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Impact of Solid State Reactions on Medicaments

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IMPACT OF SOLID STATE REACTIONS ON MEDICAMENTS

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Abstract
The development of successful solid dosage forms is closely concerned with all types of reactions in the solid state. Polymorphic transitions, chemical reactions and the influence of quality of raw materials are reviewed.

INTRODUCTION

The aim of the industrial pharmacist is to find a formulation which allows the greatest possible effect at the right place and time: in fact,the best bioavailability. Since the active ingredient and the excipients are chemical molecules, they are subject to reactions leading to loss of activity and undesirable side effects.
The majority of medicines are solid dosage forms. The development of successful dosage forms is closely concerned with all types of reactions in the solid state (1-5).

Solid state reactions fall into several categories: solid-solid reactions, solid-gas reactions, and solid transformations including polymorphic transitions, rearrangements, phase changes and decomposition.

POLYMORPHIC TRANSITIONS

The first transformations which may occur by the action of heat and pressure are the polymorphic transitions. Polymorphs have different crystalline behaviour and in the solid

state may behave like different molecules.
Each crystalline form of a molecule has its own thermodynamic and stability characteristics which may influence the biological activity of the molecule. As a rule, the most thermodynamically unstable form is the most active. Hydrates and solvates, called "pseudo-polymorphs", give rise to the same difficulties for the pharmaceutical industry as polymorphs.
The main properties affected by polymorphism or pseudo-polymorphism are: melting and sublimation temperatures, heat capacity, conductivity, all enthalpies of transformation or reaction in the solid state, solubilities, dissolution rates, morphology, volume, density, viscosity, surface tension, diffusivity, crystal hardness, shape, colour etc...

The most important difference may be the dissolution rates or solubilities leading to different bioavailabilities.

Figure 1 deals with metolazone, the alpha form of which is highly undesirable in the commercial gamma form (5)

Melting temperatures of polymorphs may differ only by 1 °C or up to 100 °C. Their melting enthalpies may be iden-

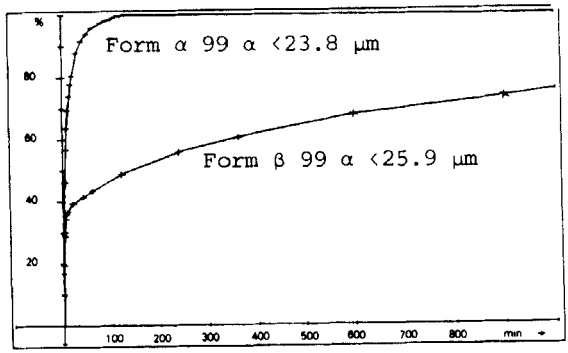


FIGURE 1. Dissolution rate curves for the 2 crystalline modifications of metolazone

tical or differ up to more than a factor 100. The same is true for solubility.

We measured very different densities, for example 3.05 for the hygroscopic anhydrous form of an ergot alkaloid and only 1.24 for the corresponding monohydrate (18)

Electron microscopy shows the different morphology (see 2 different drugs fig. 2 and 3). The needles of the crystal form A (fig. 2) are not suitable for its galenical processing in the dosage form.

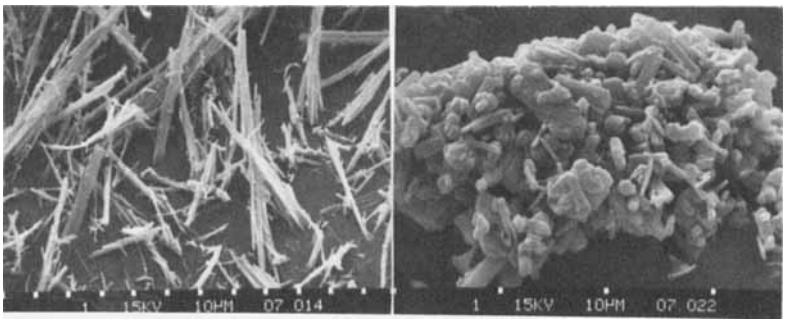


FIGURE 2. 2 different modifications (A and B)

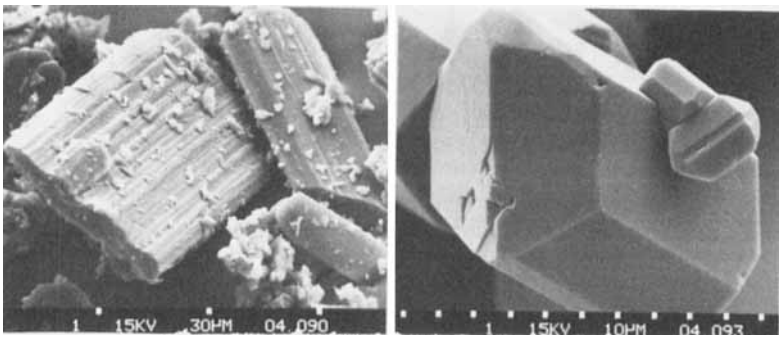


FIGURE 3. New modification appearing with methanol

The behaviour of 2 modifications of a benz-isoquinoline hydrochloride is summmarized in Table I showing the risk of transformation during granulation.

