were prepared using an excenter press EK0 (Emil Korsch Maschinenfabrik, Berlin, Germany). The upper punch force amounted to 10 kN. The tabletting speed was 30 strokes/min. The tensile strength was determined using a Schleuninger instrument (Solothurn, Switzerland).

2.4. Isothermal heat-conduction microcalorimetry

The calorimeter used in these studies was the 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Sweden). The design principle was previously described in detail (Suurkuusk and Wadsö, 1982; Angberg et al., 1988). The system consisted of a 25 l water bath with a temperature accuracy of $< \pm 2 \times 10^{-4}$ K. Four calorimeter units were installed and ran simultaneously. Each unit could register the difference in heat flow (Φ in μW), respectively in heat output (Q in J), between a sample and a reference as a function of time. The sensitivity of the system reached 0.1 μW. The short-term baseline noise was ± 0.05 μW, basline-drift was < 0.2 μW/24 h. In the present study, 5 ml stainless steel ampoules were used that were tightly sealed. The volume of the sample in the vial was above 80% for limiting the air space to below 20%. The samples were assayed in duplicate at 80°C. Before lowering the ampoules in the measurement position, which is in the middle of the water bath, they had to reach the corresponding temperature. For that the vessels were left in the equilibrium position for 1 h. After that they were slowly lowered into the measurement position between two thermopiles through which the heat is transported and detected. Empty stainless steel ampoules were used as reference to ensure thermal inertness. The monitoring of the heat flow signal was then started by the computer program DIGITAM (Thermometric AB, Sweden) and this time point was referred to as $t = 1$ h. Before each experiment an electrical calibration of 100 or 300 μW, respectively, was performed depending on the expected heat.

2.5. HPLC

The tablets were also examined by HPLC after storage in controlled temperature ovens. The mixtures were placed in 0.3 ml glass vials that were tightly sealed with teflon coated butyl rubber discs and aluminium caps. The volume of the powder sample in the vial also was above 80% as in the calorimetric assays. The tablets were placed in 3 ml glass vials. For limiting the air space below 20%, glass pellets were placed on the tablets. The samples were stored at 80, 70, 60 and 40°C. The vials were removed after different time intervals and stored at 5°C until the HPLC analysis was performed. The HPLC assays were carried out using a Merck-Hitachi chromatograph (L-6220 Intelligent Pump, AS 2000 A Autosampler, L-4500 Diode Array Detector, D-6000 A Interface, Merck-Hitachi, Darmstadt Germany). A C_{18} reversed phase column (LiChrospher 60 Select B RP 18, 125 mm × 4 mm, 5 μm, E. Merck, Darmstadt, Germany) and a guard column (LiChrospher 60 RP-select B, 5 μm, E. Merck, Darmstadt, Germany) were used. The mobile phase consisted of

Table 1
Investigated systems, each batch was prepared twice, once containing 10% of drug and once containing no drug (placebo)[a]

Preparation 1	Amount (g)	Preparation 3	Amount (g)
S 95 5740	10.0	S 95 5740	10.0
MCC	30.0	Lactose	30.0
Emcompress®	55.0	Emcompress®	55.0
Corn-starch/colloidal silica 4+1	2.5	Corn-starch/colloidal silica 4+1	2.5
Mg–stearate	2.5	Mg–stearate	2.5
Preparation 5	**Amount (g)**	**Preparation 6**	**Amount (g)**
S 95 5740	10.0	S 95 5740	10.0
Potato-starch	30.0	–	–
Emcompress®	55.0	Potato-starch	85.0
Corn-starch/colloidal silica 4+1	2.5	Corn-starch/colloidal silica 4+1	2.5
Mg–stearate	2.5	Mg–stearate	2.5
Preparation 7	**Amount (g)**	**Preparation 11**	**Amount (g)**
S 95 5740	10.0	S 95 5740	10.0
–	–	MCC	30.0
Emcompress®	85.0	$CaHPO_4$ extra fine powder	55.0
Corn-starch/colloidal silica 4+1	2.5	Corn-starch/colloidal silica 4+1	2.5
Mg–stearate	2.5	Mg–stearate	2.5
Preparation 13	**Amount (g)**	**Preparation 15**	**Amount (g)**
S 95 5740	10.0	S 95 5740	10.0
Lactose	30.0	Potato-starch	30.0
$CaHPO_4$ extra fine powder	55.0	$CaHPO_4$ extra fine powder	55.0
Corn-starch/colloidal silica 4+1	2.5	Corn-starch/colloidal silica 4+1	2.5
Mg–stearate	2.5	Mg–stearate	2.5
Preparation 17	**Amount (g)**		
S 95 5740	10.0		
$CaHPO_4$ extra fine powder	85.0		
Corn-starch/colloidal silica 4+1	2.5		
Mg–stearate	2.5		

