JOURNAL OF MATERIALS SCIENCE **39** (2004) 5117–5120

# Mechanochemical modification and synthesis of drugs

V. V. BOLDYREV
*Institute of Solid State Chemistry and Mechanochemistry SB RAS, Kutateladze str., 18, Novosibirsk, 630128, Russia; Research and Educational Center "Molecular Design and Ecologically Safe Technologies" at the Novosibirsk State University, Pirogov str., 2, Novosibirsk, 630090, Russia*
*E-mail: boldyrev@solid.nsk.su; boldyrev@nsu.ru*

Various aspects of the application of mechanochemistry and mechanical activation in the study of pharmaceutical materials are presented including the use of mechanical activation for modification of the physical and chemical properties of drugs and solid state synthesis of the drugs by mechanochemical methods. It is necessary to take the mechanochemical factors into account during grinding and tabletting the drugs.


Changes in reactivity under mechanical treatment of solids are known to be connected not only with an increase in specific surface (which usually accounts for a fraction of about ten per cent of the total change in the reactivity of substances subjected to mechanical treatment) but also with the formation of various defects in crystals due to their plastic deformation [1]. Accumulation of defects leads to distortions of structure, disordering, and finally to the disappearance of the order in the positions of atoms or molecules in crystal, i.e. to amorphization of the substance. In addition to amorphization, mechanical treatment can cause the transition from one crystal structure to another, i.e. polymorphous transformations. All of these phenomena are the reasons for changes in physicochemical properties of solids, including those important for pharmaceutical industry and pharmacy (reactivity of crystals, their solubility, stability during storage, biological activity, etc.) [2].

## 1. Mechanical modification of the properties of drugs due to their amorphization

The appearance of the amorphous state as a result of mechanical activation was observed in investigations of cephalexine [3], cephalotine [4], clonidine [5], and some sulphanilamide medications [6].

Amorphization of molecular crystals entails changes in their physicochemical properties. For example, amorphization of griseofulvin [7, 8] leads to substantial increase both in the rate of crystal dissolution and in the solubility of crystals. A similar phenomenon is observed for cephalexine [9]. Another result achieved by mechanical treatment of molecular crystals used in pharmacy is a decrease in their stability on storage. For instance, a decrease in stability was observed for ergocalciferol [10], ampicillin trihydrate [11] and cephalexine [9].

Unfortunately, no mechanism has yet been proposed to explain effects related to amorphization. One of the reasons is that, unlike highly symmetrical inorganic systems in which amorphization process has been studied in detail, the nature of amorphous state in molecular crystals has not yet been studied extensively.

## 2. Modification of the properties of medical products due to polymorphous transitions caused by mechanical action

Polymorphism is the ability of one and the same compound to be crystallized in several crystal forms. In the case of molecular crystals, polymorphism and polymorphous transformations are characterized by a number of features. These features are consequences of the fact that organic molecules have a shape different from spheroid, and they are bound to each other in crystals by hydrogen and Van der Waals bonds. This leads to new kinds of polymorphism, which are unknown in classical solid state chemistry, for example conformational polymorphism, polymorphism connected with the packing of molecules, etc.

In our works, we investigated the effect of mechanical treatment on polymorphous transformations in sulphathiazole [12]. It is known that sulphathiazole can exist in at least three crystal modifications and in the amorphous state [13]. It was discovered that a part of the medical product passes into an unstable amorphous state as a result of mechanical activation—depending on the treatment conditions, the amorphous form can be transformed either into metastable modification or return into the stable form.

Polymorphous transformations of amobarbital and indomethacin from the stable form into metastable one was observed by researchers [14, 15] who studied the effect of mechanical treatment at different temperatures.

Along with polymorphous transitions which are caused artificially by the activation of medical products, the pharmaceutical industry involves polymorphous transformations of medical products during technological operations, such as pressing and tabletting. Investigation of the behaviour of 32 medical substances during pressing demonstrated that nearly a half of them exhibit the ability to transform into metastable polymorphous forms [16].

Polymorphous transitions caused by mechanical activation in an activator and during tabletting do not necessarily lead to results favourable for the use of medication. For example, the biologically active form of chloramphenicol palmitate passes (completely or partially, depending on pressing conditions) into a biologically inactive poorly soluble form [17]. Pressing metastable forms of caffeine, sulphobenzamide, macrotylin [16], barbital [18] leads to their transformation into stable forms.