TABLE I Polymorphism behaviour of a benz-isoquinoline hydrochloride

	Modification A	Modification B
Melting °C	304	311
ΔH (Kcal/mole)	12	11
time for 90 % dissolution:		
pH 1.2	3 min.	4 min.
pH 7.5	3 min.	6 min.
Particle size 99 %<	194 µm	80 µm
gain of weight:		
1 day 92 % r.h.	0 %	3.2 % (hydrate)
1 month 92 % r.h.	0 %	3.2 % (hydrate)
Transition in alcohols	A	B->A

The two modifications may be determined by means of IR in Nujol (figure 4a) and X-ray diffraction (figure 4b).

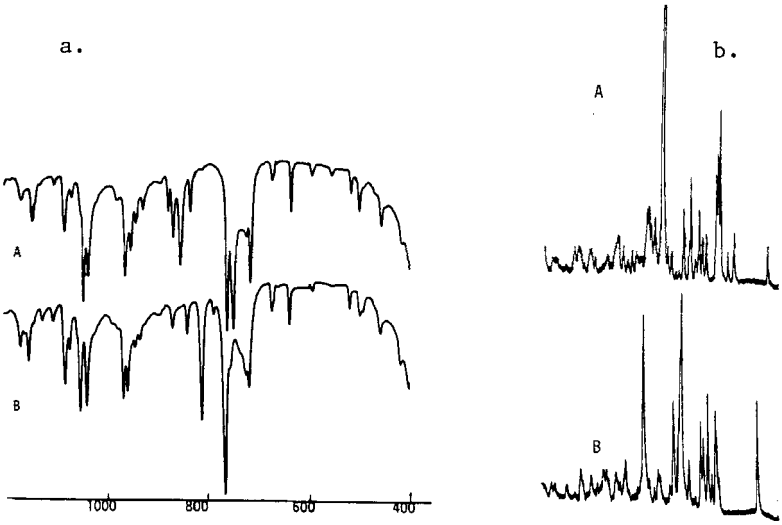


FIGURE 4. IR and X-ray diffraction

As a first step, analytical work deals with preparation of polymorphs, characterisation (physico-chemical parameters), and quantitation (DSC, IR, FT-IR, X-ray diffraction, solid state NMR...) of raw materials.

Quite often the amorphous state or a metastable state is manufactured in order to obtain a better bioavailability. It is obvious that this state must be maintained. Polymorphic transitions occurring within the solid state are governed by the free energy of the phases. At any given temperature and pressure, the phase with the lowest free energy is the most stable. The compound, therefore, tends to exist in this phase. If the temperature and pressure are changed, the condition of minimum free energy may require the compound to undergo transition from one phase to the other.

Once the crystalline modification of the drug substance is fixed, galenical processing and storage conditions must be defined in order to maintain it.

The mechanical milling of raw material may give rise to transformation. Takahashi et al. (7) have studied intensively the effect of grinding, of compressing and milling on the transformation of the crystalline modification II of Fostedil. They observed the influence of the excipients microcrystalline cellulose and corn starch upon the transformation, dependance on the type of mill and suggested the use of a Hammer mill. They reported 100% transformation after 2 hours grinding or by submitting to compression of 1000 kg/cm^2. Such changes through mechanical activation or during tabletting have been observed for acetylsalicylic acid, procaine, penicillin (6) sulphathiazole (7), barbiturates (8), sulfanilamide phenylbutazone (9), α and β cyclodextrins, cephalexin (10) and chloramphenicol palmitate (11). Compression studies involving 32 drugs known to exhibit polymorphism revealed that 11 of them were transformed under compression (34).

Not only pressure and mechanical activation are responsible for transition on processing. It has been observed that the temperature rises up to 50 °C (12) during tabletting of aspirin. We observed partial melting at 60 °C of a tablet whose components have an eutectic behaviour. In some mills, higher temperatures may also be attained in certain parts of the powder.

Solid transitions during heating are often observed and for that reason are not detected in classical melting point determination. Figure 5 shows the influence of temperature on a polymorphic transition of a new drug substance.