[a] Each preparation was examined in form of a mixture as well as a tablet.

two solutions: solution A, aqueous ammonium acetate solution 0.1%; solution B, 80% (v/v) acetonitrile; 20% (v/v) aqueous ammonium acetate solution 0.1%. Solution A + solution B (90 + 10) were used during the time intervals 0–5 min and 16–20 min and solution A + solution B (50 + 50) during the time interval 6–15 min at a constant flow rate of 1 ml/min. The peak obtained by UV detection at 230 nm was well separated from those of the decomposition products and was used for quantitative determination using pure drug as external standard. Calculation of the peak area was performed online by a computer program (DAD system manager Merck-Hitachi model D-6500) connected to the UV detector. The samples were weighed into 25 ml volumetric flasks and filled up with solution B. Aliquots of 25 μl were injected. The assay accuracy was better than ± 1% (S.E.M.) for the pure drug.

2.6. HPLC data treatment

Stability data treatment was performed by the Sigma-Plot graph fitting package (SigmaPlot version 3.0, Jandel Scientific Software GmbH, Erkrath, Germany).

$$-\frac{dc(A)}{dt} = k^*[c(A)]^v$$

was used as a model function, and then a nonlinear regression procedure by using the Marquardt–Levenberg-algorithm (Marquardt, 1963) was carried out to estimate the values of k^* and v. The natural logarithm of k^* was then plotted versus the reciprocal of the absolute temperature T^{-1} (K^{-1}) to determine the activation energy in order to predict the room temperature stability.

2.7. X-ray powder diffraction

For Emcompress® X-ray powder diffraction patterns were determined before and after calorimetric runs at room temperature. A STOE Transmission X-ray powder diffractometer (STOE&CIE GmbH, Darmstadt Germany) was used combining a focused $K\alpha_1$ incident beam from a Germanium monochromator with linear and curved position sensitive detectors (PSDs).

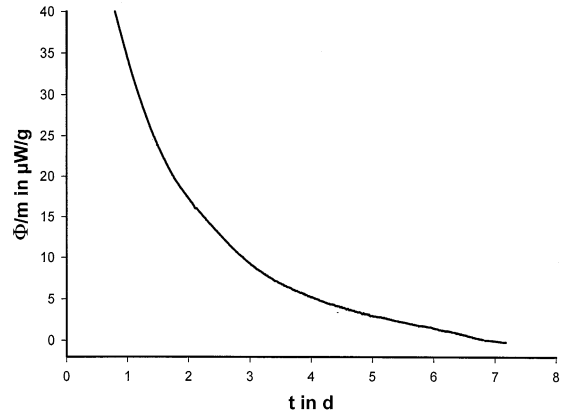

Fig. 1. Heat flow-time curve of Emcompress® ($CaHPO_4$) at 80°C.

The samples were scanned in steps of 0.02° from 0 to 35° (2θ).

3. Results and discussion

3.1. S 95 5740

S 95 5740 in the pure solid state showed an exothermic heat flow that amounted to 6.2 μW/g at 80°C, which was due to chemical decomposition (Selzer et al., 1998).

3.2. Excipients

The excipients potato-starch, α-lactose-monohydrate, microcrystalline cellulose (MCC), talcum, calcium hydrogene phosphate anhydrous extra fine powder, Emcompress®, and colloidal silica showed heat flow time curves in the range of [− 5 μW/g; 5 μW/g]. (Selzer et al., 1998).

