Potential of Mechanochemical Technology in Organic Synthesis and Synthesis of New Materials

ALEXANDER V. DUSHKIN

Institute of Solid State Chemistry and Mechanochemistry, Siberian Branch of the Russian Academy of Sciences, Ul. Kutateladze 18, Novosibirsk 630128 (Russia)

E-mail: dushkin@solid.nsk.su

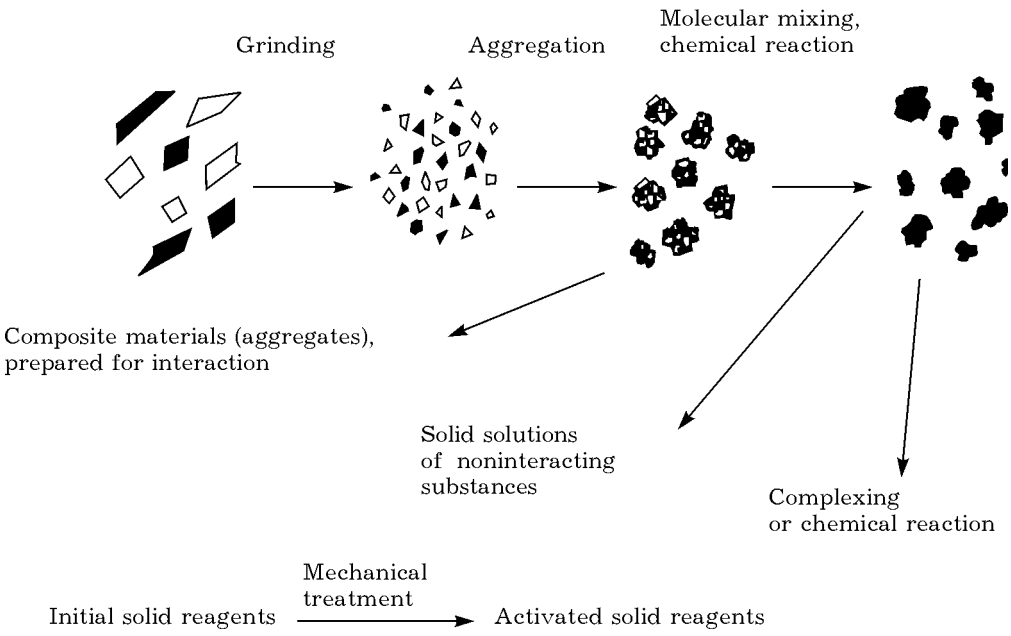
Abstract

Possible applications and advantages of mechanochemical technologies are formulated. They include one-stage chemical reactions between solids, preparation of solid disperse systems (aggregates) of chemically interacting solids, formation of solid solutions, formation of solid reagents possessing increased activity in subsequent chemical transformations, and chemical modification of natural polymers. Comparative tests of activator mills have been carried out, recommendations for their application depending on the type of product have been worked out, and methods for ranging some mechanochemical processes for «flow» vibratory centrifugal mills have been developed. An original, readily soluble pharmaceutical of acetylsalicylic acid and its production process have been developed. The advantages of mechanochemical technology include one-stage process (mechanical treatment of the powdered material), absence of solvents and technological operations using them, simplification and increased productivity of technological equipment compared to equipment typically used in liquid-phase processes, and reduced time necessary for obtaining the product.

INTRODUCTION

Many technological processes involving treatment of low-molecular organic compounds are carried out with participation of liquid phases. Solid substances are placed in a solution or melt, in which chemical reactions or other physicochemical processes leading to the target product take place. After that, the product (often a solid) is separated from the reaction mixture. In view of the definite complexity of the technological operations of preparation and fulfillment, as well as product isolation, the possibility of direct chemical interaction between reagents in the solid state seems to be of interest. In our opinion, the use of solid-phase processes in laboratory practice and in chemical technology has a number of advantages, namely, rejection of solvents and melts and reduced total time of the process, which is important for chemical synthesis of some organic compounds. Low rate and degree of conversion, however, are serious hindrances to the application of these processes. Therefore, the so-called mechanochemical method of increasing the reactivity of solids has recently attracted special attention [1–3]. Reaction systems are subjected to intense intermittent or prolonged mechanical action. In the former case, the necessary devices are mills, including high-intensity (planetary) mills in which shock attrition is realized; in the latter case, these are Bridgman's anvils or extruders. All these devices help to create high pressure (from several units to dozens GPa) and shear deformations. The applicability of these devices is determined by the physicomechanical properties of the systems, namely, by the plasticity to fragility ratio of particles. In the case of fragile molecular crystals of low-molecular organic compounds, whose mechanochemical transformations are the subject of the present paper, it is reasonable to use pulse mechanical action when working with amounts from several grams to tons.

However, the possibilities of mechanochemistry are not limited to acceleration of solid-phase chemical reactions. A sequence of phys-



Scheme 1.

icochemical transformations in powdered mixtures of compounds treated in shock-attrition devices is presented in Scheme 1.

Based on the above scheme and our results, we distinguish four kinds of product obtained by mechanical treatment of mixtures of solids:

1 – composite materials (aggregates of particles);

2 – solid solutions of chemically noninteracting components;

3 – products of chemical interaction between solid reagents;

4 – crystalline phases with high concentrations of defects, whose reactivity increases in subsequent chemical interactions.

The goal of the present work is to estimate the possibility of laboratory and industrial application of the above-indicated processes and products.

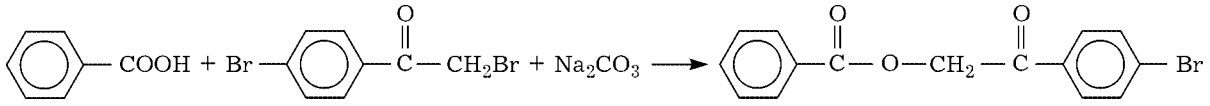
1. MECHANOCHEMICAL SYNTHESIS OF LOW-MOLECULAR ORGANIC COMPOUNDS

1.1. Estimating the feasibility of solid-phase mechanochemical synthesis for different classes of reactions

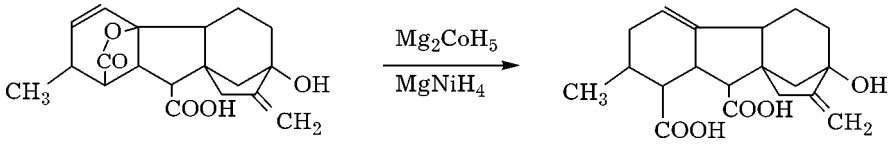
A number of solid-phase mechanochemical reactions of organic synthesis have been described in the literature [4]; however, the majority of reactions considered therein were carried out under very exotic conditions, namely, using Bridgman's anvils in which the mass of the sample is ~10^{-2} g. Therefore, it seems appropriate to continue the discussion of mechanochemical reactions by considering reactions carried out under conditions of shock-attrition. Moreover, new results have been obtained during the time that passed after publication of [4].

Investigations of solid-phase mechanochemical synthesis were not systematic, and they employed different types of activator mills, including a laboratory mortar; moreover, the total number of investigations in this area is very limited. As a consequence, no criteria for evaluating the feasibility of mechanochemical reactions have been elaborated; it is difficult to reproduce the results with other activator mills and to scale them.

In order to estimate the possibility of carrying out solid-phase mechanochemical syntheses of low-molecular organic substances in high-energy strain planetary ball mills of AGO and APF types [5] (see also Section 7), experiments with different classes of potential reagents were carried out. Chemical yields and composition of the products of mechanochemical reactions were compared with those of the classical liquid-phase reactions. Chemical analysis was performed by HPLC. This section describes esterification, cyclization, oxidation-reduction, neutralization of organic acids, halogen substitution [6], and acylation reactions [7].



Scheme 2.



Scheme 3.

Esterification. Under the conditions of mechanochemical synthesis from carboxylic acids and alkyl halides in the presence of Na_2CO_3 esters were obtained with yields not less than 90 % of the theoretical value (Scheme 2).

Reductive hydrogenolysis. Reductive hydrogenolysis of gibberellin A_3 with fine powders of Mg_2CoH_5 and $MgNiH_4$ results in the formation of reduction products with yields of 60 and 90 %, respectively (Scheme 3).

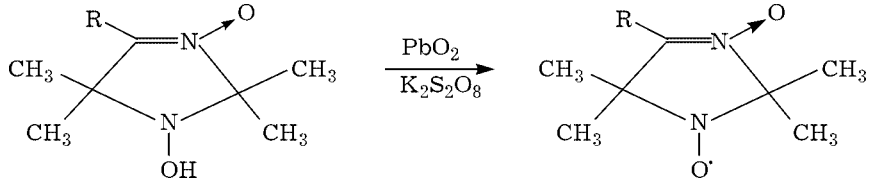
Oxidation. Stable nitroxides formed in solid-phase oxidation of 1-hydroxy-4R-2,2,5,5-tetramethyl-3-imidazoline-3-oxides (R = methyl, phenyl, *etc*.) with lead dioxide or potassium persulfate (Scheme 4).

The formation of nitroxides was registered by EPR [8]; in our case, reaction mixtures with conversion from 0.01 to 100 % could be studied. This unique feature underlies our method for quantitative comparison of the intensities of mechanical activation devices (see Section 7).

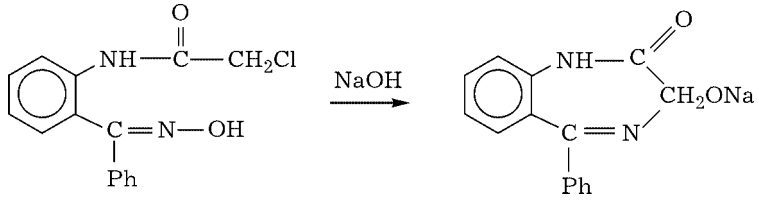
Cyclization. An example of a reaction of this class is the formation of sodium salt of oxazepam during mechanical treatment of a mixture of 2-chloroacetamido-5-chloro-benzophenoxime with sodium hydroxide (Scheme 5).

The yield of the target product under the conditions of mechanical treatment in an AGO-2 mill reaches 80 % within a few minutes, while in ethanol (industrial liquid-phase synthesis) the same yield is achieved after several hours.

