Mechanochemical solid acid/base reactions for obtaining biologically active preparations and extracting plant materials

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ABSTRACT
Mechanochemically assisted extraction involves the mechanical treatment of powder mixtures of plant materials and convenient reagents in special mill-activators to solubilize the biologically active substances. The reactions of the solid hydroxides, carbonates, and hydrocarbonates of alkali metals are the subject of this paper. During mechanochemical treatment, insoluble biologically active substances are transformed into water-soluble or highly reactive mechanocomposites. The types of reagents used depend on the chemical nature of the biologically active substance and the possible chemical reactions between the substance and reagents. Solid-state mechanochemical reactions between active acids and solid bases and between biogenic amines and acids and the formation of soluble complexes of biologically active substances with water-soluble and insoluble polymers were explored in this study. The advantages of using these reactions in mechanochemically assisted extraction are presented in this review.

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1. Introduction
The aims of the present review are to analyze the physicochemical bases of biologically active preparations produced from plant materials and to discuss the recent achievements in mechanochemical technology toward producing these biologically active preparations. We present information relating to the biology of plant raw materials, destruction of composite plant materials under the action of mechanical treatment, and mechanochemical processes assisted by the components of plant tissues. The chemistry discussed in this review is focused on the mechanochemical use of acid–base reactions as well as on the effects of the cellulose-containing components of plant raw materials on mechanochemical processes. The ultimate goal of the studies in this area is to increase in the yield of biologically active substances from plant raw materials and to develop phytopreparations with both a high content and high rate of dissolution of the biologically active substances.
2. Structural features of plant raw materials for a comprehensive understanding of the mechanochemical processes

2.1. Cell structure of the plant raw material

The sizes of plant cells vary from 10 to 100 μm. The number of cells in plant tissues is very large. For example, there are more than 100 million cells per leaf. The cells of different plant organs differ from each other substantially. In particular, different plant cells have different concentrations of biologically active substances. Even greater differences are observed between the concentrations of different parts of plant cells. It is necessary to pick out the structural features that are most relevant for phytochemists, in particular, those engaged in the mechanochemistry of plant raw materials and mechanochemically stimulated extraction.

The native contents of a plant cell – organelles – are located in viscous cytoplasm. The final products of cellular metabolism are deposited externally on the cell walls and are also stored inside the cytoplasm inside vacuoles containing cellular fluid. Individual cellular components are separated by permeable lipid membranes. The lipid content of these membranes is a likely reason for the use of organic solvents instead of water during plant raw material extraction protocols. The goal of alternative mechanochemical methods is to avoid the technological and ecological problems associated with the use of organic solvents and with the denaturizing effect of solvents on some biologically active substances. Under mechanochemical action, membranes composed of bimolecular lipid layers are destroyed and no longer prevent the transport of substances in aqueous solutions.

The strongest element of a plant cell is the cell wall, which is composed of cellulose and hemicellulose. With aging, lignin is also incorporated into the cell walls. Hence, the composite material of the cell wall acquires increased mechanical strength. Unfortunately, many biologically active substances with complex structures become denatured or decompose during intense mechanical treatment. One of the least studied technical aspects of the mechanochemistry of plant materials is the optimal conditions for mechanical treatment that allow biologically active substances to remain stable while maintaining high levels of technological extraction.

2.2. Localization of biologically active substances in the cells

Vacuoles are of particular interest in the study of phytochemistry for pharmaceutical applications because vacuoles are organelles with cellular fluid that contains low-molecular-weight biologically active substances – plant metabolites. Cellular fluid contains dissolved saccharides (glucose, fructose, sucrose, and inulin), organic acids (oxalic, malic, citric, tartaric, formic, and acetic acids, and complicated organic acids, such as triterpenic acid), various glycosides, tanning agents, alkaloids, vitamins, pigments, soluble proteins, and enzymes. Inorganic compounds are also dissolved in the cellular fluid. The total concentration of all the components of an aqueous solution of cellular fluid is approximately 10%.

Vacuoles may contain solid or liquid substances formed during the vital activity of a cell that are stored as reserves or as wastes. Typical crystals that are formed by the inclusions of inorganic substances can be observed under a microscope.

The cytoplasm is a viscous transparent colloid solution that is 60–90% water and is alkaline; the substances dissolved in the cytoplasm are proteins (10–20%), lipoids (2–3%), organics (1–5%), and inorganic compounds (2–3%).

Cell walls protect cells by preventing cell mechanical deformation and rupture. The primary cell wall is formed immediately after cell division and is composed mainly of cellulose and hemicellulose. Secondary cell walls become lignified and are composed mainly of lignin and cellulose. Cellulose is the component with the highest mechanical strength and highest chemical stability; it is insoluble in water, acids, and alkalis.

Mechanochemical treatment leads to an increase in the extraction yield of biologically active substances from the inner part of a cell and accelerates the dissolution kinetics. These processes may be facilitated by altering the structures of the polymer compounds (cellulose, hemicellulose, lignin), which are the major components of cell walls. The present review discusses approaches for increasing the solubility and dissolution rate of pharmaceutical substances by forming dispersions and molecular dispersions of biologically active substances that interact with the insoluble and soluble polymers of cell walls. These approaches are investigated to help answer a vitally important but poorly studied question concerning the mutual effects of the components during the mechanical treatment of plant raw materials and their mixtures.