Emcompress® exhibited an exothermic heat flow of 60.8 μW/g $\exp(-0.614d)$ that was probably due to a change in crystallinity (Fig. 1). Fig. 2 shows X-ray diffraction patterns of (a) Emcompress®, (b) Emcompress® after storage of 7 days at 80°C, and (c) calcium hydrogen phosphate extra fine powder. The X-ray diffraction patterns became progressively sharper going from (a) to (c) which can be attributed to a higher degree of crystallinity. Thus it can be concluded that Em-

compress® contained a slightly higher amount of crystall flaws, which were partially reduced at 80°C. The crystal structure of Emcompress® yielded in the direction of the structure of calcium hydrogene phosphate extra fine powder. This was accompanied by a gain in energy as shown by the calorimetric data.

3.3. Tablets

The calorimetric assays were performed at 80°C in view of the following circumstances:

1. Interactions between excipients can cause heat flow signals which superimpose the drug decomposition. In order to characterize these interactions, each batch was prepared twice, once containing 10% of drug and once containing no drug (placebo).
2. In tablets, processes like relaxation, lengthening or hardening may occur, which could all result in thermal events. In order to investigate this, each preparation was examined before and after tabletting, i.e. the mixtures as well as the tablets were investigated.
3. Since Emcompress® caused a substantially high heat flow signal, which cannot be observed with calcium hydrogen phosphate extra fine powder, this process was more closely studied in order to see to which degree it would interfere and mask the heat flow originating from the drug decomposition. For this purpose, each preparation was prepared with Emcompress® as well as with calcium hydrogene phosphate extra fine powder.

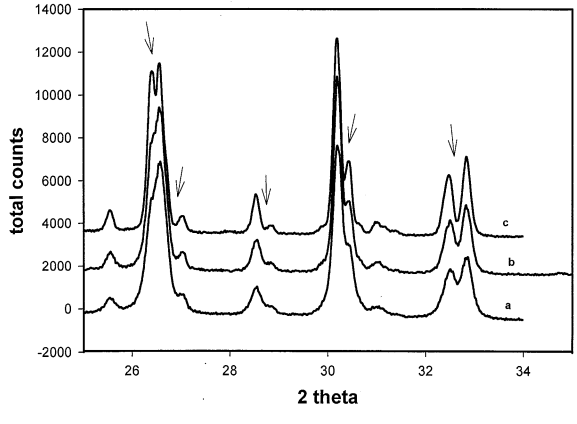

Fig. 2. X-ray diffraction patterns of (a) Emcompress®, (b) Emcompress® after 7 days storage at 80°C, (c) $CaHPO_4$ extra fine powder.

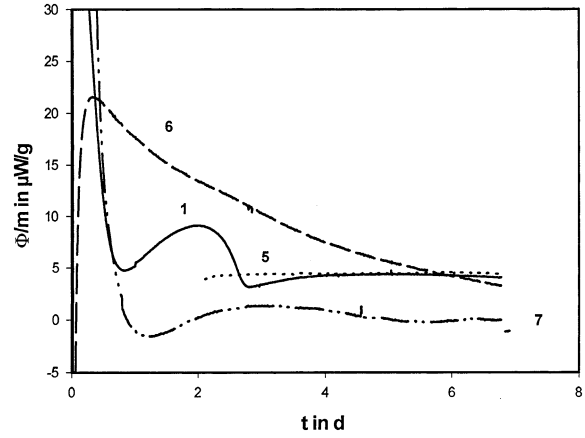

Fig. 3. Drug associated heat flow-time curves after substraction of the heat flow of the placebo tablets from that of the drug-containing tablets (Φ(tab)–Φ(pla)) for the Emcompress® containing tablets.

3.3.1. Drug associated processes within the tablets

In order to characterize the drug associated processes in the tablets, the heat flow of the placebo tablets was substracted from that of the drug containing tablets. The resulting heat flow was either caused by the drug alone or by an interaction between the drug and the excipients in the tablet.