Neutralization of organic acids. This reaction was described in patent [9]. In order to accelerate neutralization, the authors added water and additionally heated the mixture to temperatures close to the melting points of the reagents. Under the conditions of our experiments (AGO-2 mill, see Section 7), neutralizations of benzoic, salicylic, acetylsalicylic, citric, sebacic, indolylacetic, and ascorbic acids and gibberellin A_3 with hydroxides, carbonates, and bicarbonates of alkaline metals were complete within 1–3 min without using the above-mentioned additional conditions:



Scheme 4.



Scheme 5.

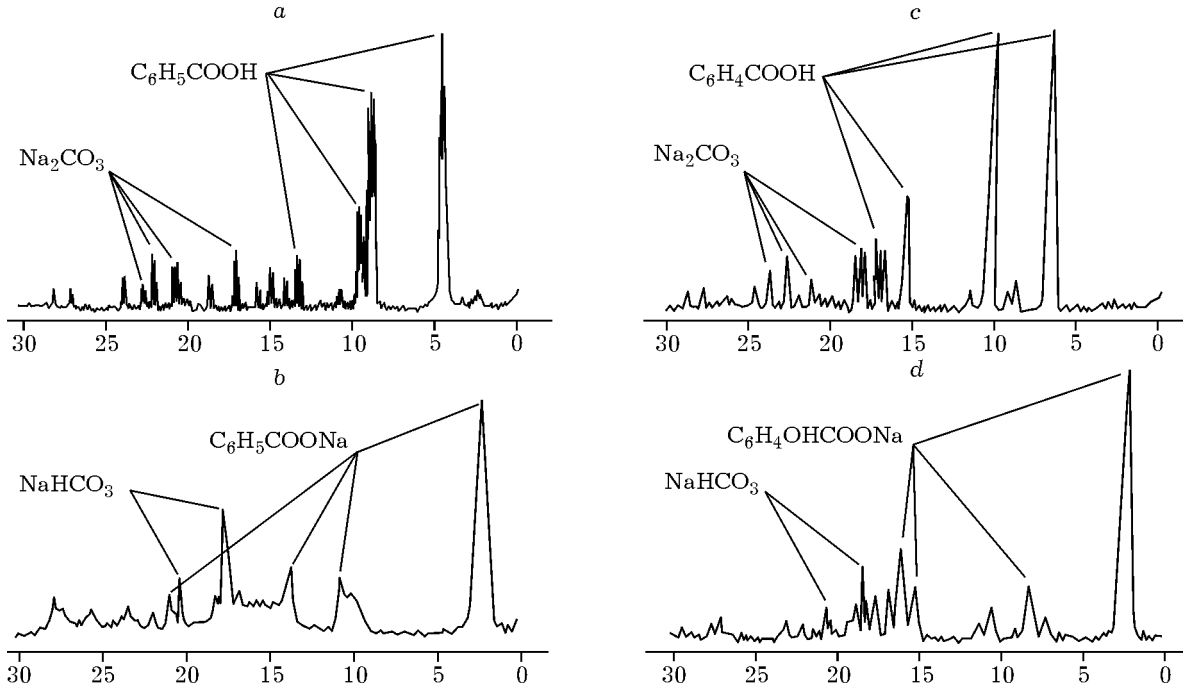


Fig. 1. X-ray diffraction patterns of mixtures of benzoic (*a*, *b*) and salicylic (*c*, *d*) acids with sodium carbonate before (*a*, *c*) and after (*b*, *d*) mechanochemical activation.

$$RCOOH + M_2CO_3 \rightarrow RCOOM + MHCO_3 \quad (1)$$

$$RCOOH + MHCO_3 \rightarrow RCOOM + H_2O + CO_2 \quad (2)$$

$$RCOOH + MOH \rightarrow RCOOM + H_2O \quad (3)$$

where M = Li, Na, K.

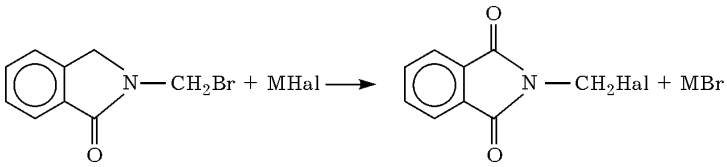
The reaction was detected from changes in the IR spectra and diffraction patterns of the reaction mixtures (Fig. 1). DTA and NMR studies of the reaction showed that the process is likely to be autocatalytic and to involve the formation of a mobile microphase "water–carbonate, bicarbonate, hydroxide–reaction product".

However, with calcium carbonate as a neutralizing agent for benzoic, salicylic, acetylsalicylic, ascorbic, and citric acids, mechanochemical reaction does not proceed under "dry" conditions. In this case, insolubility in water and high lattice energy of calcium carbonate hinder the formation of the above-mentioned mobile microphase and prevent direct mechanochemical reaction. An indirect evidence for the latter is the occurrence of reaction after the addition of 3–5 % water.

Halogen substitution. A series of reactions proceeding according to Scheme 6 have been investigated.

It was shown that reaction products formed only under mechanical activation of mixtures of powdered reagents. The yields of reaction products depending on the time of mechanical activation are shown in Table 1. The time of mechanical treatment in an AGO-2 mill sufficient for an equilibrium product ratio to be established was 5–10 min in all cases. Similar reactions carried out in polar solvents are usually completed within several hours.

Acylation. The reactions of N-acylation of *p*-toluidine with solid carboxylic acids –



M = Li, Na, K, Cs, Hal = F, Cl, I

Scheme 6.

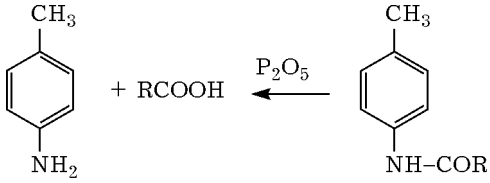
TABLE 1

Yields of substitution products according to Scheme 9 depending on the nature of halide and on the time of mechanical activation

MHal	Yield, % of theoretical after	
	5 min	15 min
NaF	1	1
KF	15	12*
KCl	10	28
LiI	43	75
KI	75	78
CsI	81	58*

*Partial decomposition of reaction products is possible.

chloroacetic, benzoic, and maleic – in the presence of phosphoric anhydride were studied:



(4)

RCOOH is benzoic, chloroacetic or maleic acid

The yields of products correlate with the number of carboxylic groups in the acid. The authors assumed that the salts of *p*-toluidine and acids form at the first stage, then nucleophilic substitution forming the N–C covalent bond takes place. Phosphoric anhydride acts as a dehydrating agent and shifts the equilibrium toward amide [7].

Mechanochemical solid-phase reactions of fullerene C-60 with amines, leading to dimers and other derivatives of fullerene, are treated in [10, 11].

1.2. Fluorination of chloroaromatic compounds

In order to study the possibility of mechanochemical synthesis of fluorinated aromatic compounds by substituting chlorine by fluorine, powdered mixtures of chloroaromatic compounds: hexachlorobenzene (HCB), pentafluoropyridine (PFP), and octachloronaphthalene (OCN) and inorganic fluorides were treated in an AGO-2 planetary mill at room temperature. Alkaline metal or alkaline earth fluorides and composite mixtures based on them were used as fluorinating agents [12, 13]. The reactions proceed according to the scheme

$$ArCl_n + MeF \rightarrow ArCl_{n-m}F_m + MeCl \qquad (5)$$

where n = 5–8, $m \leq n$, Me = Li, Na, K, Rb, Cs, Ca, Sr, Ba and NH_4.

Depending on the experimental conditions and the nature of substances, the reaction products contained either partially substituted fluorochlorinated derivatives or completely fluorinated compounds. Therefore, in order to estimate the reactivity of reagents, we used the value of consumption of the starting reagent $ArCl_n$. The results of experiments are listed in Tables 2 and 3. KF was the fluorinating agent.

TABLE 2

Conversion of chloroaromatic compounds into fluorinated derivatives during treatment in an AGO-2 planetary mill depending on the initial $ArCl_n$

$ArCl_n$	Activation time, min	Conversion, %
HCB	10	Traces
	120	22.0
OCN	10	31.5
	120	75.0
PCP	10	4.4
	120	35.4

Note. HCB is hexachlorobenzene, OCN is octachloronaphthalene, and PCP is pentachloropyridine.

TABLE 3

Conversion of OCN into fluorinated derivatives depending on the mechanical treatment time in an AGO-2 planetary mill

Activation time, min	Conversion, %	Composition
10	31.5	1-2F
20	43.4	1-2F
60	70.5	1-6,8F
120	75.0	1-3F
300	1000	Tar products (~99 %)

Thus, we succeeded [12, 13] in completing for the first time solid-phase mechanochemical reactions of chlorine substitution by fluorine in aromatic compounds. In all cases we observed the products of partial substitution having a complex composition. Under the chosen conditions, OCN is the most easily fluorinated reagent, while HCB is the most difficultly fluorinated one. A similar tendency is also observed for traditional synthesis in an autoclave (see Section 2).

For the reaction of octachloronaphthalene with potassium fluoride, the effect of treatment time has been investigated (see Table 3). When the time of mechanical activation increases, higher degrees of substitution are achieved; however, under the synthesis conditions the products undergo destruction into tar products. In addition, the effects of reagent charge and background temperature have been investigated.

Then we studied the comparative activity of fluorides of different alkaline metals and alkaline earths (Table 4). The activity of these fluorides under the conditions of solid-phase mechanochemical synthesis is in agreement with the activity of fluorides under the conditions of fluorination by conventional methods. The activity of the fluorinating reagent increases from lithium to cesium and from calcium to barium, and correlates with changes in the lattice energy of fluorides in the indicated series. Only rubidium fluoride is somewhat out of this sequence.

TABLE 4

Effect of the nature of metal fluoride as a fluorinating agent on the conversion of OCN into fluorinated derivatives

Fluorinating agent	Conversion, %	Composition
NH_4F	14.0	1,3F
LiF	15.5	1-3F
NaF	16.5	1-4,8F
KF	39.5	1-5F
RbF	23.7	1-4F
CsF	57.5	1-2,3,4F
CaF_2	9.7	1,3-6,8F
SrF_2	19.7	1,2,4,5,8F
BaF_2	31.5	1-2,3,4F

Note. Molar ratio fluorinating agent : OCN = 5 : 1; mechanochemical treatment time in AGO-2 is 10 min.