2.3. Changes in the plant raw material during drying

After drying the plant raw material under the conditions provided by various pharmacopeia rules, the material contains 6–12% water (by mass) (1). The liquid contents of the cytoplasm and vacuoles lose approximately 75–
85% of their mass and are distributed as a thin layer over the inner surface of the cell wall. The thickness of this layer is approximately 1–5 μm. The organic contents do not crystallize, as observed by means of microscopy or X-ray diffraction. The organic contents are likely to be present in the form of amorphous solutions or in a nanocrystalline form.

Many types of plant raw materials contain tissues with a medium degree of lignification (lignin content 10–20%). The dried parts of plants become harder but more fragile. Microscopic studies have shown that the regions of lignified and nonlignified cells are grouped together (2). The lignin concentration increases toward the outer part of the plant that is exposed to external forces.

3. Destruction of the cell structure of plant raw materials during mechanical treatment

3.1. Destruction of the cell wall composed of biopolymers (cellulose, hemicellulose, and lignin) during the mechanical treatment of dry plant materials

Cracks generated during tissue destruction pass along the boundaries of lignified cells because the deposition of lignin in the intercellular spaces makes these regions more fragile (3). Particles up to 50 μm in size that are formed during the destruction of the cell wall consist mainly of groups of lignified or nonlignified cells. Nonlignified cells form layered particles. The shapes of the cells in the lignified particles are conserved until a specific treatment intensity is reached (4, 5). Increasing the time or intensity of treatment under the conditions of brittle fracture at room temperature or below causes the cell walls to fragmentation into 2–3 μm particles (6). The fragmentation studies performed to date have been applied to the problem of obtaining powder fuel and to the biotechnological processing of plant biomass; these studies have mainly involved cereal straw (3). The problems related to choosing the appropriate type of mechanochemical mill-activator and treatment conditions for plant raw materials from the viewpoint of cell wall destruction were considered in a recent review (5).

3.2. Mechanical amorphization of cell wall cellulose

Plant cell walls are mainly composed of polysaccharides. In addition to polysaccharides, cell walls may also contain lignin, proteins, lipids, pigments, and mineral salts. Only the lignin content in lignified sclerenchyma tissues is comparable to the polysaccharide content; the other components usually do not account for more than several percent of the total mass.

Cellulose, beta-1,4-D-glucan, is a polymer with a substantially varied number of glucose residues. Polymer molecules with chain lengths from tens to several thousands of units are arranged in the cell wall parallel to each other, forming a characteristic lattice. As a result of the covalent interactions and hydrogen bonds between the polymer molecules, microfibrils are formed. Microfibrils are very thin fibers that comprise the structural framework of the cell wall. They are 10–30 nm in diameter and may reach several micrometers in length. Amorphous regions periodically occur in microfibrils, which affect the mechanical and chemical properties of cellulose. With the help of hemicellulose, microfibrils are united into macrofibrils that are 0.4–0.5 μm thick and visible under an optical microscope. Cellulose macrofibrils are elastic and possess high rupture strength.

The mechanical treatment of cellulose destroys the macrofibril structure, disorders and amorphizes the crystalline regions, ruptures the intermolecular hydrogen bonds, ruptures the polymer chains at the glycoside bonds, and changes the molecular mass distribution of the polymer molecules. All these changes modify the chemical properties of cellulose. The availability of the samples for various reagents and the reactivity of the polymers during heterogeneous reactions increase.

After grinding, the diffraction peaks in the diffraction patterns of cellulose disappear, and a halo that is characteristic of the amorphous state appears (8). The mechanical treatment of various cellulose-containing materials leads to similar diffraction patterns of amorphous cellulose (6).

Microfibrils and macrofibrils are covered by plastic glass, which is a complicated mixture of polymers. Among these polymers, the prevailing compounds are lignin and polysaccharides with different molecular masses: hemicelluloses and pectic substances (oxidized saccharides). Hemicellulose polysaccharides are branched polymers that do not have a crystalline structure. The amorphous structure is conserved even after drying the plant raw material.

The polysaccharides of hemicellulose can be extracted using alkaline aqueous solutions. The composition of hemicelluloses includes a wide range of polysaccharides: arabans, xylans, glucans, xylomannans, galactomannans, arabinogalactans, galactoglucomannans, polyuronic acids, etc. (9). Hemicelluloses polysaccharides from different plant species differ from each other by the composition of the elementary links of their main and sidechains, their structure, and their branching degree.
The mechanochemical treatment of hemicelluloses leads to changes in the polysaccharide composition in comparison with that of the initial plant raw material (10). As a rule, polymers with a smaller molecular mass are formed.