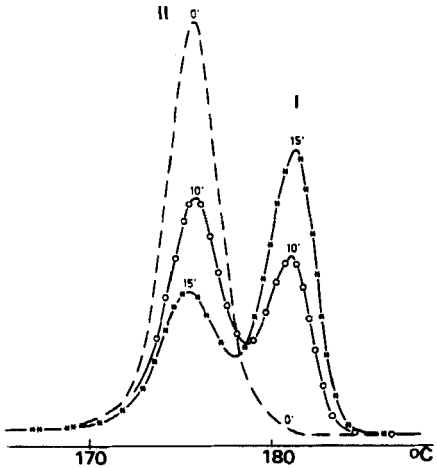


FIGURE 5. DSC study of the transition of a metastable modification II into the stable modification I

Crystallinity change to an amorphous state, due to the action of excipients, has been observed. For example hydrocortisone acetate and tetramethasone dipropionate become amorphous by grinding with crystalline cellulose, increasing the potency in vivo (15). Grinding with activated charcoal to obtain a suitable amorphous soluble state has been proposed (16).

The spray drying technique (17) is specially critical for reproducibility. Polymorphism changes have been detected not only for the drug substance in the presence of certain excipients, but also for excipients themselves, for example mannitol or lactose (18).

Polymorphic transitions during storage have to be avoided: e.g. transitions in gelatin capsule of oxytetracycline, crystallisation of theophylline (20) or excipients (21) at the surface of tablets, transition of the amorphous to crystalline state in solid dispersions.

All suppositories have potential problems with polymorphism of the excipient. The suppository masses are mixtures of natural or synthetic glycerides with three different modifications having different melting points. Freshly melted suppository masses are in the α state after cooling and slowly go through the β'state to the stable β form of higher melting point. This aging effect is illustrated figure 6 for paracetamol suppositories (32).

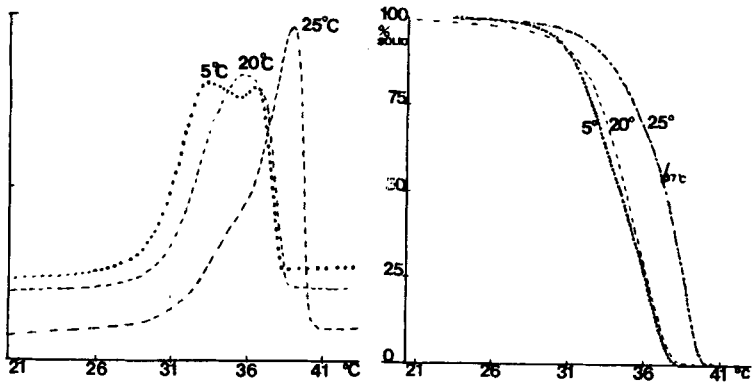


FIGURE 6. DSC curves and plot of % solid of compressed suppositories of paracetamol after 18 months storage at different temperatures (5,20, 25° C).

After 18 months storage at 25 °C, the suppository mass is only 50 % melted at 37 °C.

If suppositories are manufactured through melting, the hardening state of the excipient before manufacturing does not have any consequences, but for compressed processing, wrong storage of the excipient leads to bad reproducibility as seen in figure 7 (32) for compressed suppositories manufactured at 6 months intervals with the same raw materials. Industrial consequences reflects the choice of the fat, of the process, the conditioning after manufacture and the storage conditions (22).

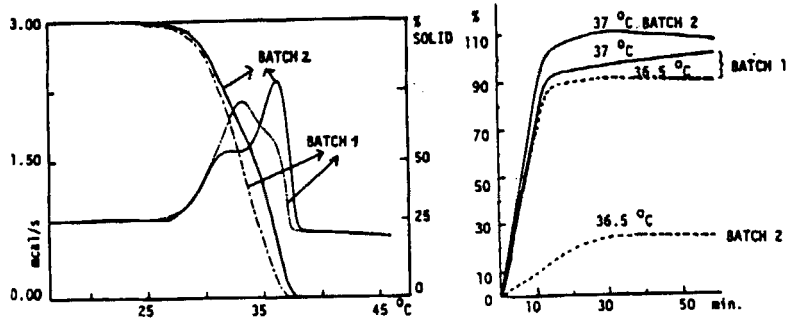


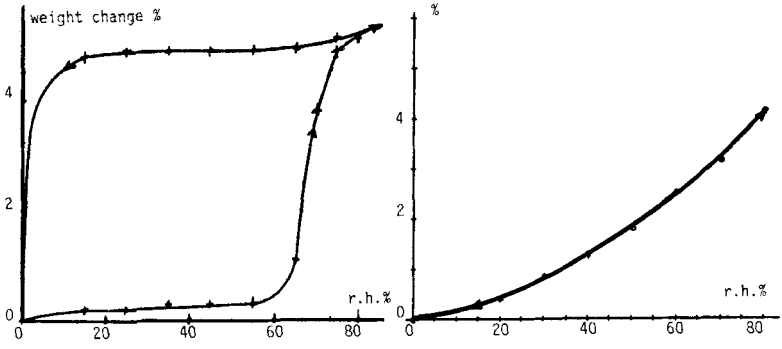
FIGURE 7. a) DSC curves of compressed suppositories with Witepsol H15 of the same composition,
b) dissolution rate curves of the 2 batches

During granulation, especially wet granulation, hydration of the drug substance may occur (phenobarbital, codeine, caffeine (13, 14).