Unfortunately, extremely high parameters of mechanical activation are necessary to carry out the majority of the described reactions of organic synthesis. They can be achieved only with special laboratory equipment (planetary mills with acceleration 40–60 *g* and with up to 100 g reagent samples), which mostly restricts feasibility of mechanochemical synthesis under laboratory conditions.

In conclusion of this section on mechanochemical organic synthesis, we can say that a broad range of reactions involving two or three solid reagents are possible. This is supported by the fact that these reactions occur in solution (or as heterogeneous processes involving a liquid and a solid).

However, it is difficult to formulate criteria of feasibility for solid-phase mechanochemical reactions. In particular, the application of thermodynamic calculations is hindered by poor knowledge of thermodynamic characteristics of solid organic compounds. That is why researchers are to rely mainly on the empirical approach.

2. PRELIMINARY ACTIVATION OF REAGENTS

Vigorous mechanical treatment of solids leads to increased concentrations of lattice defects and forms active centers on the surface. These factors generally increase the reactivity of solids in chemical processes.

Metal fluorides accumulate potential energy and lattice distortions during mechanical treatment. This is exhibited as broadening of reflections on powder diffraction patterns resulting from mechanical activation. If broadening of reflections is used as a measure of activity, the maximal degree of activation is achieved for CaF_2 from the series KF, NaF, CaF_2, while less activation is observed for NaF and even less for KF. Heating to 600 °C eliminates ("anneals off") the accumulated activation completely, so that the broadening observed on the diffraction patterns is also eliminated.

In this work, preliminary mechanical activation of potassium fluoride, which is the most popular fluorinating reagent, was employed for autoclave heterophase process of HCB fluorination:

$$C_6Cl_6 + KF \rightarrow C_6Cl_{6-n}F_n \quad (6)$$

where $n = 1-6$.

The results of experiments are shown in Table 5.

The parameters of mechanical activation were as follows: APF-1M planetary mill was used as an activator, acceleration 40 *g*, treatment (activation) time 20 min.

The parameters of autoclave processes were: temperature 470 °C; activation time 10 and 20 h; mass ratio of components.

The reaction mixtures were monitored by GLC (mean values are presented).

As can be seen from the data of Table 5, mechanical activation of KF accelerates fluorination and increases the yields of polyfluorinated benzenes or decreases the reaction time [14–17].

Similarly, using a mechanically activated solid disperse system HCB/KF under autoclave conditions increased the yields of products and accelerated the halogen exchange process.

3. SYNTHESIS OF SOLID SOLUTIONS

The fact that reactions between solid reagents go through to completion under the conditions of mechanical treatment indicates that the mixing may occur even at the molecular level. This is confirmed by the formation of solid solutions of chemically noninteracting low-molecular organic compounds; the most favorable conditions are provided by mechanical treatment of mixtures of solids where one of the reagents is in excess. X-ray phase analysis does not always offer an unambiguous explanation to this phenomenon, because the observed broadening and disappearance of reflections of the crystalline components can often be assigned to the formation of a solid solution or to amorphization of the substance. In addition, this method has substantial restrictions in sensitivity.

However, the formation of solid solutions may be proved by other methods. We investigated the EPR spectra of the stable iminoxyl radical 1-oxyl-4-methyl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (Scheme 7) during its mechanical treatment with carbamide in mass ratios of 1/(100–1000) (Fig. 2).

It is known [18] that the shape of the EPR spectrum is sensitive to the local concentration

TABLE 5

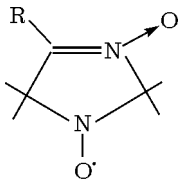
Yields of fluorinated products for different times of autoclave treatment

KF/HCB mass ratio	Mass of isolated mixture, g	Composition of the mixture, %					
		F-6	F-5	F-4	F-3	OFT	F-6 + F-5
				t = *10* h			
3/1*	50	4	25	38	–	–	29
3/1**	62	62	25	9	–	4	87
2/1**	57	49	21	2	–	14	70
				t = *20* h			
3/1*	54.6	47.2	31.0	9.9	8.7	0.4	78.2
2/1*	50.0	39.5	29.4	15.2	4.5	3.5	68.9
3/1**	50.0	63.0	26.5	–	–	2.0	89.5
2/1**	51.4	65.2	15.1	1.1	0.6	2.7	90.3

Note. F-3, F-4, F-5, and F-6 are fluorobenzenes with the corresponding number of fluorine atoms, OFT is octafluorotoluene.

* Nonactivated KF was used.

** Mechanically activated KF was used.



R = methyl (I)

Scheme 7.

of paramagnetic centers, that is, to the distance between them. Thus, a singlet with a width of 10 G is observed in the EPR spectra of the radical in the crystalline or amorphous phase. The absence of fine structure on the spectrum is due to strong spin-spin interaction between closely located paramagnetic centers. In contrast, in solid solutions obtained by fast freezing to 77 K of dilute toluene solutions of the radical, a three-component signal is observed, which is characteristic of matrix isolated radicals [8]. Changes in the EPR spectra of the radical depending on the time of mechanical treatment are shown in Fig. 2. The initial and final spectra in pure form correspond to the condensed phase of the radical and to the solid solution. In intermediate cases, spectrum superposition indicates that these solid phases coexist. These experimental results serve as a convincing proof of the possibility to obtain solid solutions by mechanical treatment of mixtures of solids.

Referring to practical importance of materials based on solid solutions, these materials may be used when the presence of one of the components in a condensed state is undesirable. For instance, release of a pharmacologically active compound from preparative dosage forms (powders, tablets, *etc.*) into solution is substantially determined by the solution rate of its crystalline phase. However, many medical substances dissolve very slowly in water, mainly due to poor wetting and high stability of the lattice. Evidently, synthesis of solid solutions of substances of this kind in a readily soluble filler will promote the dissolution process.

In order to confirm this opinion, we studied the effect of mechanical treatment of oxazepam mixtures with various fillers on the solution rate of oxazepam [19] (Fig. 3). The best results were obtained with lactose. Electron microscopy and X-ray phase analysis data suggest that solid solutions of oxazepam form in lactose. Pharmacokinetic tests of the preparation in the blood of laboratory animals (rabbits) after oral intake revealed that bioavailability of mechanically treated mixtures increased by a factor of 1.5.

To conclude this section, solid solutions of low-molecular organic compounds may be obtained by quickly cooling the solutions and melts. However, this method is inapplicable when one of the components is thermally unstable. A system of this kind is a mixture of oxazepam with lactose or cellulose because car-

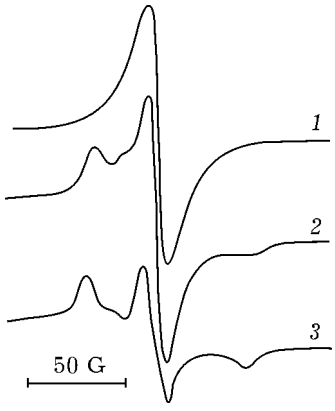


Fig. 2. EPR spectra of a 1 : 100 mixture of 1-oxyl-4-methyl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide radical with carbamide without activation (*1*), mechanically activated in an AGO-2 mill for 1 (*2*) and 3 min (*3*).

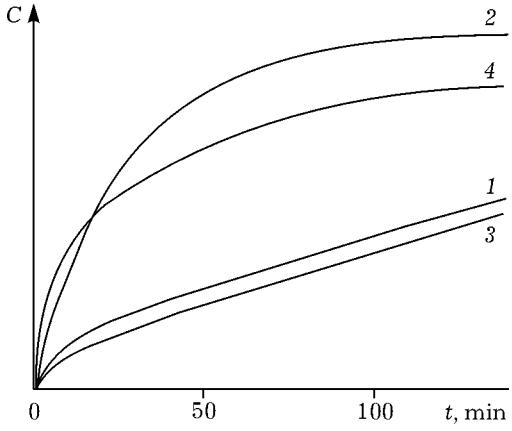
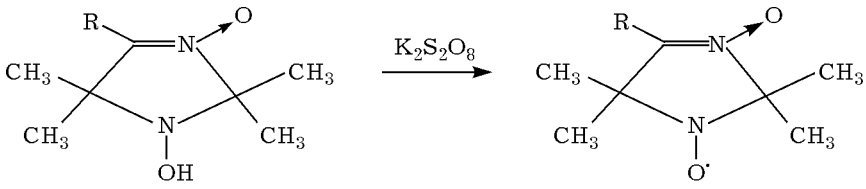


Fig. 3. Kinetic curves of dissolution for mixtures of oxazepam with lactose (mass ratio is 1 : 10) (*1*, *2*) and with microcrystalline cellulose (1 : 10) (*3*, *4*): *1*, *3* – mixtures of preliminarily ground powders; *2*, *4* – powders were preliminarily activated for 5 min in an AGO-2 mill.



R = methyl (I) or phenyl (II)

Scheme 8.

bohydrates decompose upon heating. Thus mechanochemical synthesis is the only possible route to the desired product.

4. INVESTIGATION OF REAGENT PARTICLE AGGREGATION AS A FACTOR OF REACTIVITY FOR SOLIDS

4.1. Formation of stable iminoxyl radicals

We investigated solid-phase oxidation of the diamagnetic derivatives of imidazoline oxides with potassium persulfate, resulting in the formation of free radicals [20, 21] (Scheme 8). This reaction is well investigated for solutions and is distinguished by high selectivity.

After mechanical activation of mixtures of (I) or (II) with potassium persulfate in an AGO-2 mill, an intense signal characteristic of the so-called matrix-isolated imidazoline radicals was observed in the EPR spectra of the products (Fig. 4). Note that the reaction products are likely to be distributed not over the interface between the reagents but as a solid solution in the matrix of the starting organic compound (see Section 3). The degrees of conversion of the starting compounds did not exceed several per cent; at any rate, no changes in the IR spectra or diffraction patterns have been observed.

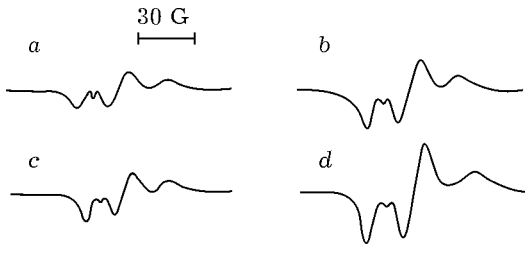


Fig. 4. EPR spectra of mechanically activated mixtures of (I) + $K_2S_2O_8$ (*a*, *b*) and (II) + $K_2S_2O_8$ (*c*, *d*): *a*, *c* – activated for 1 min, *b*, *d* – for 3 min.