4. Physicochemical processes during the mechanochemical treatment and subsequent extraction

The general methods for plant material extraction are based on the dissolution of biologically active substances in a wide range of solvents (11, 12). The use of physical actions before or during component separation, such as using pulsed electric fields, microwave and ultrasonic irradiation, and extrusion treatments in supercritical fluids, is characteristic of enhanced extraction technologies (13). Mechanochemically assisted extraction is one of these physical extraction-enhancing methods. This method has some specific features. Solid-state mechanochemical reactions are used to produce more soluble and more biologically effective chemical forms of substances. One of the most popular reactions involves the interaction between solid acids, which are components of plant materials, and specially introduced solid alkalis.

The known methods are compared with mechanochemically assisted extraction (14) in Figure 1.

The left part of Figure 1 shows the most widespread extraction scheme, in which the plant raw material is ground and extracted in a series of organic solvents with different polarities. The final step of these technologies is to isolate the extract through solvent evaporation. The right part shows the scheme for mechanochemical extraction. A mixture of the plant raw material and a solid reagent is treated in special mills – mechanochemical reactors. During mechanochemical treatment, the target substance is transformed into its chemical form that has the highest solubility in water. The extract is isolated using water.

A powder product is obtained as a result of the mechanochemical treatment. After the addition of water, this product releases the soluble form of the biologically active substance. This new product may be used separately for various purposes, for example, as a food additive or a component of functional nutrition. The product can be obtained with a higher yield and a higher purity, and it may differ in composition from the extracts isolated using organic solvents.

The processes that utilize plant raw materials differ from the processes that occur in a system using pure substances. Cellulose and lignin are major components of each plant raw material, so the interactions of the solid acids and alkalis with cellulose and lignin must be considered.

Grinding and the corresponding changes in dispersity are the starting steps of mechanochemical treatment. The reactivity of a solid usually increases with an increase in dispersity. These types of processes are widely studied in pharmaceuticals in which synthetic crystalline substances with large particles are used as the starting material.

4.1. Differences between the properties of crystalline and dispersed biologically active substances

Developing new medicines that contain synthetic components that are well known and have been in clinical use for a long time is a promising approach for progressing modern pharmacy. Among these synthetic components, there are a great number of crystalline substances that have insufficient biopharmaceutical properties. For many known active substances, it is necessary to improve their solubility, dissolution rate, bioavailability, stability, flowability, compressibility, or hygroscopicity (15). Solubility is a key biopharmaceutical property (16). The mechanochemical approach provides an effective interdisciplinary approach for enhancing the solubility of solids (17).

The mechanical treatment of individual solid organic substances, such as solid acids or alkalis, decreases the crystal size, formation of defects and lattice disordering, amorphization of solids, and conformational changes in molecules. Polymorphic transitions can be realized in some cases. All of these physical effects that occur
during mechanical treatment alter the molecular interactions and change the reactivity of solids; hence, mechanical treatment is an alternative method for optimizing drug properties. However, intense mechanical treatment disrupts chemical bonds, causing the formation of decomposition products, and it is necessary to prevent this process while developing new drug technologies (18).

In the case of mechanically treating a mixture of solid crystalline substances, the following stages can occur: a decrease in the crystal size, the redistribution of particles and formation of mechanocomposites, the amorphization of the components and formation of molecular dispersions, and the formation of co-crystals and crystalline products. Indeed, only a few stages can be clearly differentiated; the process can be stopped once a definite product is formed, and this product can be used for subsequent medical preparations.

There are two main groups of reasons for the physical, chemical, and biological changes in the properties of the products during mechanical treatment with solid alkali mixtures. First, the surfaces of the reacting particles define the rates of the heterogeneous reactions, including the rate of dissolution. Thus, increasing the surface area leads to an increase in the reactivity. Second, the structurally accumulated energy implies an excess of free energy and free enthalpy, which enhances the rate of the chemical reactions (19, 20).

4.2. Mechanochemical interactions between the solid acids and alkalis and the formation of soluble nanocomposites

The kinetics of the heterogeneous reactions depend on the surface areas of the solid particles (21). The kinetics of the solid–solid reactions are defined by the total contact surface of the reacting solid particles (22) and the reactivity of the solid phase. The reactivity depends on the structure and defects in the solids (23). The reactions and dissolution of the solids are generally dependent on the heterogeneous relation.

The comminution of organic substances and the formation of small particles are the simplest ways to enhance the powder surface and to increase the rate of dissolution. However, these effects have some limitations. After the particles reach a certain size (for organics, it is usually near one micron), the particles start to agglomerate, and the powder surface starts to decrease. Therefore, generally, there is an optimal comminution time for mechanical treatment. The surface area of organic particles after treatment in a disintegrator or in a jet mill is 1–10 m²/g.

Some special approaches, such as using low processing temperatures and special comminution equipment, expand the possibilities of this method. The minimal achievable size depends on technical parameters, namely, the intensity of the mechanical treatment (the relative velocities of the particles and milling tools), the residence time of the substance in the mill, the temperature, and the presence of water, which can increase the surface area up to 400 m²/g for saponic acid (with calculated particle sizes less than 5 nm). Fine powders of sulfanylamides with enhanced dissolution rates have been obtained (24, 25).

