

PREPARATION OF BEAD POLYMERS UNDER THERMICALLY MILD CONDITIONS

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In preparing of thermically unstable drugs in beads it is necessary to prepare these products under thermically mild conditions.

In our opinion, there are two ways. The first, the later incorporation of drugs in beads has already been done by us and the results have been published (2).

The second way is characterized by the modification of reaction conditions. The reaction temperature must be reduced strongly. Till now, we have polymerized beads at a temperature of 78-85°C. We work on the basis of acrylates, the monomers being methylmethacrylate and acrylic acid.

There are many possibilities for polymerizing these monomers at temperatures between 20-60°C. The simplest method is the use of *l,l'*-azo-bis-isobutyronitrile (AIBN) and benzoyl peroxide (BPO) as initiators. You must find the minimal working temperature at which the initiators still produce radicals at a high rate. Figure 1 indicates the thermal decay of AIBN and BPO.

In the method of bead polymerisation, a monomer (or mixtures of monomers) with drug is dispersed by strong mechanical agitation into droplets, suspended in a second liquid phase in which both the monomers and the polymer formed are essentially insoluble.

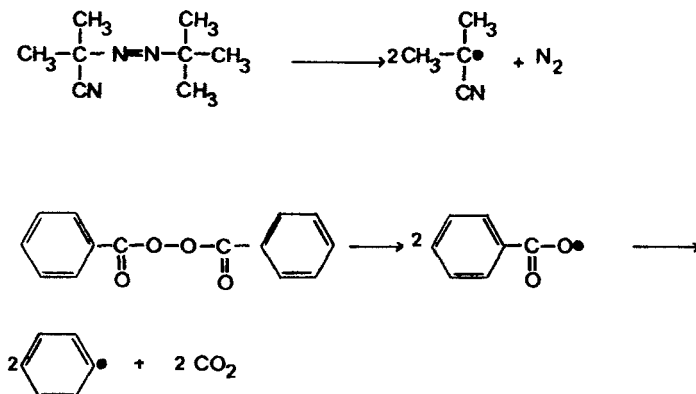


Fig. 1

To the suspending liquid, which is mostly water, suitable agents are added, which hinder the coalescence of the droplets during polymerisation. As suspending liquid we use a 25% solution of sodium sulfate in 0,01 N sulfuric acid and as suspension stabilizer we use a 40% solution of polyacrylic acid. The initiator is dissolved in the monomer or mixtures of monomers. The bead size is 0,16-1,6 mm.

The velocity of a polymeric reaction is dependent on the rate of decay, the radical yield and the concentration of the initiator (9). In our investigation we have found an ideal concentration of initiator of 1% related to the monomers.

In this way we can reduce the temperature of polymerisation as well as AIBN and BPO of 60°C. The lowering of temperature is connected with a prolongation of the time of polymerisation, indicated in figure 2.

It is possible to shorten the time of polymerisation with the help of AIBN in comparison with BPO. The reason is a greater activity of azo-compounds in comparison with peroxides. AIBN decays strictly according to a

Initiator	T [°C]	Composition of monomers [%]			Time of polymerisation [min.]
		Methyl-methacrylate	Acrylic acid	Vinylacetate Crotonic acid	
AIBN	80	70	30		15-20
	80	40	30	30	15-20
	70	70	30		70
	60	70	30	30	200
	60	40	30	30	200
BPO	80	70	30		20-30
	80	40	30	30	15-20
	70	70	30		90
	70	40	30	30	60-70
	60	70	30		240
	60	40	30	30	200

Fig.2 Times and temperatures of polymerisation under various conditions

reaction of first degree function. In the peroxides the induced decay of initiator plays a leading part. It strongly reduces the radical yield.

A second possibility to reduce the time of polymerisation at fixed temperatures is the use of copolymers from vinylacetate and crotonic acid (92:8). These copolymers are solved in the acrylic monomers. We can confirm the results of Jecklin (1) that a shortening of the time of polymerisation is only true for the peroxides, not for AIBN. We explain this acceleration with the "Trommsdorf-effect". By the use of solutions with high viscosity the diffusion of the growing radical chains is hindered so that a coincidence of the radical chains with their activ centers is less probable, but the diffusion of the monomers to the growing radical chains is not influenced.

The use of unstable peroxides is a further possibility to polymerize acrylates at lower temperatures. The use of unstable peroxides requires special precautions, because they are explosive, special peroxides with a lower carbon content are very explosive (10). They are practically used only in diluted solutions (3). For our investigations we used the diisopropylperoxydicarbonate (DIPP) in 40% solution and a concentration of 1% related to the monomers.

Figure 3 shows a summary of preparation and yield of bead polymers with Phenobarbital and Meprobamat as drugs, prepared with the aid of DIPP. We cannot prepare bead polymers with Meprobamat at temperatures of 30°C. In our opinion, the lowering of the temperature can be different from drug to drug.