The concentration of the radical products is linearly dependent on the time of mechanical activation (Fig. 5). One can see that the rates of the reactions involving (I) and (II) differ substantially (by a factor of 2.6 ± 0.5). At the same time, in the case of liquid-phase oxidation, the reaction rates almost coincide, which is actually logical for the compounds in view of the similarity of their nature.

Storage of the activated samples also led to changes in the EPR spectra, which showed that chemical interaction continued (Fig. 6). Radical (II) again exhibited higher reactivity in comparison with (I). Changes in the shape of the

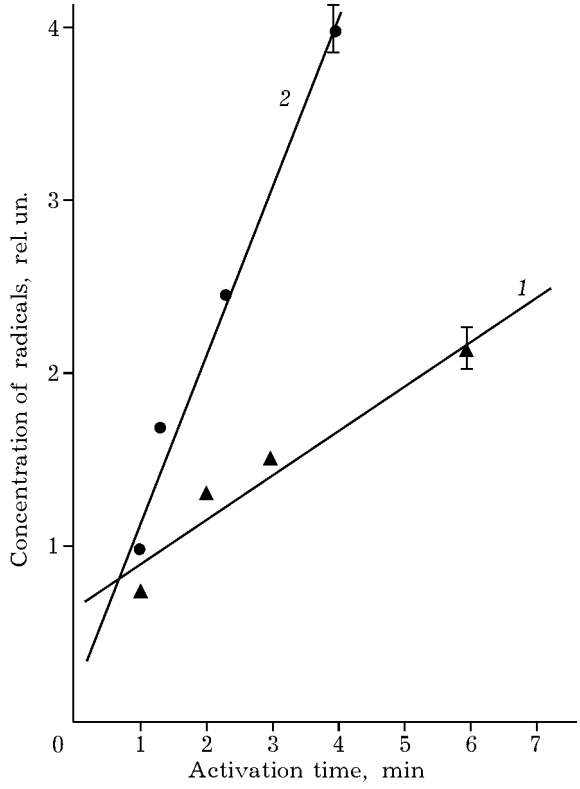


Fig. 5. Changes in the concentration of the radicals during mechanical activation of mixtures of (I) or (II) with potassium persulfate: *1* – (I) + $K_2S_2O_8$, *2* – (II) + $K_2S_2O_8$.

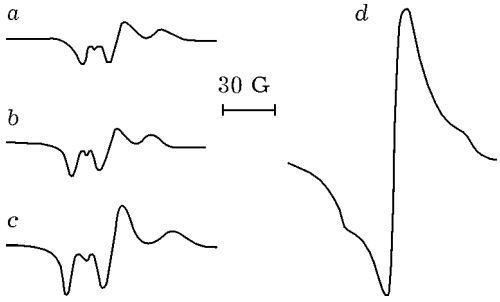


Fig. 6. EPR spectra of activated mixtures: (I) + $K_2S_2O_8$ (*a*, *b*) and (II) + $K_2S_2O_8$ (*c*, *d*): *a*, *c* – immediately after activation; *b*, *d* – after storage for 100 h at 25 °C.

EPR signal after storage mainly relate to the central component of the spectrum, which increased in intensity (Fig. 6, *d*). This observation may be explained by the fact that the radicals are separated by short distances and that their EPR spectra are subjected to exchange narrowing. Thus it is reasonable to assume that the radicals are formed in the region of direct contact between the solid reagents, the contact areas differing between the systems of (I) and (II).

Furthermore, changes in morphology of reagent particles were studied by electron scanning microscopy (Fig. 7). One can see that mechanical activation of reagent mixtures leads to aggregates of fine particles, probably of mixed composition. The degree of aggregation of (I) + $K_2S_2O_8$ is substantially lower than that for (II) + $K_2S_2O_8$. This is confirmed by specific surface measurements.

In our opinion, divergence in the aggregation ability is responsible for the differences in the reactivity of the systems. Aggregation of particles leads to a contact between the solid reagents – reaction interface. The larger the area of this contact, the higher the rate of the mechanochemical reaction. That is why the rates of mechanochemical reactions differ, in contrast to liquid-phase oxidation. At the same time, in aggregates (composites) already formed, radical formation also takes place after mechanical activation, but proceeds at a lower rate. In this case we also observe higher reactivity of (II) in comparison with (I).

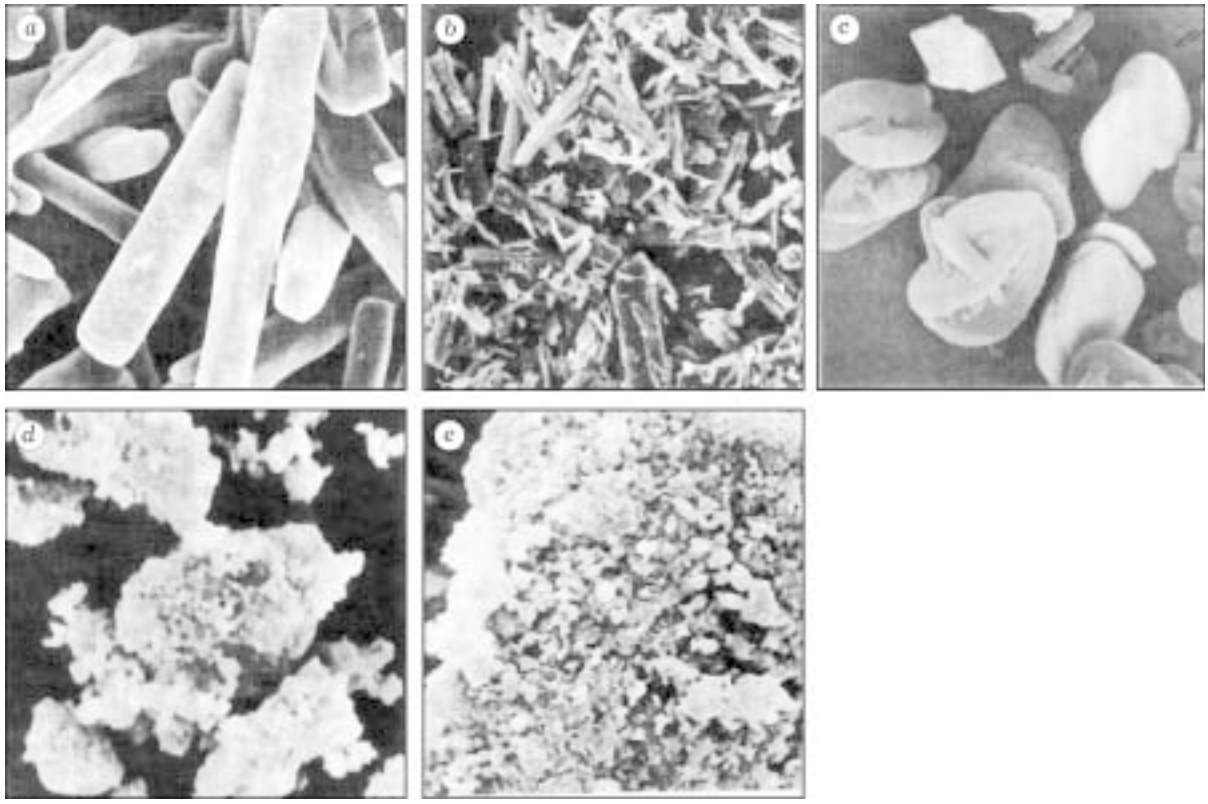


Fig. 7. Electron micrographs of initial substances and mechanically activated mixtures: *a* – (I), magnification 500; *b* – (II), magnification 500; *c* – $K_2S_2O_8$, magnification 35; *d* – (I) + $K_2S_2O_8$, magnification 2000; *e* – (II) + $K_2S_2O_8$, magnification 2000.

During mechanical activation under shock-attrition conditions, the reaction interface experiences permanent renewal. Zones of plastic deformation with increased diffusion mobility arise at contact sites under the action of mechanical loading. Due to this, the radicals are removed from the interface region and are distributed in the matrix of the starting compound. After mechanical activation, mass transfer of the radical product from the interface zone has almost ceased, and radicals appear in the zone of the solid-phase interaction.

Thus the ability of solid reagents to form aggregated composite particles under mechanical activation is an important rate-determining factor in solid-phase reactions.

4.2. Neutralization of carboxylic acids

The possibility to obtain composites involved in subsequent chemical reactions was demonstrated by studying solid-phase neutralization of solid carboxylic acids – benzoic (BA), salicylic (SA), and acetylsalicylic (ASA) – with sodium carbonate according to reaction (1). We investigated neutralization reactions induced by mechanical activation in ball mills [20]. Previously, it was noticed that the solution rate of mechanically activated but unchanged mixtures is often much higher than the solution rates of the starting substances and the products of neutralization (salts). In view of the low solubility of the starting acids, the unchanged or partially changed samples dissolve if a neutralization reaction occurs.

The starting acids are poorly soluble in water. Their readily soluble salts are formed as a result of the mechanochemical neutralization reaction. The comparative solution rates of mixtures of these acids with sodium carbonate subjected to mechanical activation under different conditions were investigated, along with physicochemical differences in the resulting substances. Two modes of mechanical activation were used: intensive (in an AGO-2 planetary mill, acceleration 60 *g*) and mild (in a VM-1 roller ball mill, acceleration 1 *g* (see Section 7)). In the first case, neutralization was complete and fast (1–2 min) according to reaction (1); in the second case, no noticeable changes were observed (Fig. 8), judging from the IR spectra and X-ray structural analysis data.