A particle-size analysis was proposed to predict the dissolution rate and bioavailability of different substances (26); the experimental study produced controversial results. A decrease in the size of benzonal particles by a factor of 6.4 after mechanical treatment led to an increase in the solubility and dissolution rate by a factor of 1.5. In the case of erythromycin, a two-fold decrease in the particle size resulted in a decrease in the dissolution rate by a factor of 1.7 (27). The comminution was not effective in cases of amoxicillin trihydrate and prothionamide. In some cases, there was a direct correlation between the amorphization degree and the solubility of the pharmaceutical (24).

The possible reasons for decreases in the solubility include the instability of the organic substances under mechanical treatment, dehydration of crystal hydrates, and reorganization of intramolecular bonds. It is necessary to consider the fact that most organic medicinal substances are unstable during mechanical treatment; the real processes are defined by the competition between substance transformation and substance decomposition. Unfortunately, until now, the technological success of such treatments has been unpredictable.

In the case of the mechanical treatment of solid mixtures, composite particles are formed. The size of these particles is several tens of microns, but they consist of small particles of the initial substances with a size of one micron or smaller. These composite particles have a large-contact interphase surface area. A great number of atoms or molecules with enhanced reactivity exist on the surface and near the surface. The excess energy of this system is close to the thermal energy of the final product; this energy is accumulated during several minutes of mechanical treatment (28).

The formation of mechanocomposites as intermediate products was discovered during the mechanochemical treatment of organic acids and inorganic alkalis (29). The structure of an “acetylsalicylic acid – hydrocarbonate” mechanocomposite indicated the presence of phases with a submicron size and a well-developed contact interphase between the substances (30). Mechanocomposites have enhanced reactivity, so
reactions in which they participate can be easily initiated using different actions, such as heating, microwave irradiation, and the addition of water.

The method for obtaining effervescent quickly dissolving medicines containing acetylsalicylic acid was developed on the basis of this effect. Dehydrated carbonate salts of sodium, potassium, and lithium were used as neutralizing alkaline reagents. The molar ratio acid/alkali was chosen to obtain hydrocarbonates.

Since competitive reactions occur during the formation of carbonates using metals that are catalyzed by water, the water content in the initial reagents and the amount of water that is formed as a reaction product must be limited. Another problem connected with the formation of water is the hydrolysis of acetylsalicylic acid to acetic and salicylic acids (31). To prevent the formation of byproducts, to make medicines more attractive and provide effervescence (32), a range of additional substances has been introduced into medicines, including soluble and insoluble polymers, saccharides and polysaccharides, and flavoring substances (33).

The bioavailability of the mecanocomposites of acetylsalicylic acid and hydrocarbonate was compared with the availability of commercial forms of soluble aspirin. The time dependence of acid penetration into rabbit blood plasma after oral intake of the conventional and mecanochimically produced aspirin medicines was similar (34).

4.3. Mechanical synthesis of crystal salts and co-crystals

The solubility of the salts of organic acids with alkali metal is 100–1000 times higher than the solubility of the initial acids. A large number of modern medicines are represented in the salt forms of active organic acids and active compounds with nitrogen functional groups (35).

Water is a product of the neutralization reactions between solid acids and alkalis. The solid–solid characteristics of these reactions during grinding are currently under discussion in chemical studies (36). However, in any case, crystalline salts are rapidly and easily obtained after the mechanical treatment of the initial components (37). The introduction of moisture scavengers, such as sodium carbonate, can accelerate the synthesis.

The technology used for producing the alkali metal and alkali-earth metal salts of ascorbic acid and the calcium salts of alaninic and folic acids has been described previously (38). The mecanochimical neutralization of benzoic, salicylic, sebacinic, and ascorbic acids using sodium, potassium, and calcium hydroxides and carbonates proceeds easily. Equimolar reagent ratios lead to the complete transformation of these acids into salts (29). X-ray phase analysis is used to confirm the formation of the crystalline products. Mechanochimical technology consists of a smaller number of operations and is ecologically friendly due to the absence of wastewater (20).

Solid-state solvent-free mecanochimical technologies became popular in recent decades (39, 40), but only the reactions between organic acids and organic bases with the formation of C–C, C–N, and C–O bonds have been considered in these review books.

Co-crystals or the molecular complexes of acids and bases contain equimolecular quantities of biologically active substances and co-crystal formers. The components of co-crystals can be bonded together by hydrogen bonds or van der Waals forces. Hydrogen bonds are formed between the molecules of weak organic acids and weak organic bases with nitrogen-containing functional groups. In the case of relatively strong acids, such as HOOC(CH₂)nCOOH, the bonds between the acids and bases may be partially ionic. The degree of ionicity sharply decreases with an increase in the chain length n from 1 to 7 (41).

Researchers have focused on these types of medicines on because of promising possibilities in variation of their properties. To rapidly transport within the fluids of an organism, the active substance must be present in the form of an ionic salt, while the preferable form for penetrating through biological membranes is the molecular form. Co-crystals that also form non-ionized molecules are more likely to exhibit medicinal activity. The possibility of patenting such co-crystals makes these compounds a promising area of research (42, 43).

Mechanochemistry is a simple and promising method for obtaining co-crystals (44), Friscic and co-authors (45) presented the possible mechanisms of mecanochimical synthesis, including disordering the components, mechanically mixing the components, and solid-state crystallizing the co-crystals. The stages in which amorphous phases participate play a key role in co-grinding the starting substances (46).