We determined the different hydration steps of a very hygroscopic new drug substance, depending on the granulation time and how the granulate was processed (18).

Sorption isotherms give the best information on the type of bonding with water.

The sorption isotherm of figure 8 case a is typical for hydrate formation and the case b for reversible adsorption.



a. b.

FIGURE 8. Examples of Sorption isotherm of drug substances at 30 °C, Case a: Hydrate formation, Case b: Reversible adsorption

DECOMPOSITION

Chemical reactions in the solid state are auto degradation, solid-gas reactions and solid-solid interactions.

AUTO-DECOMPOSITION

The influence of light gives rise to auto-degradation, including isomerisation, breakdown, cyclisation. Three processes may occur:

$$M \xrightarrow{h\nu} M^*$$

(a) Formation of decomposition products

(b) Reaction with other molecules

(c) Energy transfer to other molecules

Different decomposition products may result from UV or visible radiation as demonstrated in figure 9 for nifedipine.

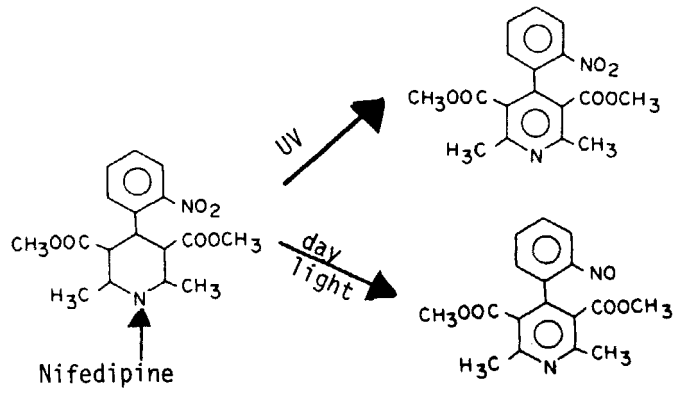


FIGURE 9.

Sterilization by gamma rays is often a cause of breakdown or dimerisation, as for example for butylhydroxytoluene.

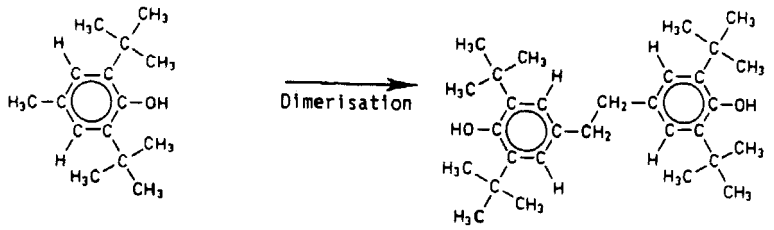


FIGURE 10. Ionizing radiation: dimerisation of BHT (30).

Isomerisation, condensation, polymerisation, cyclisation, internal rearrangement, cleavage, dehydration, decarboxylation, pyrolysis etc. take place under the influence of heat.

SOLID-GAS REACTIONS

Solid-gas reactions depend on a complex set of factors including temperature, gas vapor pressure, crystal packing, defects and crystal properties, surface area, etc... They are often different than in solutions. Reaction may occur only at the surface if the crystal is not permeable to oxygen.

Oxidation is a prime cause of product instability because it is impossible to remove it totally. Often not only one oxidation product is formed, but a chain of degradation products as shown in figure 11 for thioridazine