Under our experimental conditions, the concentration of saturation was not achieved; the acid residue dissolved completely in all cases. However, the solution kinetics differed. With BA, a 75 % level of solution was achieved within the same time, 20 min, for all samples. In the cases of SA and ASA, the 75 % level was achieved after 5 and 15 min for samples treated under mild and rigid conditions, respectively, and after 9 min for nontreated mix-

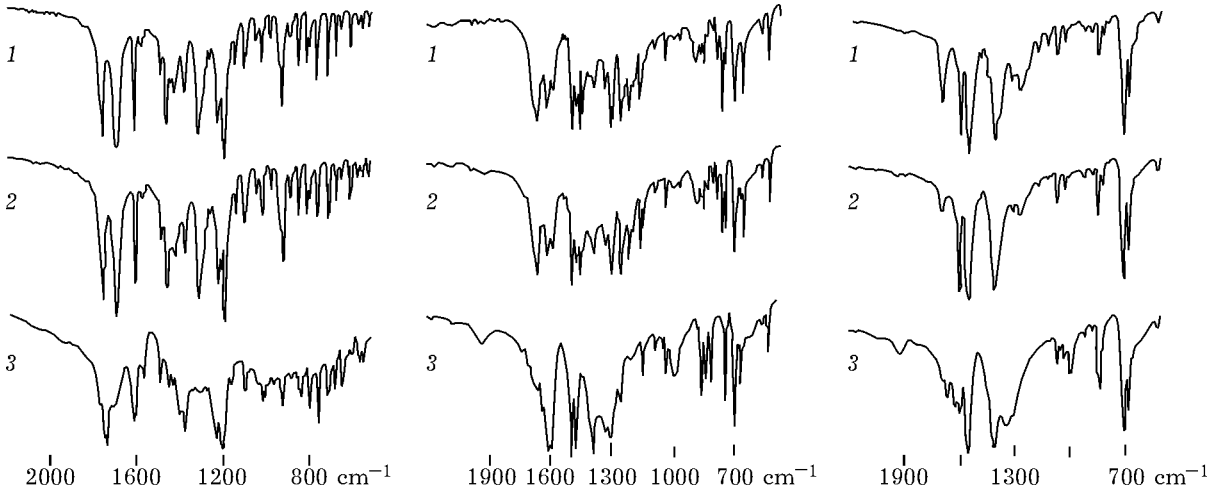


Fig. 8. IR spectra of equimolar mixtures of acetylsalicylic (*a*), salicylic (*b*), and benzoic (*c*) acids with sodium carbonate: *1* – mixtures without treatment; *2* – mixtures treated under mild conditions in a VM-1 mill; *3* – mixtures treated under rigid conditions in an AGO-2 mill.

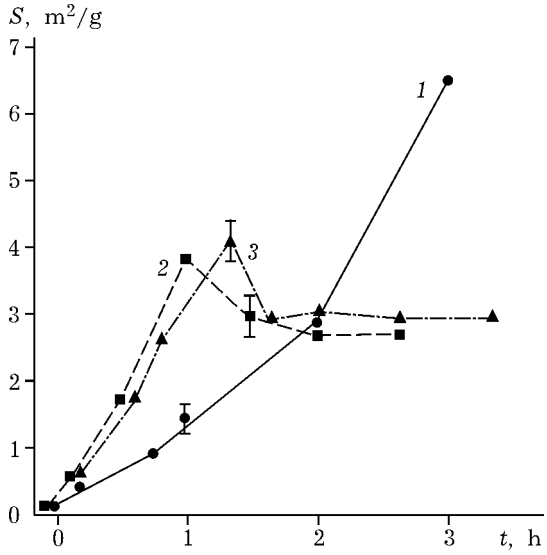


Fig. 9. Changes in the specific surface of equimolar mixtures of benzoic (*1*), salicylic (*2*), and acetylsalicylic (*3*) acids depending on the time of treatment under mild conditions in a VM-1 mill.

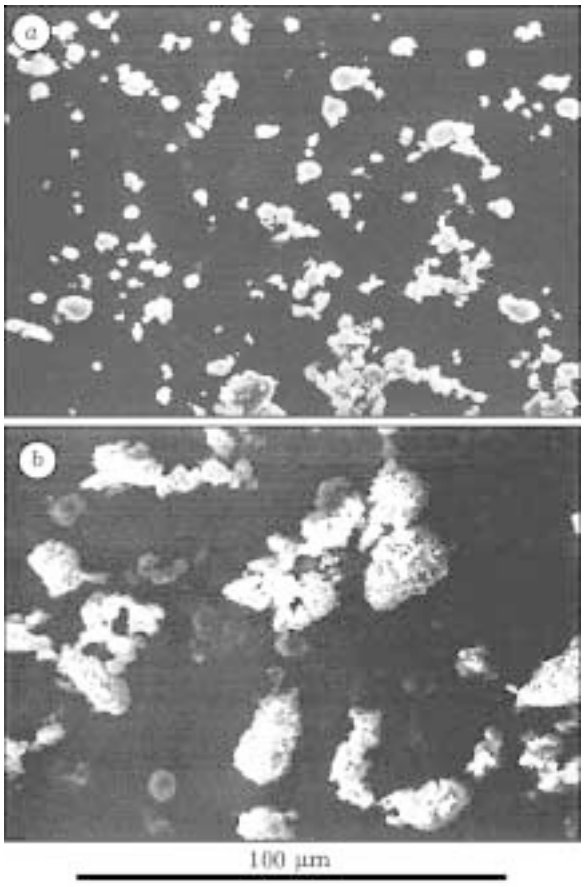


Fig. 10. Electron micrographs of equimolar mixtures of benzoic (*a*) and acetylsalicylic (*b*) acids with sodium carbonate after treatment under mild conditions in a VM-1 mill for 3 h.

tures. A qualitatively similar situation (but with increased difference in the rates) was also observed for powdered mixtures. It is interesting that weak evolution of CO_2 accompanies dissolution of the mixtures of salicylic and acetylsalicylic acids with sodium carbonate activated under mild conditions. The mechanisms of dissolution differ from each other in the investigated samples: dissolution of the formed sodium salts of carboxylic acids occurs in the samples treated under rigid conditions, while in the samples obtained by simple mixing of the components without mechanical activation, as well as in the samples activated under mild conditions, neutralization proceeds together with dissolution. For our purpose (investigating the mechanisms of activation), these cases are to be compared first of all.

The dynamics of changes in the specific surface of powdered mixtures depending on the time of mechanical activation is shown in Fig. 9; electron micrographs of the resulting powders are shown in Fig. 10. It follows from these data that the mixtures based on SA and ASA are prone to form dense aggregates of ground solid reagent particles under the mild activation conditions. In our opinion, this phenomenon is important for explaining the differences in dissolution rates. During aggregation, a contact region between the solid reagents (reaction interface) is formed; the substances partially interact in this region. However, the total fraction of the converted substance is small and independent of the method used. In the case of hydration of the material, water diffusion is most likely to occur along the contacts between the phases, thus initiating further neutralization reaction. During this process, local deviations from the general stoichiometry of reaction (1) can take place, which lead to the evolution of carbon dioxide:

$$2RCOOH + Na_2CO_3 \rightarrow 2RCOONa + H_2O + CO_2 \quad (7)$$

This process, in turn, leads to loosening and decomposition of the aggregates into ultrafine, rapidly dissolving reagent particles (Scheme 9).

In the case of powdered systems of reagents not inclined to form composite aggregates, the effective surface of the organic material

Aggregate of particles → Hydration Disaggregation → Ultrafine reagent particles → Fast dissolution → Solution

Scheme 9.

interacting with water is likely to be smaller, which decreases the dissolution rate.

Unfortunately, due to the limitations of the methods in the case of organic compounds, traditional electron microscopy methods allow one only to record aggregate formation in mechanically activated systems and to estimate their dimensions. However, the most interesting questions from the viewpoint of solid state chemistry, namely, contact sites between solids, internal structure of aggregates, mutual arrangement of particles, and phase states remained uninvestigated. In order to study these issues, we used cryofractography by recording a replica obtained in high vacuum from the break surface of a frozen sample. Using this method we investigated structural changes during mechanochemical solid-phase neutralization of acetylsalicylic acid [22].

For comparison, two processes were investigated: interaction of ASA with sodium carbonate (A), resulting in the formation of sodium acetylsalicylate, and mechanical activation of acetylsalicylic acid with calcium carbonate (B), which also produces the effect of increased solution rate, but does not cause neutralization and salt formation. The reacting mixture was investigated in the mild mode, with different activation times until the reaction was complete. The main part of the section area of the samples during the initial period of activation (Fig. 11) is occupied by oblong crystals of acetylsalicylic acid about 1 mm in size. In addition, smaller crystals (about 200 nm in size) and other microcrystals are present, and they probably belong to the sodium or calcium carbonate phases. Thus analysis of micrographs has revealed a composite nature of the aggregates.

Increased activation time does not cause (until a definite moment) any qualitative changes in chip morphology. The density of aggregates increases, while the size of ASA crystals decreases. The state of dense aggregates corresponds to the peak of solubility of the powders for both systems. When the activation time

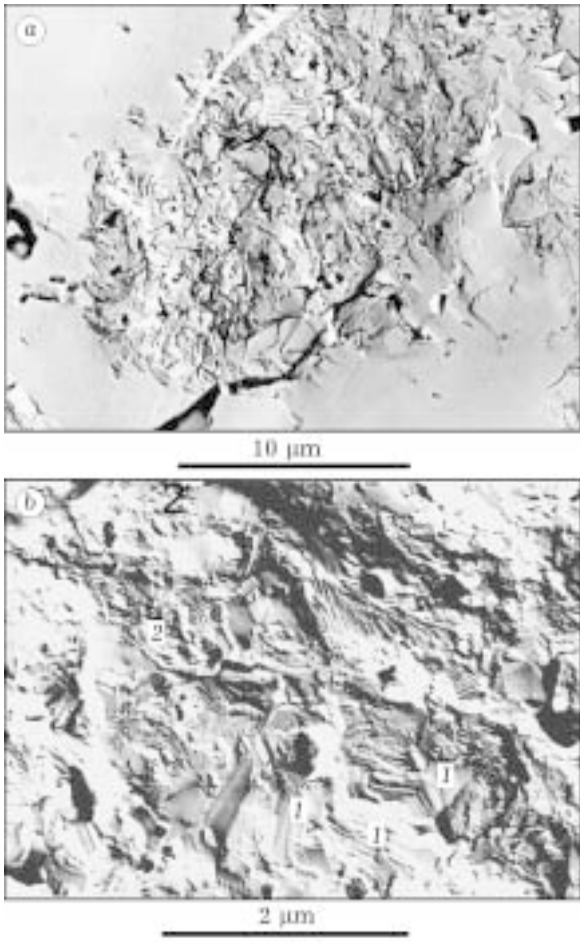


Fig. 11. Electron micrograph of a chip of an aggregate of powder particles of a mechanically activated mixture of sodium carbonate and acetylsalicylic acid. Photo *b*: microcrystals of acetylsalicylic acid (*1*), chip of the microphase (*2*).

exceeds 12 h, the structure of system A becomes very different from the structure of system B. In the first case, sodium acetylsalicylate is formed. A chip of the powder particles after the formation of the sodium salt (treatment for 24 h) is shown in Fig. 12. Judging from their uniform shape and small scatter of size, the crystals grew from several crystallization centres simultaneously. In the calcite system, no reaction of this type proceeds.