The aspect of the synthesis mechanism under discussion is mainly concerned with the nature of the mass transport mechanism. The main components that form co-crystals possess significant vapor pressure, so the gas phase can take part in the reaction. Methods for measuring the temperature and pressure at local sites where mecanochimical reactions proceed under a mechanical impact or shift do not exist. The use of mecanochimical reactors under impact or shift action was shown to be a specific method for controlling the synthesis of co-crystals (47). The reaction temperature is limited by the stability of the substances. The addition
of liquid phases accelerates the process drastically \((48)\). During the reaction of serine and oxalic acid, with the formation of different crystallographic modifications, the contents of the products depend on the water content in the initial mixture. The reaction proceeds in the water layer on the surface of the reactants; mechanical treatment enhances the contact surface of the reactant particles \((49)\).

Special methods for liquid-assisted grinding have been developed using this effect. In the “solvent drop” method, a very small amount of liquid (less than 0.1 mass \%) is necessary \((50)\).

Special thermogravimetry \((51)\), Raman spectroscopy \((52)\), and wide-line nuclear magnetic resonance (NMR) \((53)\) are used to identify the formation of co-crystals in addition to the general solid-state chemistry methods.

The effect of solution supersaturation due to biologically active substances was discovered during the course of a co-crystal dissolution during the dissolution of mechanically comminuted, dispersed, or amorphized substances \((54)\), and is shown in Figure 2.

### 4.4. Mechanochemical formation of amorphous mixtures and molecular dispersions in the presence of biopolymers

Molecules in crystalline organic substances are connected through relatively weak hydrogen or van der Waals bonds. During mechanical treatment, the bonds are damaged, so the substance eventually becomes amorphous. The effect of reflection broadening in X-ray diffraction patterns is used to characterize the degree of amorphization within of solids; for example, this phenomenon has been observed in experiments using sulfamides \((24, 25)\), sulfathiazole \((55)\), and acetylsalicylic acid \((56)\). Unfortunately, amorphization is not the only reason for X-ray reflection broadening. A decrease in the crystal size below one micron also results in broadening, so this method is not quantitative. It is difficult to obtain a completely amorphous substance only using mechanical treatment, but mechanically formed medicines exhibit good bioavailability \((57)\). During dissolution kinetics experiments, the formation of solutions with concentrations higher than those observed when the solutions are in thermodynamic equilibrium were observed because of kinetic effects, when the rate of dissolution from the amorphous or partially amorphous state is higher than the rate of crystallization \((58, 59)\).

Mechanically treating solid substances with solid accessorional compounds (adjuvants) is the simplest method used to change the solubility level and kinetics to achieve the appropriate bioavailability. This treatment can lead to an increase or decrease in the dissolution rates. The treatment of poorly soluble substances with a soluble adjuvant of a different nature increases the rate of dissolution above the thermodynamic rate of dissolution. The mechanochemical treatment of arabinogalactan, an irregular polysaccharide polymer from the cell walls of *Larix daurica*, can increase the solubility of some medicinal substances by a factor of 100 \((60)\).

Supersaturated solutions formed after dissolution in water can be stable for many hours and can take part in metabolic processes in living organisms. The solubility level can also be elevated because of the formation of new substances with the adjuvants. In this case, the new solubility level will be a thermodynamic property of the new complex substance.

The phase state of the substance after mechanical treatment depends on the intensity, treatment time, and changes in the “solid dispersion – nanodispersion – molecular dispersion” sequence.

Using cellulose, soluble cellulose derivatives, chitosan-containing amine functional groups, and pectin-containing acid groups is of special interest to us because of the presence of cellulose and hemicellulose in all plant materials. Pectin is also present in a broad range of materials, such as fruit and berries. Chitosan is a component of the cell walls of microorganisms. Insoluble adjuvants are used to produce medicines with depot action.

One of the driving forces of the formation of molecular dispersions originated from damaging the hydrogen bonds in the initial substances, conjugates \((61)\) and substances with an adjuvant; for example, the amide groups of chloramphenicol (Synthomycine) and rifampicin can interact with the hydroxyl groups of soluble polymers \((62)\).

Hydrogen bonding in unstable substances with adjuvants can be used to stabilize medicines. As far as the influence of hydrogen bonding on the solubility is concerned, the formation of hydrogen bonds with an
insoluble adjuvant can increase or decrease the dissolution rate of the initial substance. Mechanochemically prepared systems containing oxazepam, Mezapam, and Sibazon with cellulose exhibit enhanced dissolution rates in comparison with mixtures without mechanical treatment or with mixtures of comminuted substances (63). The mechanochemical treatment of piroxicam with microcrystalline cellulose and chitosan produces medicines with high solubility and dissolution rates (64). Some general methods in solid-state chemistry, such as X-ray phase analysis, IR-spectroscopy (65), and differential scanning calorimetry (66), have been applied to mechanically treated mixtures of piroxicam, cellulose, and chitosan. Partial amorphization of the components and an increased formation of hydrogen bonds between the components were observed.