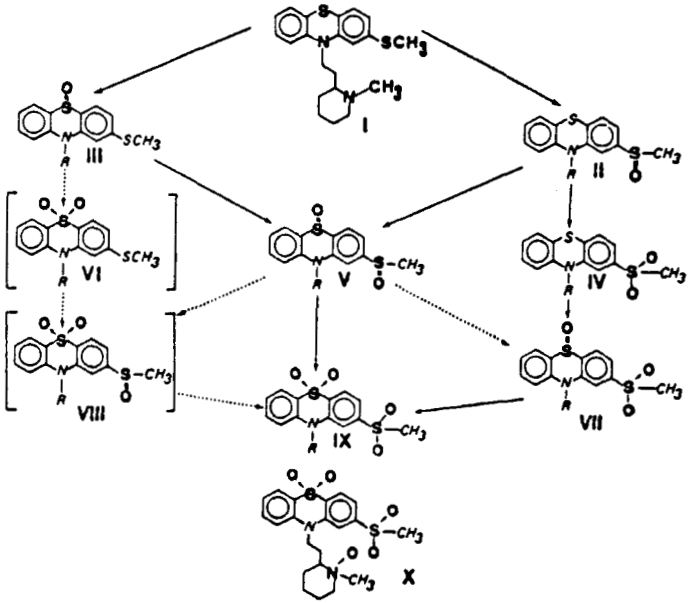


FIGURE 11. Thioridazine and its degradation products

Oxidation is catalyzed in general by traces of metallic impurities. Oxidation of solid dialuric acid is accelerated in a high humidity atmosphere (13).

Reaction of solids with water is quite common and, like oxidation, very difficult to avoid totally. It is impossible to prove whether these reactions are true solid-gas reactions or solution reactions occuring in an adsorbed moisture layer.

Esters, thiolesters, amides, sulphonamides, imides, lactams, lactones, etc... are subject to hydrolysis. Often not only one reaction product is obtained but complex subsequent reactions may occur (figure 12).

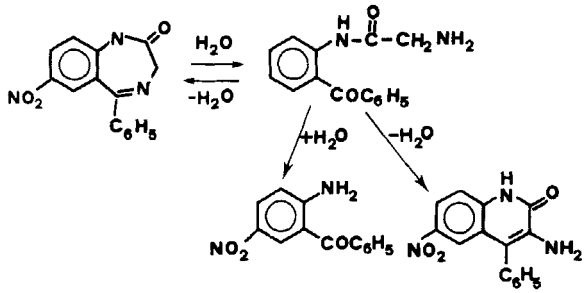


FIGURE 12. Nitrazepam

Excipients may accelerate hydrolysis through hygroscopicity or pH effects.

For example stability is improved by addition of organic acids with a low pK_a (13). Table II illustrates the influence of tablet moisture on the rate of hydrolysis of an ester (23). After only 48 hours in a 65 % r.h. atmosphere without protection, the tablets take up enough humidity to increase the degradation.

The degradation scheme for ergotamine (figure 13) shows how all types of reactions may be observed, depending on the functional groups of the molecule. In the pharmaceutical industry all types of reaction must be analysed and the formulation chosen in order to stabilize the product.

TABLE II Influence of moisture of tablets on the rate of hydrolysis of an ester (23). Results show the content of the ester.

	After 1 year	After 2 years
Tablets 48 h at 21 °C, 65 % r.h. then blistered	94 %	92 %
Tablets in glass with dessiccant	98.2 %	98.3 %