Thus, cryofractography in a matrix allows one to investigate complex organic powders,

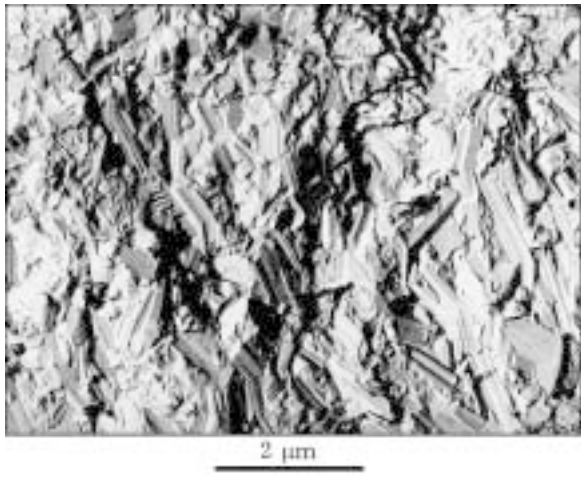


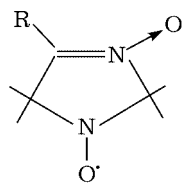
Fig. 12. Electron micrograph of a chip of powder particles of a mechanically activated mixture of sodium carbonate and acetylsalicylic acid after neutralization.

their extent of aggregation, and the internal structure of the aggregates.

5. MODIFICATION OF NATURAL POLYMERS

The application of mechanochemical solid-phase technology is reasonable in the case of insoluble natural polymers, first of all plant cellulose and lignocarbohydrate materials of raw wood (for example, see [23, 24]).

In our opinion, it is promising to use shock-attrition activator mills to modify the above-indicated materials (distinguished by low plasticity) by binding them with low-molecular organic compounds through intermolecular interactions or through formation of covalent bonds. We investigated the possibility of using the mechanochemical solid-phase reaction to introduce into cellulose spin labels – stable imidazoline nitroxides 1-oxyl-4R-2,2,5,5-tetramethyl-3-imidazoline-3-oxides:



(8)

R = –CH_3 (I), –COOH(III), –CH_2Br (IV)

Our goal was not only to obtain spin-labeled cellulose samples, but also (taking into account the high sensitivity of the EPR technique) to carry out quantitative estimation of the possibility of solid-phase mechanochemical grafting of low-molecular organic residues to cellulose [25].

To solve this problem, we used the following.

1. Joint mechanical treatment of microcrystalline cellulose (MCC) and radical (I) for the purpose of intercalation or adsorption of the latter by cellulose and its retention due to intermolecular interactions.

2. Joint mechanical treatment of MCC and radical (III) in order to obtain an ester bond between the carboxyl group of the radical and the hydroxyl groups of cellulose.

3. Joint mechanical treatment of MCC and radical (IV) in the presence of sodium hydroxide in order to obtain an ether bond between the methylene group of the radical and the hydroxyl groups of cellulose.

Mechanical treatment was carried out in an AGO-2 planetary ball mill (see Section 7).

After mechanical treatment, the material was washed sequentially with three portions of water, acetone, and isopropyl alcohol. The number of washing steps was determined when a constant EPR spectrum was achieved.

Figure 13 shows the EPR spectra of the initial powdered radical (III), its mixture with MCC after mechanical treatment, and the washed samples. The EPR spectra of the analogous samples of radicals (I) and (IV) are qualitatively similar and differ from each other mainly in signal intensity.

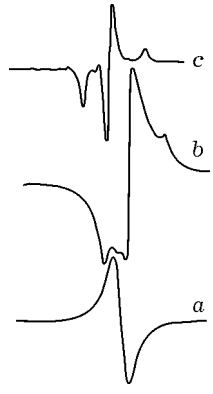


Fig. 13. EPR spectra of radical (III) (*a*), mechanically activated mixture of (III) and cellulose (*b*), the same mixture washed with water, acetone, and isopropyl alcohol (*c*).

In all cases, the EPR spectra of the initial powdered radicals are singlets 10 G wide, arising from exchange interactions between neighboring spins in crystal. At the same time, in mechanically treated washed cellulose samples, we observed only the EPR spectrum characteristic of the so-called matrix-isolated, chaotically oriented nitroxides [8, 18].

The concentration of paramagnetic centres in the washed samples was calculated by means of double integration of the spectra with respect to the standard sample; it was $7\ 10^{18}$, $1.4\ 10^{21}$, and $3.5\ 10^{20}$ spin/g in cases 1, 2, and 3, respectively. The lowest concentration was obtained for radical (I); after further washing with solvents, it decreased even more. The highest concentration of the grafted spin label was achieved under conditions that favor covalent bonding between the stable radical and cellulose (radicals (III) and (IV)). After further washings, the EPR signal did not decrease. It also remained unchanged after storage for 1 year in air at room temperature.

Simple calculation shows that in case 2 (radical (III)) the number of tightly bonded paramagnetic centers approximately corresponds to the number of monomer links in the cellulose chain molecule, that is, a spin label is attached approximately to each link. In case 3 (radical (IV)), the degree of modification is smaller. In all cases under consideration, the shape of the EPR spectrum is evidence of the uniform distribution of the grafted paramagnetic centers in the chain macromolecules of cellulose.

Evidently, the introduction of bulky substituents should distort the system of hydrogen bonds of hydroxyl groups in cellulose. Indeed, the corresponding changes are observed in the IR spectra in frequency regions related to the stretching vibrations of hydroxyl groups at 3000–3900 cm^{-1}. The minimum of the band is shifted toward higher frequencies; the contour of the band changes. According to estimations using the method of [26], mechanochemical interaction of cellulose with radical (I) does not lead to noticeable distortion of the system of hydrogen bonds; at the same time, when the tightly bonded substituent radical (III) is introduced, the hydroxyls involved in the strong hydrogen bond decrease in number.

Comparison of the diffraction patterns of the initial MCC with the patterns of the mechanically treated samples indicated that partial amorphization of cellulose occurs during mechanical treatment. Moreover, the unwashed samples have residues of the crystalline phase of the starting radicals, which agrees with previous observations of the EPR spectra. It can be seen that mechanical treatment of cellulose with radical (I), which does not interact chemically with MCC, decreases the degree of cellulose crystallinity. However, the largest changes in the structure of cellulose (amounting to almost complete amorphization) take place in the case of tightly bonded spin labels.

Thus the results obtained indicate that mechanochemical processes of cellulose modification are quite effective and may be used to obtain new cellulose-based materials.

6. SYNTHESIS OF REACTIVE COMPOSITE MATERIALS AS SUBSTRATES FOR FAST-DISSOLVING DRUGS

6.1. How to increase the solubility of drugs

As mentioned above, for mechanochemical reactions of organic compounds it is reasonable to use activator mills of high intensity. Small amounts of charged materials in this case limit the application of these processes to the laboratory level.

However, at the intermediate stage, mechanochemical reactions form composite systems of solid reagents. These composite materials, which are solid disperse systems of substances (reagents), possess increased reactivity (see Section 4). They are ready for chemical interaction, which can easily be launched and carried out to completion using relatively weak (not mechanical) types of treatment, for example, hydration or heating. Thus in definite situations, instead of the final products of chemical interaction, one can use mechanochemically obtained composites. In this case, milder conditions of mechanical treatment may be employed, for example, activator mills of low energy; combining the latter with vibrocentrifugal flow mills one can expect rather high productivity with respect to the yield of the treated material.

Synthesis of fast-dissolving materials based on solid organic acids and bases seems to be one of the promising directions of research. This is a hot topic in pharmaceutical and food industries. Many pharmaceutical and biologically active substances are characterized by low solubility in water. At the same time, they possess acidic or basic properties. These products are often manufactured in the form of salts. Thus pharmaceuticals with basic properties are produced as hydrochlorides, while organic acids are manufactured as salts of metals or organic bases. The salts are obtained by liquid-phase neutralization followed by isolation (drying) of the product. This requires great amounts of solvents, complex equipment, and large working areas. Moreover, the target product can decompose during drying.

One of the most popular pharmaceuticals is acetylsalicylic acid, or aspirin. Its low (0.2–0.3 %) solubility in water decreases its pharmacological efficiency and causes undesirable side effects when the substance is used in drugs. The salts of ASA with alkaline or alkaline earth metals synthesized in the early 20th century possess increased (~100 times higher) solubility. Pharmacological tests revealed evident advantages of these forms over the initial ASA. Due to the increased solubility and dissolution rate of these substances, the drugs quickly appear in maximal concentrations in blood; *i. e.*, their action is accelerated. Higher concentrations enhance the pharmacological effect. The undesirable effect of stomach irritation (ulcerogenic effect) is decreased [27].

However, with all advantages of ASA used in the form of salts, these are expensive drugs manufactured on a small scale. All of the existing technological processes forming salts are carried out in aqueous or water-alcohol phases and are followed by drying of the product. During these procedures, ASA undergoes partial decomposition into salicylic and acetic acids as a result of hydrolysis:

$$C_6H_4(OCOCH_3)COOH + H_2O \rightarrow C_6H_4(OH)COOH + CH_3COOH \quad (9)$$

The existing requirements to the purity of the product make the production process more complex and the product more expensive.

Alternative forms are so-called effervescent pharmaceuticals. The salt formation effect is achieved during the dissolution of tablets or granules containing the ASA substance and relatively large amounts of neutralizing fillers – sodium bicarbonate or carbonate (for example, see [28]). In addition to the indicated components, these compositions should always include a solid water-soluble organic acid (citric, malic, or ascorbic) to accelerate the destruction of a tablet or granule due to the evolution of carbon dioxide during the interaction with carbonates and bicarbonates. However, the presence of an acid of this kind requires that the composition should incorporate neutralizing agents in substantial excess over the amount necessary to neutralize pure ASA. A typical disadvantage of the preparations is low mass fraction of ASA: 10–16 % for the above examples, the total mass of the tablet being 3–3.5 g. It is impossible to swallow such a tablet; it should be preliminarily dissolved in a large amount of water. In addition, auxiliary substances are undesirable for intake by patients with respect to some characteristics, for example, sodium content; increased material capacity causes an increase in the net cost of the pharmaceutical form.