The original total heat output (before substraction) observed with preparations 1, 3, 5 and 7 (Table 1) was significantly higher than that of the corresponding preparations 11, 13, 15 and 17. This can be explained by the exothermic process caused by Emcompress®, which also occured within the tablets. Fig. 3 shows the resulting heat flow-time curves (after substraction) for the Emcompress® containing tablets, and Fig. 4 for the corresponding tablets containing calcium hydrogene phosphate extra fine powder. In Table 2 the evolved heat $Q(7d)$—the value is obtained after substraction of the placebo heat flow from the heat flow of the drug containing tablets and following integration—is compared with the amount of the decomposition product for $t = 7$ day

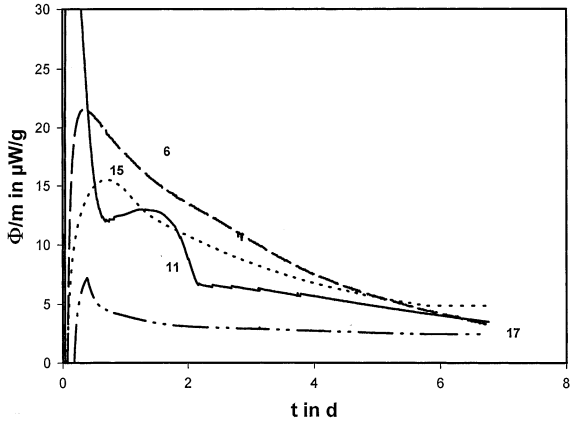

Fig. 4. Drug associated heat flow-time curves after substraction of the heat flow of the placebo tablets from that of the drug-containing tablets (Φ(tab)–Φ(pla)) for the tablets containing $CaHPO_4$ extra fine powder.

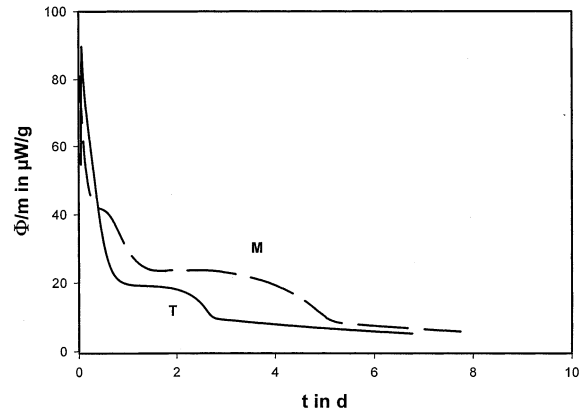

Fig. 5. Heat flow-time curves for the preparation 1 with microcrystalline cellulose (MCC) (T, tablets; M, mixture). The 'bulges' are caused by a water transport from MCC to the drug.

(HPLC-data). Concerning the tablets without Emcompress® the calorimetric data is in accordance with the HPLC-data. The drug stability increased in the following order for preparations 6, 15, 11, 17, i.e. with increasing content of calcium hydrogen phosphate, respectively with decreasing content of water. For the tablets containing Emcompress® (1, 5, 7) the evolved heat is not in accordance with the preparations 11, 15 and 17. Between preparations 1 and 5 no difference is discernible. For the preparation 7 the heat flow cannot be distinguished from zero. Consequently, the exothermic heat flow of the excipient Emcompress® resulted in such way, that the signal after substraction did not represent the drug decomposition with sufficient accuracy.

Hence the use of microcalorimetry to evaluate the drug stability within tablets is only possible if the drug associated heat flow is substantially higher than the sum of the other heat flow signals caused by further processes, unless these further processes show a nearly 100% reproducibility.

3.3.2. Comparison between tablets and mixtures

Figs. 5 and 6 show the heat flow-time curves of tablets and mixtures for the preparations 1 and 3,

Table 2
Drug associated evolved heat over 7 days (the value is obtained after substraction of the placebo heat flow from the heat flow of the drug containing tablets and following integration), amount of decomposition product after 7 days (HPLC-data) and corresponding enthalpy change[a]

Preparation	Q(drug) (J/g drug)	n(decomposition product) (mmol/g drug)	$\Delta_R H = Q/n$ (kJ/mol)
Tablets 1	26.6	1.069	24.9
Tablets 3	–		–
Tablets 5	26.6	1.284	20.7
Tablets 6	63.3	1.566	40.4
Tablets 7	–		–
Tablets 11	36.9	1.069	34.6
Tablets 13	–		–
Tablets 15T	53.1	1.284	41.3
Tablets 17T	17.1	0.508	33.7

[a] For preparations 3, 7 and 13 the heat flow is not attributable to the drug decomposition.

i.e. for the preparations with 30% MCC and 30% lactose. For preparation 1 an exothermic 'bulge' and for the dispensing 3 an exothermic 'peak' can be observed. Both signals can be attributed to a water transport from MCC and, respectively, from lactose to the drug (see Selzer et al., 1998). Between the tablets and the mixtures a significant difference is obvious. For the mixtures this water-transport continued for a longer time and to a higher extent. One explanation could be that the contact area between MCC, respectively, lactose and the drug was lower within the tablets, since the calcium hydrogene phosphate and the drug came together during compression. Hence the drug was mostly surrounded by the calcium hydrogen phosphate. The mixtures can be regarded as loose bulk goods, and a water transport between the particles was more preferential than within a compressed system. Consequently, the water transport could take place to a higher degree within the mixtures.