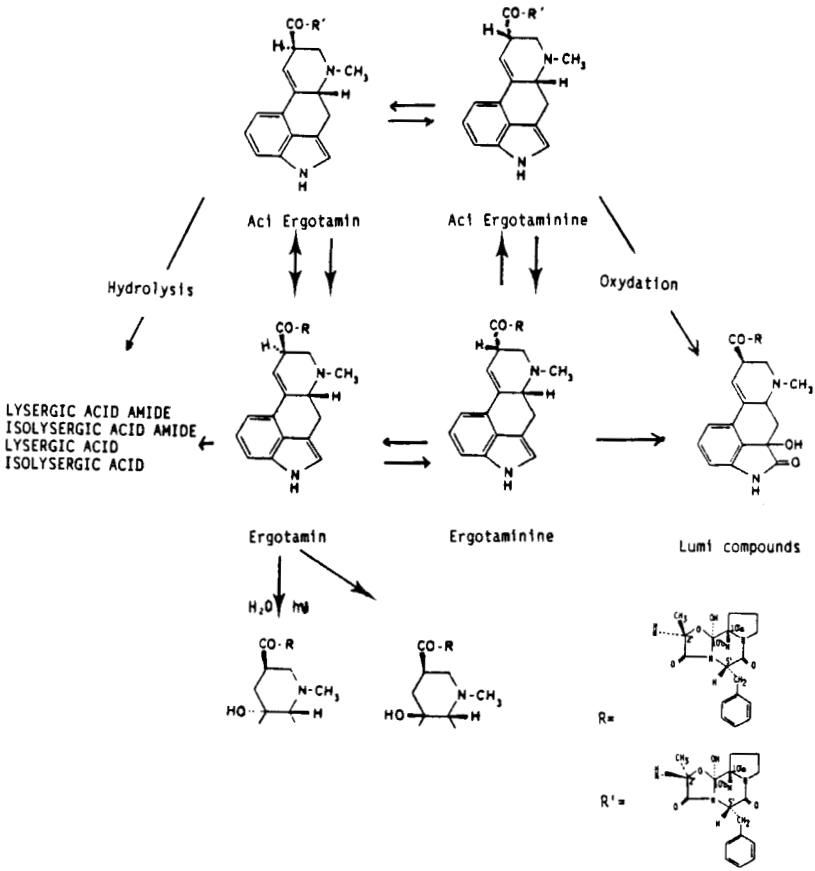


FIGURE 13. Degradation scheme of ergotamine

SOLID-SOLID REACTIONS

Decomposition by interaction between components are observed with drug and excipients. For example, ester or amide formation has been observed with stearic acid or magnesium stearate (figure 14) (24), reduction with polyethylene glycol or its impurities (24). The browning reaction of isoniazide with lactose is a typical Maillard reaction. All primary amines are able to react with ascorbic acid (30).

Cases of drug-drug interactions occur only in multiple component dosage forms. J.T. Carstensen (3) reported the study of aspirin-codeine and aspirin-phenylephrine interactions.

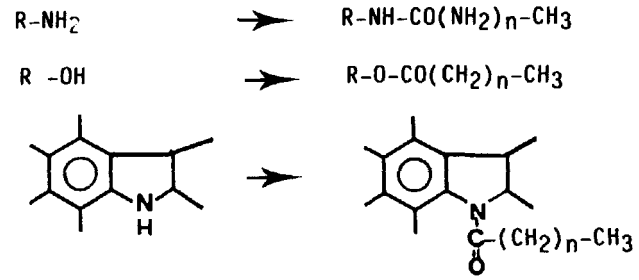


FIGURE 14. Reactions of drug substances with stearic acid or magnesium stearate (n = 14 or 16)

DISCOLORATION

Discoloration of components of the dosage form may occur under the influence of light, heat, oxygen or humidity. Some degradation products are often coloured and are usually present in very small amounts. Excipients may accelerate the process or delay it. Photo-oxidation of coatings may occur, e.g. indigotin in blue hard gelatine capsules. Colorimetry allows objective measurement of color changes. The diagram: log of slope of colorimetric coordinate L and b against 1/T

yielded straight lines enabling prediction of the shelf-life and storage temperature (25). Figure 15 shows the Δb and ΔL values observed after 1 year storage of a drug substance at different temperatures without substantial loss of content (26).

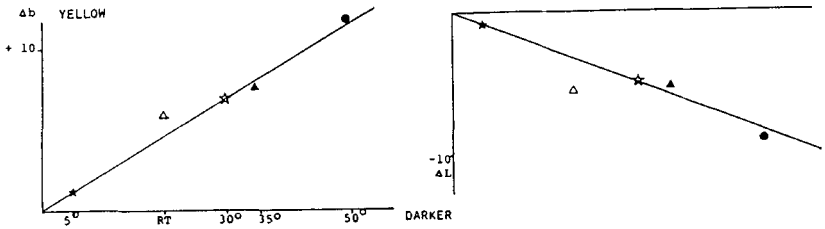


FIGURE 15. Difference ΔL and Δb between initial values of L and b and measurements of these values of a batch stored 1 year at different temperatures.

Figure 16 shows on the contrary a good correlation between discoloration and loss of content for a dihydergot tablet.

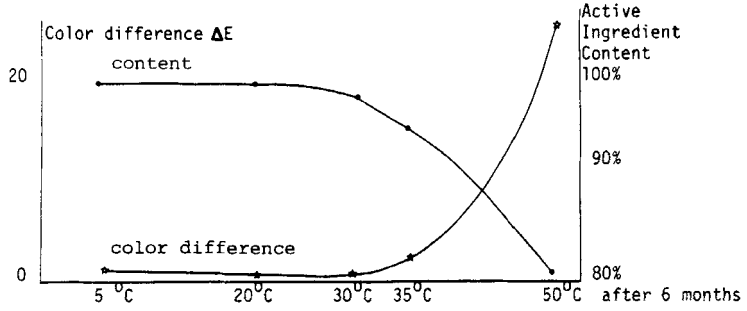


FIGURE 16. Use of colorimetry to detect influence of degradation on the discoloration of dihydergot tablets ($\Delta E = \Delta a^2+\Delta b^2+\Delta L^2$)

INFLUENCE OF RAW MATERIALS

INFLUENCE OF THE SALT FORM

Walking et al. (27) studied the solid-state stability of four salts and the free base of xilobam at 70 °C and 74 % relative humidity. They report a 99.6 % content of xilobam for the 1-napsylate after 7 days while 70-80 % remains intact for the other salts, but only 18 % of the base. We established a set of experimental data on which to base a suitable choice for a salt of a new drug with reference to such factors as feasibility, stability, compatibility, solubility, hygroscopicity and polymorphic behaviour of the different salts (24)

INFLUENCE OF THE CRYSTALLINE MODIFICATION ON STABILITY

The behaviour of the 3 crystalline modifications of salicylidine anilines under light is a classical example. Due to steric effects only the gamma form is stable, whilst alpha and beta forms give the dimer.