6.2. Development of fast-dissolving drugs based on acetylsalicylic acid

Based on our experience we made an attempt to apply the mechanochemical approach to obtain soluble materials based on ASA for the purpose of their subsequent use as drugs.

Section 4.2 described efforts aimed at obtaining composite materials based on sodium carbonate and a series of solid organic acids including ASA. The results were adopted as a basis for developing fast-dissolving composite materials – solid disperse systems of ASA with a series of metal carbonates. We rejected metal bicarbonates, since preliminary experiments demonstrated chemical instability of their mixtures with ASA.

In order to obtain fast-dissolving solid disperse systems based on ASA, we used anhydrous lithium, sodium, potassium, calcium, and magnesium carbonates. The stoichiometric

ratio was chosen such that it could provide complete neutralization during hydration, forming colorless solutions.

For nonactivated mixtures, the components pass into solution at different rates: (alkaline metal) carbonates are the first to dissolve, and then acetylsalicylic acid passes into the resulting solution. In the case of insoluble magnesium and calcium carbonates, a reverse sequence takes place. The total time of dissolution is from several dozen minutes to several hours and depends on the mixing rate. The composite powders obtained by mechanical activation dissolve in water very rapidly (within a few seconds) with slight gas evolution; carbonates and ASA pass into solution simultaneously.

Based on the results of our investigation, we decided to develop first of all a fast-dissolving acetylsalicylic acid drug with a mass ratio of ASA/Na_2CO_3 = 64.0/36.0 %.

The effervescent tablets "Aspirin + C" manufactured by the Bayer company (Germany) were chosen as a reference drug of soluble aspirin with identical characteristics. Our preparation and "Aspirin + C" had identical dosages of acetylsalicylic acid, but differed in the production process and in the auxiliary substances.

Our next task was to develop a pharmaceutical dosage form – tablets, whose characteristics allow one to realize the potential advantages of mechanochemical technology. As mentioned above, large amounts of auxiliary substances is the main disadvantage of the existing fast-dissolving aspirin tablets. In our case, these substances amount to only 36 %. This means that with a therapeutic dosage of ASA of 0.400 g, the total mass of the pellet will be only 0.64 g. These tablets are quite suitable for intake by swallowing. Since the rate of absorption in stomach is about 0.25 h^{-1}, it is desirable that the time of complete dissolution in stomach be no longer than 15 min. In this case, from pharmacological viewpoint, swallowing a pellet will be equivalent to intake in solution. At the same time, it is necessary not only to attain the maximal possible rate of pellet dissolution, but also to provide the possibility of taking medicine in the form of a solution after preliminary dissolution of the pellet. These two requirements are met when dissolution time is 2–5 min.

The pressing force factor produces the greatest effect on the dissolution rate of tablets prepared from ASA/metal carbonate solid disperse systems. Experiments revealed that this value should be within $(3.0–7.5) \cdot 10^7$ N/m^2. If the pressure is less than $3.0\ 10^7$ N/m^2, the tablets do not possess the required strength; when the pressure is higher than $7.5\ 10^7$ N/m^2, they dissolve in more than 5 min.

The criteria of application efficiency of soluble ASA tablets developed by us were the pharmacokinetic characteristics and bioavailability of the preparation for two methods of intake: as a solution of a tablet and as a tablet used without preliminary dissolution, determined on laboratory animals (rabbits). For this purpose, we carried out standard measurements of the concentration dynamics of the main metabolite of aspirin, that is, salicylic acid, in blood (Table 6). One can see that, within the experimental error, the pharmacokinetic char-

TABLE 6

Pharmacokinetic characteristics of the soluble ASA tablets developed at the ISSC&M and tablets of "Aspirin + C" preparation (Germany)

Preparation, method of intake*	C_{max}, μg/ml	T_{max}, h	AUC, rel. un.	Rate of absorption, h^{-1}
Aspirin + C (Bayer, Germany), solution of tablets	397.0±25	0.58±0.08	1714.7±258	0.25±0.04
ASA (ISSC&M), solution of tablets	429.5±31	0.5±0.1	1869.5±267	0.26±0.031
The same, tablets	417.5±29	0.7±0.1	1852.8±268	0.25±0.03

Note. C_{max} is the maximal concentration in blood; T_{max} is the time of maximal concentration in blood; AUC (bioavailability) is the area under the pharmacokinetic curve.

*Samples of preparations were taken in equivalent concentrations with respect to the active substance.

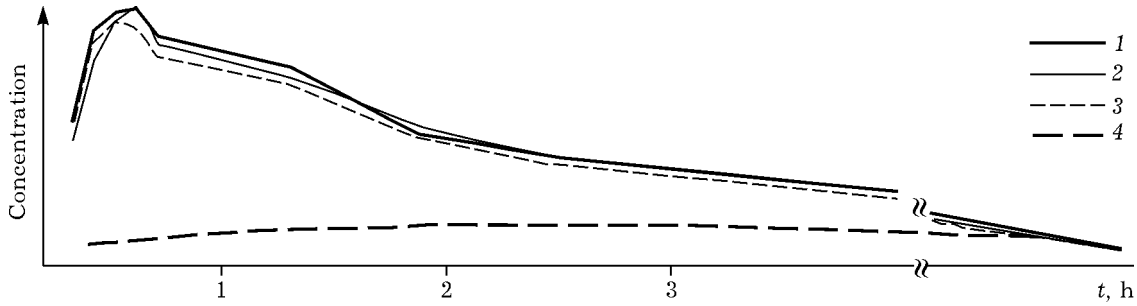


Fig. 14. Dynamics of changes in the concentration of salicylic acid (ASA metabolite) in the blood of laboratory animals (rabbits) after oral intake of a solution of "Aspirin + C" tablets (*1*), solution of tablets of the preparation developed at the ISSC&M, SB RAS (*2*), tablets of the developed preparation without preliminary dissolution (*3*), and standard (insoluble) tablets (*4*).

acteristics of these preparations and methods of intake do not differ. Thus the two methods of intake of the developed tablets of soluble aspirin are biologically equivalent. Pharmacological tests showed that the developed drugs and the reference preparation are similar in pharmacological activity. Figure 14 shows the dynamics of changes in the concentration of salicylic acid (ASA metabolite) in the blood of laboratory animals (rabbits) after oral intake of a solution of "Aspirin + C" tablets (*1*), solution of the tablets of our preparation (*2*), and tablets of our preparation without preliminary dissolution (*3*). Two RF patents were obtained on the basis of the results of this investigation [29, 30].

Studies of other pharmacological parameters also indicated that the preparations are similar in pharmacological activity. However, the advantages of our preparation are small mass of the tablet and the possibility of intake by swallowing. Table 7 compares the characteristics of the most frequently used soluble aspirin tablets.

The advantages of our tablets are listed below:

– the total mass of the tablet decreased by a factor of 5;

– auxiliary substances decreased in number;

– gas evolution during dissolution is reduced;

– the possibility of intake both after preliminary dissolution of the preparation and by swallowing the tablet washing down with water is achieved; for foreign analogs, it is impossible to swallow a tablet because of its large size and substantial gas evolution;

– net cost of the preparation decreased.

The disadvantages include the lower rate of dissolution in cold water (10–25 °C).

TABLE 7

Comparative characteristics of the soluble ASA tablets developed at the ISSC&M and their foreign analogs

Characteristics	Developed at ISSC&M	Aspirin + C (BAYER)	UPSARIN (UPSA)
Diameter, mm	12	27	23
Height, mm	4.7	4.0	5.5
Mass, g	0.64	3.3	3.5
ASA content, g	0.40	0.40	0.33
Relative ASA content, %	62.5	12.1	9.4
Time of complete dissolution in 100 ml of water, min:			
at 25 °C	4–6	2–3	1–2
at 35 °C	1–3	1	0.5–1
Volume of CO_2 evolved during dissolution, ml:			
in water	6.5	75	100
in 0.1 M HCl	25	<200	<200

TABLE 8

Promising drugs based on fast-dissolving substances obtained mechanochemically

Fast-dissolving substance	Dosage form	ASA dose, g	Development
63 mass % ASA/37 mass % Na_2CO_3	Fast-dissolving tablets	0.4	Preparation registered in RF
	Fast-dissolving granules or powder	0.5	TPA (temporal pharmacopoeial article) for the substance is available
78 mass % ASA/22 mass % $CaCO_3$	Soluble tablets	0.5	Pharmacopoeial article project for the substance and tablets, preclinical tests
		0.1	The same
64.0 mass % AK/64 mass % $CaCO_3$	Fast-dissolving tablets	–	Laboratory samples, analytical procedures
62.6 mass % AA/15.6 mass % AA/ 21.9 mass % $CaCO_3$	» »	0.4	The same

Note. ASA is acetylsalicylic acid, AA is ascorbic acid.

The preparation has successfully passed preclinical and clinical pharmacological tests and was registered for medical application [31, 32].

Thus our principle of obtaining fast-dissolving acidic and basic disperse systems was used to manufacture pilot samples of fast-dissolving drugs, which differed from the existing ones in fewer auxiliary substances and improved consumer characteristics (Table 8). The obtained fast-dissolving substances can be used in compositions with other pharmaceutical or biologically active substances [33, 34].

7. CHOOSING THE DESIGN OF ACTIVATOR AND SCALING MECHANOCHEMICAL TECHNOLOGY

When choosing equipment for mechanical activation, it is first of all necessary to decide which kind of mechanical action is required in the given case; this, in turn, depends on the physicochemical character of the process. In our case, for multicomponent systems, it is desirable to provide the maximal possible contact between the solid particles of reagents and constant renewal of contact to prevent reaction products from inhibiting further interaction. These requirements are met by combining pressure with shear deformations. Then devices with a continuous or pulse method of creating mechanical load can be used, which depends on the physicomechanical characteristics of the materials. For example, for plastic materials such as polymers, it is convenient to use the first version, realized in extruders. In systems with low-molecular organic compounds distinguished by low plasticity, it is preferable to use the pulse method effectively realized in ball, planetary, vibratory mills, attritors, etc. These devices provide the so-called constrained shock action. The powdered reaction mixture is subjected to periodic action of pressure and shear during collisions of milling bodies with each other or with the walls.