Soluble inorganic substances such as sodium and ammonium carbonates can form molecular dispersions with organic substances for medicinal use (67). Insoluble substances such as silica and silicates (68) are used as dispersion-forming materials with controlled dissolution rates.

Unfortunately, systematic investigations concerning the influence of the solid-base properties of solid adjuvants on dispersion effects do not exist.

4.5. Increased dissolution rate, solubility, and biological assimilability of the products of mechanochemical interactions

The solubility of substances under normal conditions is a thermodynamic parameter and cannot be changed without changing the chemical composition of the substance to be dissolved. Increased dissolution rates (in cases when the equilibrium concentration does not exceed the equilibrium solubility) are determined from the additional energy accumulated during the formation of crystal and lattice defects.

However, using various methods to increase the reactivity of substances allows one to increase the rate of dissolution substantially. For kinetic reasons, the concentration of the soluble substance may exceed the equilibrium concentration in cases where the dissolution rate becomes so high that the rates of the inverse process -- the crystallization of the substance -- are not sufficiently high to form the equilibrium phase. Most frequently, the limiting stage of crystallization is the heterogeneous stage of the formation of crystal nuclei in the new phase, which depends on numerous process conditions. In this case, the concentration of the substance in the solution may temporarily exceed the thermodynamic level. The time during which an increased concentration is maintained is comparable to the duration of the metabolic processes that occur in humans or animals (a few hours) (27). Some examples of the experimental confirmation of this effect in systems in which biologically active substances participate are described below.

The kinetics of the release of Mezapam from dispersions with polymers is shown in Figure 3 (69).

The solid dispersions of Mezapam with polyethylene glycol and β-cyclodextrin possessed increased dissolution rates but nearly equal equilibrium concentrations. In the case of polyvinylpyrrolidone, there was an oversaturation effect within 5–20 min of the dissolution.

A decrease in the concentration of a substance in solution to its equilibrium level or below may also be connected with other processes involving a chemical transformation in the substance, such as degradation.

5. Application of mechanochemical interactions to enhance the efficiency of the plant raw material extraction and to obtain powder preparations

One of the main achievements in mechanochemistry was the discovery of chemical reactions that occur during the mechanical treatment of mixtures with low-molecular-weight organic compounds with solid reagents. In particular, the possibility of solid-phase neutralization, exchange, etherification and re-etherification, nucleophilic substitution, and acylation has been demonstrated (39, 40, 68). It was a great surprise for researchers that many reactions of organic compounds in the solid phase under mechanical treatment proceed with higher rates and higher selectivity than in a liquid medium.
From a practical viewpoint, a key item for the development of mechanochemical extraction technology is the choice of an appropriate solid reagent. It is necessary to choose a solid reagent (additive) that will interact with the extraction target component. The resulting substance has to be in one of several water-soluble bioavailable forms, such as soluble salts, complexes, glycosides, or low-molecular-weight products of depolymerization. When the reagent is chosen successfully, the technology for obtaining the new product becomes economically efficient because liquid extracting agents are not used and liquid and solid wastes are not formed. For specific examples of several alkaloids, acids, glycosides, and phytosterols, it has been demonstrated that the yield and selectivity of extraction can be increased \(^{14, 70}\).

For organic compounds exhibiting pronounced acid-base properties, the salt form is usually more soluble in water than in a molecular acid or base. By carrying out neutralization in the solid phase during mechanical activation, one may enhance the solubility of the substance and thus decrease the volume of solvents required during the subsequent extraction.

Mechanochemical treatment with solid bases under definite conditions led to the direct formation of triterpenic acid salts in the matrices of plant raw materials \(^{71}\). The yield of extraction of the target components increased by a factor of 1.5–2. Mechanical activation of *Eleutherococcus* without additional reagents led to an increase in the yield of iso-floxacin extraction by a factor of 1.5. The addition of 2% sodium carbonate caused an increase in the yield by a factor of 4 due to the formation of iso-floxacin salts, an acid synthetic antibiotic of the fluoroquinolone drug class \(^{72}\). Flavonoids from Sophora roots were selectively extracted with the help of mechanochemical treatment using solid sodium carbonate \(^{73}\). It was demonstrated by means of luminescence spectroscopy that the joint treatment of *Hypericum perforatum* herbs with solid alkalis led to the formation of the sodium salt of hypericin \(^{74}\).

Trace amounts of a solvent, mainly water, promote mass transfer and accelerate heterogeneous reactions. This effect can be easily observed in systems in which donor–acceptor interactions can occur between the acid and base. The accelerating action of water in the interactions between solid acid and base oxides, the reactions between hydroxides and acid oxides, and the reactions between solid acids and alkaline oxides is used during so-called soft mechanochemistry processes to decrease the time and intensity of the mechanical action \(^{75}\).

Mechanochemical neutralization is often stopped at the composite stage, before the stage in which the final salt is formed. The salt is formed rapidly from the composite after the addition of water or under heating. This approach provides additional technological advantages because the powder product of the reaction carried out under optimal conditions in the absence of water exhibits increased storage stability. Hence, industrial expenses for ecologically safe technology become lower. Solid-phase technologies have undoubted advantages for the production of food and forage additives from plant raw materials.