Mechanical activation can not only distort intermolecular bonds connected with disordering of the crystal structure but also affect molecular structure of medicines. An example is the behaviour of piroxicam, one of the modern anti-inflammatory medicine, under mechanical activation [19, 20]. Piroxicam is poorly wetted by water and almost insoluble in it, which decreases its biological availability. Several polymorphous forms of piroxicam differing by manners of molecule packing in crystal and by the structure of the network of hydrogen bonds are known [21]. Under mechanical activation, piroxicam passes from the stable $\beta$-form into the active zwitterionic form [19, 20].

## 3. Conservation of the active state and increase in biological activity of mechanically activated medicines by depositing them on a support

Since the amorphous state and metastable polymorphous forms obtained as a result of mechanical activation are thermodynamically unstable, the problem arises how to conserve their high reactivity and biological activity. The method applied in this case is a mechanochemical version of the known method for obtaining solid dispersed systems in pharmacy, proposed by Sekiguchi and Obi [22]. The mechanochemical method is distinguished by the following feature: the "medicine-support" composite is obtained not by the joint fusion of components or their co-precipitation from a common solvent but by mechanical treatment of the mixture. As a result of binding the medicine to the surface of a support by means of hydrogen and Van der Waals bonds, one succeeds in increasing the lifetime of metastable states and therefore in increasing the shelf life of medicines.

For instance, on depositing d-camphor and *p*-cresol on methylcellulose, it is possible to conserve the stability of these medicines even under vacuum [23]. By means of mechanical treatment of mixtures of medicines, like aspirin, benzoic and salicylic acids, methyl-*p*-hydroxylbenzoate, with $\beta$-cyclodextrin and similar compounds, inclusion compounds were obtained in which a medicine enters into the cavity of a macromolecule. In doing this, the guest compound interacts with the host molecules and changes its properties, including chemical and biological activity. For example, dimers—of which aspirin crystals are composed—decompose into more polar monomers when forming inclusion compounds; thus, the solubility increases.

Since the dissolution of many solid medicines is a micellar process, the formation of surface compounds and inclusion compounds by hydrophobic molecules interacting with polyfunctional macromolecules which are hydrophilic, helps solubilizing medicines included in mechanocomposite. This happens in the case of mechanical activation of the mixtures of medicines which are difficult to dissolve, such as diethylstilbestrol, indomethacin, griseofulvin, resorcin, ibuprofen with $\beta$-cyclodextrin, polyethylene glycol, polyvinylpyrrolidone, methylcarboxycellulose [24, 25].

However, the role of some supports used for this purpose is not only to increase the stability or solubility of medicines. Sometimes, a support plays an additional role of carrier for medicine to get through various biological barriers existing in organism [26]. Since the lipid layer coating the walls of cell membranes rejects hydrophilic molecules (note that attempts to increase the solubility of a medicine by mechanochemical treatment inevitably increase its hydrophilic character), a method is necessary which would allow the solubilized medicine to get through this biological barrier. Such supports as $\beta$-cyclodextrin, chitosan, polyvinylpyrrolidone, etc., are able, not only to conserve a medicine in highly active form, but also to interact with phospholipids thus helping medicines to overcome the repulsing action of phospholipids and get into an organism through epithelium [27].

## 4. The effect of mechanical activation on the biological activity of drugs

There are data suggesting that mechanical activation of drugs not only changes their stability and helps them to become more soluble but also affects therapeutic efficiency of the medicine. For instance, it was demonstrated in investigation of chemotherapeutic activity of sulphamonomethoxine with the streptococcal septicaemia model in white mice that mechanical activation increases the biological activity of the medicine. With the intake of usual medicine, only one third of the mice survived, while in the case of mechanically activated sulphamonomethoxine more than a half of the mice survived [28].

It was demonstrated in a number of experiments that mechanical activation leads to an increase of biological availability of drugs. For example, mechanical activation of griseofulvin, a medicine widely used to cure fungus diseases, causes (along with solubilization) an increase in its biological availability in comparison with non-activated sample by 75% due to an increase in the rate of absorption into blood plasma [29]. At the same time, the rate of excretion of the products of griseofulvin metabolism from organism increased.

Mechanical activation of phenytoin with cellulose or chitin leads also to an increase in the rate of excretion of metabolism products from organism and to an increase in the rate of phenytoin transfer into the blood plasma nearly by a factor of three [30, 31].

Tests of the biological efficiency of mechanically activated clonidine mixed with cellulose demonstrated the high efficiency of its hypotensive action in rats, compared to non-activated medicine [4].