It is well known (4) that initiators such as AIBN and BPO decay under ultraviolet radiation, specially in far uv. In this way we attempted to reduce the temperature of polymerisation. Compounds, which decay in radicals under the influence of light are termed photoinitiators. The photoinitiators contain functional groups, which absorb the necessary radiant energy for the decay, as f.e. aromatic ketones and aldehydes and azo-compounds. The initiators form through photolysis the same radicals, as they are formed through thermal decay. The photolysis needed no thermically activating energy, the energy is delivered by the incident uv-light. For this reason it is possible to lower the temperature of polymerisation.

Other organic compounds are also used as photoinitiators. For our investigation we used benzoin, which decays under ultraviolet radiation in benzoylic and benzylic radicals.

For our investigation we used normal ultraviolet light.

$T [^{\circ}\text{C}]$	Composition of monomers		drug $[\%]$	yield $[\%]$
	Methylmeth- acrylate	Acrylic acid	Pheno- barbital	
30	70	30 = 80%	20	72,3
50	70	30 = 80%	Mepro- barnat 20	72,0

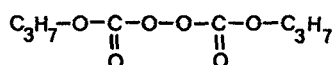


Fig.3 Preparation of bead polymers with the aid of DIPP

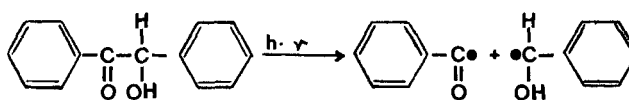


Fig.4 Decay of benzoin through photolysis

Initiator	$T [^{\circ}\text{C}]$	Composition of monomers $[\%]$			Time of polymersation $[\text{min}]$
		Methyl- meth- acrylate	Acrylic- acid	Vinylacetat Crotonic acid Copolymer	
AIBN	50	70	30		250
BPO	50	70	30		270
	50	40	30	30	215
	40	70	30		310
	40	40	30	30	250
	30	70	30		360
	30	40	30	30	310
Benzoin	40	70	30		280

Fig.5 Preparations produced with the aid of photolysis

The bead polymers, using benzoine as initiator, show a discoloration. We can show through tlc-investigations that a disintegration of the drugs does not take place.

The use of reox-systems is another way for the polymerisation of acrylates at lower temperatures. Through combination of oxidizing agent and reducing agent it is possible that sufficient radicals are available for the polymerisation (5). The mechanism and the Kinetics is not clear in many cases (6).

The growing velocity of the radical polymerisation is not so dependent on temperature, therefore it is only necessary to produce radicals at these temperatures. For our investigation we used BPO as oxidizing agent as reducing agent we used:

1. water soluble compounds, dissolving in 25% solution of sodium sulfate in 0,01 N sulfuric acid, f.e. ascorbic acid, sodium sulfite, glucose and triethanolamine
2. monomer soluble compounds, f.e. benzoine, phenylhydrazine, dimethylaniline and benzolsulfuric acid.

Our temperature of polymerisation was 40°C. We can point out, that no polymer products were obtained with water soluble reducing agents. We obtain beads with demethylaniline as monomer-soluble compound at a temperature of 20°C. The proportion dimethylaniline to BPO was 1:1 (g/g). Figure 6 indicates the reaction between BPO and dimethylaniline (11).

The beads showed an orange colour. Taeger and Runge (7) explain this discolouration with the formation of by-products, containing conjugated double-bonds.

Trommsdorff (8) obtained beads with BPO, benzoine and organic iron -(II)- compounds at 40°C. The monomer was methylmethacrylate, the time of polymerisation was 3 hours. We cannot transfer this redoxsystem of our investigations. The polymerisation was retarded after reaching a viscose stage. We cannot obtain solid beads

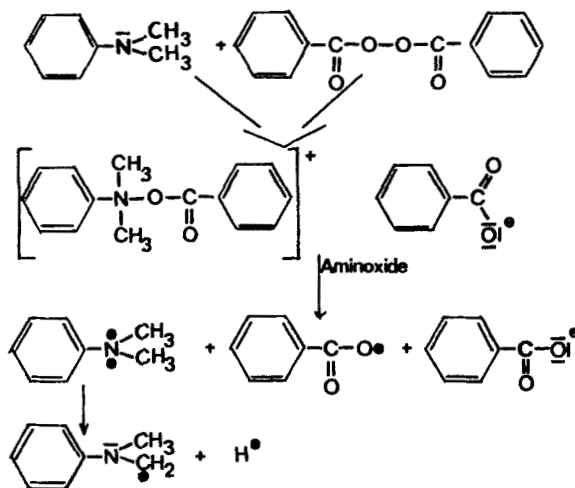


Fig.6 Reaction between benzoylperoxide and dimethylaniline

with the system BPO-benzolsulfuric acid either. The use of redox systems for the lowering of temperature of polymerisation is characterized by a high rate of interference.

SUMMARY

According to our investigations there are 4 possibilities for the incorporation of thermically unstable drugs in bead polymers.

1. The polymerisation with AIBN and BPO at minimal working temperatures
2. The use of unstable peroxides as initiators
3. Preparation of beads with the aid of photolysis
4. The use of the redox-system

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