Solid dispersions with a high rate of dissolution of biologically active components may be formed with the help of their own lignocellulose or other auxiliary components. Basic and auxiliary components may be introduced into mechanochemical reaction mixtures in the form of different types of raw materials. Chemical interactions between the components of various plant raw materials are likely to occur during the mechanical treatment of mixtures from traditional medicine \(^{7}\); however, these possibilities remain practically unstudied. Separate examples have shown that this approach can be promising. Solid-phase interactions between the galloocatechins of green tea and amorphous silica from rice husks during the treatment of mixtures \(^{76}\) resulted in efficient preparations for poultry keeping that possess antiviral activity \(^{77}\).

### 5.1. Stability of the biologically active components of plant raw materials under the conditions of mechanochemical treatment

The stability of many biologically active substances, especially antioxidants such as the galloocatechins of green tea, varies greatly between the liquid and solid phases. For example, the rate of the oxidative polymerization of gallocatechins is 100–1000 times higher in the presence of a small amount of a liquid phase. Mechanochemical reactions carried out in the solid phase substantially decelerate degradation processes and increase the yield of biologically active components \(^{74}\).

Many organic compounds, especially those with a complicated structure, are unstable during intense mechanical treatment. Different chemical reactions are responsible for the degradation and denaturation of organic compounds under the conditions of mechanical treatment. In some cases, the molecules are destroyed at the covalent bonds through heterolytic or homolytic routes \(^{18}\). Heterolytic bond rupture and the formation of radicals cause chain oxidation or the condensation of organic substances; this mechanism is characteristic of organic systems. Homolytic decomposition leads to the formation of new chemical compounds with a lower mass. The products of these
reactions decrease the activity of the biologically active preparations and may lead to uncontrollable physiological consequences. Destroying and rearranging the hydrogen bonds leave the molecules in the initial state, but a newly formed structure of complexes may be conserved in solution and change the biological activity of the preparation.

The mechanical treatment of H. perforatum was carried out in the AGO-2 activator mill using different treatment modes (76). The modes corresponded to energies of 5, 10, and 15 W/g (milling body accelerations: 200, 400, and 600 m/s² or 20 g, 40 g, and 60 g, respectively). The sample temperatures measured immediately after treatment did not exceed 50°C. Exhaustive sample extractions were carried out, and the hypericin content was then analyzed using high performance liquid chromatography (HPLC).

Figure 4 shows that the hypericin in the matrix of a plant raw material was unstable after high-intensity mechanical treatment (the calculated acceleration of the milling bodies, which is used in practical mechanochemistry as a measure of the treatment intensity, was 400–600 m/s²) and started to decompose nearly instantaneously. The hypericin rapidly decomposed after the intensity of the mechanical treatment increased to 40 and 60 g (corresponding to a mechanical treatment intensity of 5 W/g).

At 20 g, the hypericin content remained constant until the threshold time was equal to 120 s, and then, it started to decrease. Special experiments demonstrated that decomposition did not occur due to the temperature rise induced during mechanical treatment.

Hypericin neutralization through interactions with an alkali was carried out under conditions that stabilized the hypericin. During the interaction between the powders of the plant raw material and the alkali, the formation of the salt forms of hypericin was detected using luminescence spectroscopy; the conditions for obtaining highly soluble salt forms depending on the intensity, temperature of mechanical treatment, and water content were determined (74).

The yield of the catechins of green tea was increased by 50% with the help of mechanochemical treatment. The technological processes for treating the plant raw materials under investigation, involving only solid-phase stages, that is, proceeding without water or other solvents, have substantial advantages over the technologies involving solutions because the reactions responsible for degrading the unstable useful components are suppressed.

The parameters under discussion – the maximal intensity and mechanical treatment time – determine the technological conditions under which the treatment of a plant raw material should be carried out to avoid decomposing the unstable valuable substances. Mechanochemical treatment can help to increase the yield of green tea catechins by 50%. Solid-phase treatment is advantageous over procedures involving solvents because it suppresses the degradation of useful components.

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The kinetics of the degradation of green tea catechins during mechanical treatment in a ball planetary mill with different impact intensities are presented in Figure 5. These kinetics are similar to the kinetics observed in the case of hypericin H. perforatum. The resulting powder samples were exhaustively extracted, and the catechin content was analyzed using HPLC.

Figure 5 shows that catechins, either in their pure form or in the matrix of a plant raw material, are unstable during high-intensity mechanical treatments (1 g = 10 m/s²) and start to decompose almost instantly. The maximal intensity and mechanical treatment time determine the conditions under which the plant raw material should be processed to avoid unstable valuable substances. The yield of catechins from green tea can be
increased by 50% with the help of mechanochemical treatment. Powder products obtained with the help of a mechanochemical method are used in new production processes for functional nutrition (79).