An extremely important problem from the viewpoint of both research and applications is the choice of the design and operation modes of activator mills. The design is actually determined by the type of product to be obtained. In laboratory conditions, it is convenient to use standard ball mills (for example, of VM-1 type) in order to obtain aggregate systems. Referring to the example described in Section 4.2, fast-dissolving disperse systems of carboxylic acids and metal carbonates are formed after 1–10 h of treatment. In order to carry out chemical reactions and obtain solid solutions, more vigorous action is required, which is achieved in planetary and vibratory mills and in attritors. Depending on the design of a device, its operation mode, the amount of charged material,

and milling bodies, the reaction time is from several minutes to several hours. Even with the use of one-type mills, one can vary the parameters (acceleration, samples, milling bodies, substances, *etc.*) within wide limits, strongly changing the activation process. For researchers working in this field, the most important challenges are reproducibility of results with other activator mills and the possibility of scaling the results.

Unfortunately, in spite of numerous attempts to construct mathematical models of mechanical activation and carry out calculations of mills, specialists often have to resort to the empirical approach. This is especially true for processes in multicomponent systems. In this situation, in order to compare mills of different types and their operation modes, it seems reasonable to use a definite chemical system as an indicator and to measure the parameters of physicochemical changes during mechanical activation.

The formation of stable nitroxide investigated previously (see Scheme 4, PbO_2 as an oxidant) was chosen as an indicating system [21, 35].

The amount of the radical is easily measurable by EPR. The signal is stable and does not change with time. The high sensitivity of the method allows one to measure mass concentrations of the product to 10^{-2}–10^{-3} %; that is, the dynamic range of sensitivity reaches

TABLE 9

Results of comparative tests for different activator mills

Types of mills, drums, milling bodies loaded	Charged material	Efficiency, rel. un.
AGO-2 planetary mill, acceleration 60 *g*, 60 cm^3 steel drums, inner diameter 4.6 cm, steel balls loaded: *d* = 0.6 cm, mass 75 g	Reagents* – 0.3 g; total – 3 g	1.0
APF-1 planetary mill, acceleration 60 *g*, 600 cm^3 steel drums, inner diameter 8.3 cm, steel balls loaded: *d* = 1.0 cm, mass 1 kg	Reagents* – 5 g; total – 50 g	1.6
The same	Reagents* – 10 g; total – 100 g	0.29
The same, inner diameter 9.5 cm	Reagents* – 5 g; total – 50 g	0.74
Attritor, rotation frequency 850 min^{-1}, vessel volume 500 cm^{-1}, steel balls loaded: *d* = 1.0 cm, mass 500 g	The same	0.22
IE-102/I vibratory mill (Hungary), rotation frequency 231 min^{-1}, amplitude 0.5 cm, 1000 cm^3 steel drum, steel balls loaded: *d* = 0.8 cm, mass 2 kg	»	0.023
Differential planetary vibratory mill, acceleration 25 *g*, 6 cm^3 steel drums, inner diameter 2.7 cm, steel cylindrical milling body *d* = 1.75 cm	Reagents* – 0.02 g; total – 0.2 g	0.23
The same, ceramic cylindrical milling body *d* = 1.75 cm	Reagents* – 0.02 g; total – 0.2 g	0.10
VM-1 roller mill, 3 l porcelain drum, inner diameter 16 cm, rotation frequency 90 min^{-1}, ZrO_2 balls: *d* = 4.0 cm, mass 1.5 kg	Nitroxide – 5 g, PbO_2 – 100 g, NaF – 1400 g	0.005
MShK-50 ball mill, 50 l porcelain drum, inner diameter 44 cm, rotation frequency 45 min^{-1}, ZrO_2 balls: *d* = 4.0 cm, mass 71 kg	Nitroxide – 10 g, PbO_2 – 1 kg, SiO_2 – 14 kg	0.003

*An equimolar ratio of components (nitroxide and PbO_2) was used; the mixture was diluted with naphthalene by a factor of 10.

10^4. The system is extremely sensitive to mechanical loading: the EPR signal appears even when the mixture of reagents is hand shaken in a test tube. Scaling to larger quantities of the material is achieved by diluting the reagents by a factor of 10–1000 with powders that are neutral for the given reaction: quartz, sodium fluoride, naphthalene.

The slope of the initial linear region of the radical formation kinetics is accepted as a criterion of efficiency for the mechanical activator. As a first approximation, it is accepted that this slope can serve as a characteristic of the rate of the mechanochemical reaction.

Table 9 shows the results of comparative tests for different kinds of activator mills using the formation of stable nitroxides as indicating reactions. The unit is taken to be the efficiency of an activator (AGO-2 planetary mill) with fixed charges and rates. This was previously used as the standard mode for mechanochemical organic syntheses (see Section 1).

According to the data obtained, AGO-2 and APF-1 planetary mills provide the highest rates of mechanochemical reactions. The attritor is inferior to these types of mill. The widespread ball mills VM-1 and MShK are least suitable for mechanochemical syntheses. The difference in the intensity of mechanical action in these devices is two or three orders of magnitude.

On the other hand, as we have learned from Section 4, ball mills allow one to obtain solid disperse systems of reagents – composite aggregates.

The types of mills listed in Table 9 operate in a discrete charging mode and allow one to process amounts from several grams to several kilograms. Flow-through mills are convenient for treating larger amounts of material. At the ISSC&M, special vibrocentrifugal mills have been designed [5]; their productivity is from 10 kg/h to 1 t/h. Intensification of the mechanical treatment process is achieved by the circular motion of the axis of a horizontal cylindrical drum filled with the material and with milling bodies. The frequency of the circular motion may be adjusted in order to vary the intensity of treatment. In the most intense mode, centrifugal acceleration acting on the milling bodies reaches 40 *g*. The amount of charged material is adjusted according to the rate of its supply into the drum. In order to obtain especially pure products (for example, for pharmaceutical purposes), the inner surface of the drum and the surface of milling bodies can be coated with an inert material. Thus due to their flexible operation modes, activator mills may be used to prepare a wide spectrum of mechanochemical products, from aggregate multicomponent systems to solid solutions and the products of solid-phase chemical reactions.

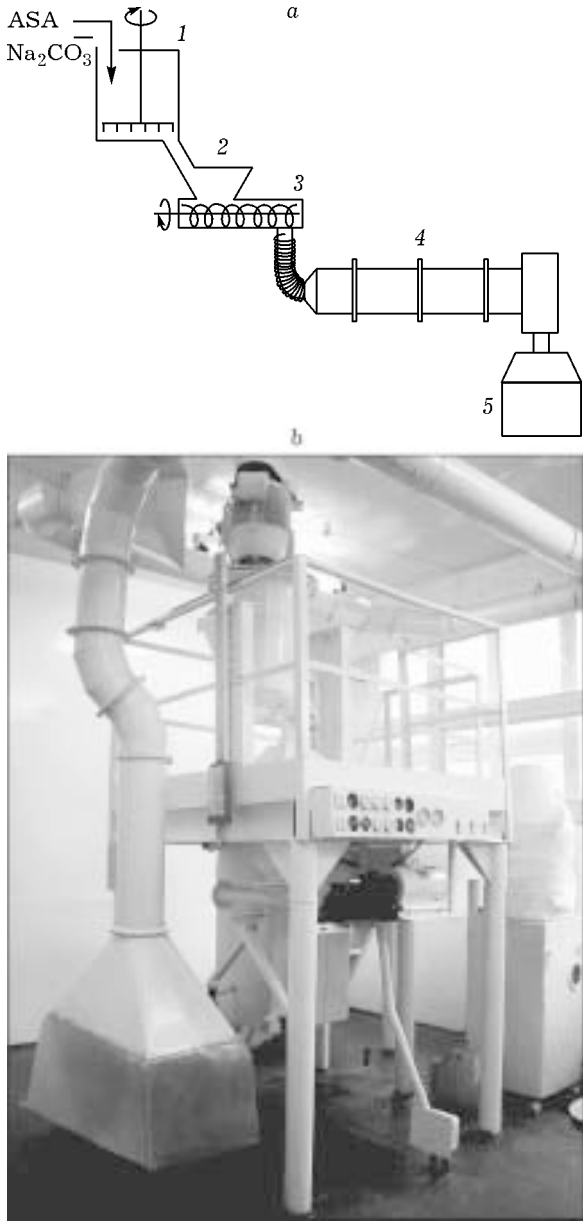


Fig. 15. Schematic diagram (*a*) and photograph (*b*) of a mechanical activation set-up for the production of fast-dissolving substances of acetylsalicylic acid.

The laboratory technology for the preparation of fast-dissolving ASA substance

was scaled to vibrocentrifugal flow mills. Based on these works, a mechanical activation line has been designed and manufactured, which included turbo mixer *1*, accumulating tank *2*, feeding screw *3*, upgraded vibrocentrifugal mill VTsM-1M *4* later replaced by VTsM-10, and product collector *5*. All parts of equipment that come in contact with the treated material are made of stainless steel. The inner volumes are sealed and can be filled with an inert gas or dried air. The design allows smooth variations of the feeder productivity and mill rate. The diagram and general view of the line are shown in Fig. 15, *a*, *b*. Technological regulations for the production of fast-dissolving substance "Askopirin" (former "Aspinat") have been developed and coordinated with head departments of the Ministry of Health, Russian Federation. The production was organized at specially equipped premises of the CJSC Novits.

8. CONCLUSIONS

Thus possible applications of mechanochemical technologies have been formulated.

1. One-stage reactions between solids.

2. Preparation of solid disperse systems (aggregates) of chemically interacting solids, solid solutions, and solid phases of reagents possessing increased activity in subsequent chemical transformations.

3. Modification of natural polymers.

The advantages of mechanochemical technology are as follows:

1. One-stage process (mechanical treatment of powdered materials).

2. Elimination of technological operations involving solvents.

3. Simplification of the design and increased productivity of production equipment in comparison with liquid-phase processes.

4. Reduced total time necessary to manufacture the product.

Comparative tests of activator mills have been carried out, recommendations for their application depending on the type of the resulting products have been elaborated, and ways of scaling some mechanochemical processes to vibrocentrifugal flow mills have been developed. An original fast-dissolving drug of acetylsalicylic acid and its production process have been developed.

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