After completion of the water transport processes, the heat flow signal could be attributed to the chemical decompostion of the drug. As confirmed by HPLC-data, the decomposition rate was higher for the mixtures than for the tablets. This is in accordance with the above mentioned water transport from MCC and, respectively, lactose to the drug, occurring preferentially within the mixtures. Consequently, the water content on the surface of the drug particles increased, and accordingly the rate of hydrolysis was higher. Within the tablets the drug was bound to the calcium hydrogene phosphate and consequently protected in a certain degree from the water transport and from the following hydrolysis.

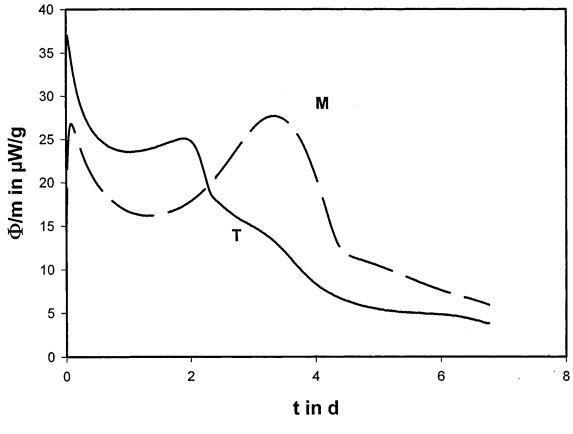

Fig. 6. Heat flow-time curves for the preparation 3 with lactose (T, tablets; M, mixture). The 'peaks' are caused by a water transport from lactose to the drug.

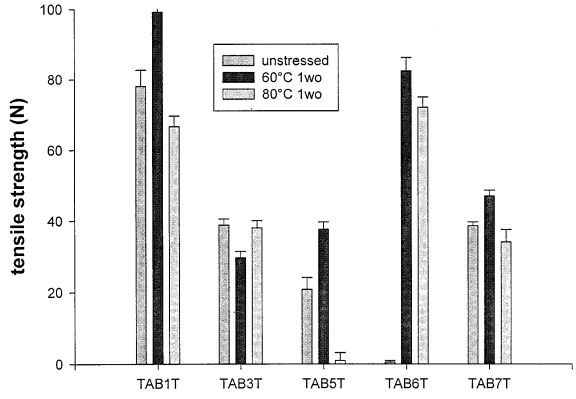

Fig. 7. Tensile strength (mean ± S.D.) of the tablets before and after 7 days storage at 60 rsp. 80°C.

Concerning the other preparations, no differences between mixtures and tablets could be observed, although there were changes in tensile strength for the tablets (Fig. 7).

Obviously these changes in tensile strength were not accompanied by an evolution or absorption of heat in the µJ-range.

4. Conclusion

Isothermal heat conduction microcalorimetry can be used to evaluate drug stability within tablets, on condition that: (a) enthalpy change and reaction rate are sufficiently high to cause a heat flow signal in the µW-range; and (b) the heat flow signals from further coexistent processes are low compared to the heat flow of drug decomposition.

Since tablets constitute heterogeneous and complex systems and since the amount of drug is in most cases low ($< 10\%$), these conditions cannot be expected a priori, but have to be assured experimentally.

However, if heat flow signals of coexistent processes interfere with the drug decomposition, they

will provide further information about interactions in dosage forms that can adversely influence the quality of a final drug product.

Acknowledgements

This work was supported in part by a grant from Hoechst Marion Roussel (HMR), Frankfurt, Germany. The authors are grateful to Mr Simon (HMR) for help of preparing the tablets and to Mrs Conrad (HMR) for analysis by X-ray-diffraction.

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