Table III gives the results published by Walking et al. (28) for the two crystalline modifications of fenretinide, demonstrating a drastic difference in stability behaviour.

Table III. Two crystalline modifications of fenretinide show very different stabilities

Form	Weeks	4 °C	25 °C	40 °C	60 °C
I	4	99.6 %	100.3 %	98.6 %	96.9 %
II	2	97.0 %	91.9 %	79.8 %	-
	4	91.4 %	87.9 %	-	-

Table IV compatibility of 3 crystalline modifications of a new drug substance.

		Mixture 1		Mixture 2	
Form	Particle size 99 % <	Hydrolysis product	other degrad.	Hydrolysis product	other degrad.
I	36.8 µm	1 %	2-5 %	1.5 %	5-20 %
II	31.8 µm	5 %	≥20 %	≥5 %	5-20 %
II	52 µm	2 %	2-5 %	2 %	5-20 %
III	40 µm	≥2 %	5-20 %	2 %	5-20 %

Table IV summarizes some preformulation results for 3 different crystalline modifications of a new drug substance. Form I has been found more stable (29).

Table V and figure 17 deal with two different batches of a drug substance. The dosage form is a solution. Therefore polymorphism is only important for the drug substance.

Table V

Sample	Form	Hygroscopic	Melting	Stress 80 °C 1 month + 4 % H_2O	compatibility with excipients
A	orthorhombic less soluble	no	194 °C ΔH = 12 cal/g	0 % degradation	better
B	tetragonal + amorphous	yes (reversible)	at 100 °C --> amorphous	1 % degradation	worst

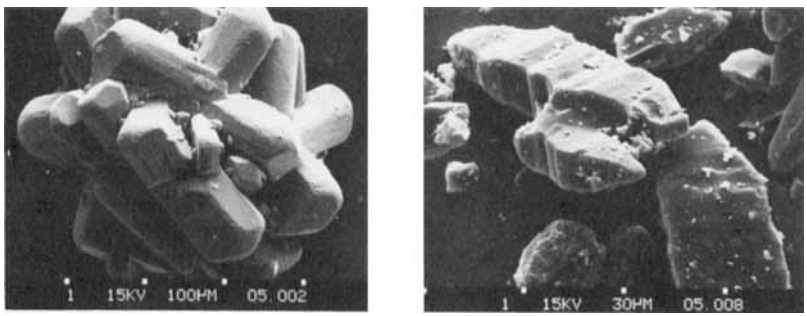


FIGURE 17. Scanning electron microscopy of 2 samples corresponding to table V

Traces of a metastable modification may have a drastic effect on solid-state reactions. Three batches of an indole were tested in a stability program: Batch 1 was form A, batch 2 form A with 2 % form B, batch 3 was the pure form B. After 1 year at 30 °C batch 2 underwent polymorphic transition into form B, while batch 1 remained unchanged A, even after 4 years at 30 °C. Batch 3 was unchanged form B (33).

Table VI shows the drastic influence of a metastable modification, form II, on the stability behaviour of different mixtures of the two modifications of fenretinide, as reported by Walking et al. (28)

Table VI FENRETINIDE. HPLC results on the content after 4 weeks at 60 °C as a function of the percentage of metastable form II in mixtures of the two modifications.

0 % II	5 % II	10 % II	15 % II	20 % II
97.6	91.7	86.6	81.3	76.8

INFLUENCE OF PARTICLE SIZE.

This is demonstrated by the four examples given in table VII

Table VII Influence of particle size
Example 1: Stability of an ergot alkaloid

Sample Preparation	Particle size 99 % <	10 days 60 °C nitrogen colour (Ph. Eur.)	10 days, 80 °C oxygen HPLC content
air jet milled	59 µm	B5	97.5 %
pin milled	17 µm	B1	93.1 %

Example 2: Hygroscopicity of a phenolic compound

Particle size 99 % <	H_2O %	H_2O % after 1 day 92 % r. humidity
126 µm	0.0	0.3 %
67 µm	0.6	1.3 %
27 µm	0.7	1.3

Example 3: Stability/Compatibility (1,2,3 = ranking order)