5.2. Effect of the biopolymers of plant raw materials on the mechanochemical processes of biologically active components

The effect of the biopolymers of plant raw materials was considered using flavonoid quercetin as an example (Figure 6). The mechanical treatment of individual quercetin powders decomposed the quercetin and decreased the quercetin content as a consequence of the decomposition. The stability of the quercetin mixtures during mechanical treatment with biopolymers was affected by the type of quercetin interactions with the polymers of the lignocellulose raw material. The quercetin sorbed onto the polymers was more stable than the quercetin in the mechanically processed polymer mixtures.

The components of the lignocellulose matrix of straw (crystalline and amorphous cellulose), which do not have a conserved natural morphological structure, were used separately to adsorb quercetin (Figure 7). The adsorption decreased the stability of the sorbed quercetin during mechanical action. Adsorption on the phenolic component – lignin – destabilized quercetin to the highest extent. In the case of carbohydrate components, the ability to decrease the stability of sorbed quercetin during mechanical action changed in the following sequence: crystalline cellulose > amorphous cellulose > hemicellulose.

The use of cellulose matrices obtained from lignocellulose raw material through the removal of hemicellulose and lignin, while considering the initial natural structure, leads to an increase in the stability of sorbed quercetin during mechanical treatment. The stability of quercetin within the plant raw material during mechanical treatment, with the goal of obtaining mechanochemical preparations of quercetin, is likely explained by the presence of quercetin in its sorbed form on the cellulose components, which conserves

Figure 5. Effect of the intensity and mechanical treatment time on the catechin content in a plant raw material.

Figure 6. Kinetics of the quercetin concentration depending on the mechanical treatment time: 1 – quercetin adsorbed on the lignocellulose matrix of straw; 2 – quercetin as an individual phase (standard); 3 – quercetin in the mechanical mixture with crystalline cellulose; and 4 – quercetin adsorbed on the crystalline cellulose.

Figure 7. Relative content of quercetin after mechanically treating (1800 s) the samples: a – quercetin (standard); b – quercetin in a mixture with crystalline cellulose; c – quercetin sorbed on crystalline cellulose; d – quercetin in a mixture with lignocellulose; and e – quercetin adsorbed on lignocellulose.
the morphological structure of the natural plant raw material.

The cellulose matrix of plant raw material exhibits stabilizing properties during the mechanical treatment of powdered raw material; the stability of catechins and hypericin increases during mechanical action.

5.3. High product extraction from the mechanochemical treatment of plant raw materials

It is necessary to consider a specific example that resulted in an increase in the yield of the target substance from a plant raw material with the help of solid-phase mechanochemical treatment. The plant raw material was the herb *H. perforatum* (St. John’s wort) (78). The extractable biologically active compounds of *H. perforatum* are dianthrones, especially hypericin. However, due to the instability of this compound in the presence of moisture and atmospheric oxygen, preparations of *H. perforatum* herb have not been standardized for hypericin content.

The efficiency of the mechanochemical interactions during the process of hypericin isolation was studied in systems using different methods to introduce alkalis: in a liquid phase or using the solid-phase mechanochemical method. The chemical composition of the studied systems remained constant in all cases.

The data from the extract analysis using HPLC are presented in Figure 8.

Thus, it has been demonstrated that it is possible to increase the yield of acidic biologically active substances from plant raw materials with the help of alkali treatment during mechanochemical activation to produce the optimal yield. The extraction of antioxidant compounds that are unstable in solution can be especially efficient. In particular, the yield of hypericin from plant raw materials increases by a factor of 10.5 in comparison with the processes without mechanochemical treatment. The degree of hypericin isolation increases to 57% of the theoretical level.

6. Conclusions

Mechanochemical interactions between solid acids and bases can be used to obtain biologically active preparations and to increase the extraction from plant raw materials. Acids incorporated in plant raw materials interact with solid alkalis to form water-soluble salts. The extraction process can be significantly simplified. Biologically active acids and alkalis can interact with auxiliary substances to form soluble mechanocomposites, dispersions, and co-crystals. Auxiliary substances are compounds that induce co-crystallization, including soluble and insoluble compounds from the cell walls (cellulose, hemicellulose, and lignocellulose) that form molecular dispersions and surface complexes with active substances.

In some case, the interaction products exhibit increased dissolution rates, which allow the concentrations of the active substances to temporarily become higher in solution than the equilibrium concentrations.

The presence of lignocellulose from cell walls in plant materials increases the stability of biologically active substances during mechanical action. The intensity and mechanical treatment time for plant raw material are determined by the threshold intensity and mechanochemical degradation time of the substances participating in the reaction. For the flavonoid quercetin case study, the highest stability was achieved due to adsorption interactions between quercetin and the lignocellulose component of the plant raw material.

Special efficiency is achieved during the application of solid-phase mechanochemical processes for extracting unstable antioxidant components.

Figure 8. Hypericin yield from sample extractions using different methods of alkali introduction: 1 – initial plant raw material, extraction by water; 2 – initial plant raw material, extraction by alkali; 3 – initial plant raw material, exposure to alkali, extraction with water; 4 – plant raw material treated mechanically without additives, extraction by water; 5 – plant raw material treated mechanically without additives, extraction by alkali; 6 – plant raw material treated mechanically without additives, exposed to alkali, extraction by water; and 7 – plant raw material mechanically activated with alkali, extraction by water.

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