Particle size 99 % <	96 h Xenon rank of stability	1 week 70 °C with excipient dried	with humidity (% degradation)
247 µm	1	1 (no deg.)	1 (2 - 5 %)
67 µm	2	2 (traces)	1 (2 - 5 %)
23 µm	3	3 (traces)	2 (>5 %)

Example 4: Hydrolysis of a lactone

	% Hydrolysis product (acid) (TLC, DSC) initial	1 month		6 months	
Sample		Glass	Poly-ethylene	Glass	Poly-ethylene
not milled	0.2 %	0.2 %	0.3 %	0.6 %	0.7 %
micronised	0.4 %	0.7 %	1 %	1.1 %	1.7 %

The influence of both particle size of a drug substance and water content of an excipient is demonstrated in table VIII for a drug substance very sensitive to hydrolysis. Subsequently, magnesium oxide had a stabilizing effect on the hydrolysis in the solid state.

Table VIII Influence of particle size and water content of excipients on the degradation of a drug substance

	Degradation 1 week 70 °C		Capsule formulation Degradation
Drug substance	with lactose	with corn starch	2 months r.t.
milled	3 - 5 %	>50 %	>5 %
unmilled	0 %	< 1 %	<2 %

INFLUENCE OF IMPURITIES

Figure 18 gives DSC curves of 3 batches of a drug substance stored at 30 °C, 75 % relative humidity. New batches show a

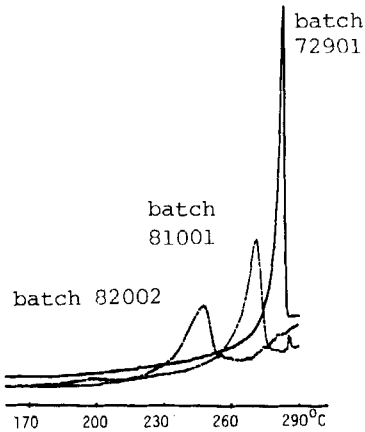


FIGURE 18. DSC curves of 3 different batches after storage 30 °C, 75 % r.h.

drastic loss of stability compared to old batches. Stress tests were performed under nitrogen and oxygen in order to compare several batches. Table IX summarizes the affected parameters, colour and degradation products, demonstrating the catalytic influence of traces of impurities.

Table IX Different stability behaviour due to traces of impurities. Stress test under nitrogen and oxygen.

Sample	Colour of the solution (Ph. Eur.)			Degradation products		
Initial		14 days 90 °C Nitrogen	14 days 90 °C Oxygen	Initial	14 days 90 °C Nitrogen	14 days 90 °C Oxygen
72901	B8	B7	B6	<1 %	1 %	1 %
72902	B8	B7	B6	<1 %	1 %	1 %
73901	B8	BY5	Y3 - Y4	<1 %	5 %	10 %
81001	B5-6	B5	BY2-BY3	~1 %	5 %	10 %
82001	B5-6	B5	BY4	<1 %	2 %	2 %
83003	B6	B6	BY4	<1 %	2 %	≤10 %

Table X compares of the stability behaviour under stress conditions of different samples of an indole obtained after different manufacturing and recrystallisation processes.

Table X Different manufacturing and recrystallisation processes.

Sample	Particle size 99 % <	HPLC content, 10 days 80 °C, oxygen	Rank of coloration
A	36 µm	97.5 %	3
B	24 µm	89.5 %	2
C	17 µm	93.1 %	2
D (partly amorphous)	23 µm	84.1 %	1

INFLUENCE OF THE QUALITY OF EXCIPIENTS

Impurities in excipients are often responsible for degradation, for example traces of heavy metals in talc, bleaching agents in starch, basic or acidic residues, peroxide content and specially water content. Furthermore excipients exhibit polymorphism e.g. magnesium stearate, sorbitol, mannitol, all waxes, aspartame etc. For example only one crystalline modification of sorbitol has been found suitable for stable formulations (31).

CONCLUSION

Solid-state reactions in pharmacy must be recognized at a very early stage of development and carefully studied in order to develop a suitable formulation and stabilize it. Chemical and physico-chemical parameters must be known and analysed with appropriate methology.

In conclusion, a suitable stability program for solid dosage forms covers first, the right choice of the salt form, the knowledge of the polymorphic transformations, the choice of a single crystalline modification and the study of hygroscopicity and degradation mechanisms. Physical properties of the raw materials, including particle size, surface area etc., are measured.

The second part of the program deals with preformulation studies with excipients, the choice of the packaging material, optimization of the formulation, accelerated stability tests and long term stability studies including an adequate analytical methodology.

Finally the follow up stability program for the marketed drug substance and dosage form must confirm the stability results of development.

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