## 5. Mechanochemical synthesis of drugs

The development of mechanochemical methods in organic synthesis has also touched the synthesis of pharmaceuticals. The transition from traditional wet technologies to dry mechanochemical methods has allowed a number of interesting results (from the industrial viewpoint) to be obtained with several examples described below.

Sodium benzoate which is widely used in the pharmaceutical industry is usually obtained by neutralization of benzoic acid with an aqueous solution of soda. A typical technological scheme includes six stages. In order to obtain 0.5 tons of the product, it is necessary to consume 3 tons of distilled water. The process takes 60 h. Sodium salicylate is obtained similarly. In both cases, reactors with a volume of 2–3 $m^3$ are necessary to perform neutralization; special equipment for filtering and vacuum drying is also necessary. Mechanochemical version of neutralization allows the same amount of the product to be obtained within only several hours. Large amounts of solvents are not necessary in this case; filtering and vacuum drying are excluded. The synthesis of the sodium salt of oxazepam by means of mechanical activation of a mixture of sin-oxime-2-benzoyl-2,4-dichloroacetanilide and sodium hydroxide takes only several minutes; the yield of the target product is about 80% [32]. The traditional industrial method of obtaining oxazepam takes several hours and requires using substantial amount of ethanol as a solvent; the synthesis itself, to say nothing of the auxiliary operation of product isolation.

In some cases, application of mechanochemical methods to the synthesis of pharmaceutical products not only decreases the number of stages in the technological chain and excludes the use of solvents, but also allows one to achieve higher purity of the final product in comparison with traditional technological processes. For example, the usual method of obtaining phthalazole in pharmaceutical industry involves heating the mixture of sulphathiazole with an acylating agent (usually phthalic acid or phthalic anhydride) in aqueous-alcoholic medium. The final product (phthalazole) is thus contaminated with phthalazole imide and phthalic ester which are side products formed inevitably during the synthesis. In the case of the same reaction of sulphathiazole acylation being performed by mechanochemical method, pure phthalazole free from impurities is formed [33].

## 6. Conclusions

Promising character of the use of mechanochemical methods in pharmacy can be seen in the above-described examples. Their special importance lies in the modification of the reactivity and biological activity of medical products. The application of mechanochemical methods in pharmaceutical industry can lead to the decrease in the number of technological stages; thus it allows one to simplify the production of medical products and make their production cheaper.

## Acknowledgments

The investigation has been performed within the Integration program of SB RAS and NO-008-X1 project under the program of CRDF and Ministry of Education RF, supported by RFBR Grant No. 02-03-33299.

## References

1. V. V. BOLDYREV, *Mater. Sci. Forum* **225–227** (1996) 511.
2. S. H. YALKOWSKY, in "Techniques of Solubilization of Drugs," edited by S. H. Yalkowsky (Marcel Dekker, N. Y., 1981) p. 1.
3. M. OTSUKA and N. KANENIWA, *Chem. Pharm. Bull.* **31** (1983) 4489.
4. *Idem.*, *Int. J. Pharm.* **124** (1990) 307.
5. V. V. BOLDYREV, A. L. MARKEL, A. YU.YAGODIN and A. V. DUSHKIN, *La Riforma Medica* **105** (1990) 49.
6. M. L. EZERSKY and A. V. SAVITSKAYA, *Zhurn. Fiz. Khimii* **66** (1992) 3109 (in Russian).
7. A. ELAMIN, C. AHLNECK, G. ALDERBORN and C. NYSTRÖM, *Int. J. Pharm.* **111** (1994) 159.
8. G. S. BABAKINA, G. P. GAIDUKOVA, A. E. GULYAEV and M. L. EZERSKY, *Khim.-Farm. Zhurn.* **25** (1991) 62 (in Russian).
9. M. OTSUKA and N. KANENIWA, *Chem. Pharm. Bull.* **32** (1984) 1071.
10. R. HÜTTENRAUCH, S. FRICKE and P. ZIELKE, *Pharm. Res.* **6** (1985) 253.
11. Y. TAKAHASHI, K. NAKASHIMA, H. NAKAGAWA and I. SUGIMOTO, *Chem. Pharm. Bull.* **32** (1984) 4963.
12. T. P. SHAKHTSHNEIDER and V. V. BOLDYREV, *Drug Dev. Ind. Pharm.* **19** (1993) 2055.
13. M. LAGAS and C. LERK, *Int. J. Pharm.* **8** (1981) 11.
14. M. OTSUKA, K. OTSUKA and N. KANENIWA, *Drug Dev. Ind. Pharm.* **20** (1994) 1649.
15. A. IKEKAWA and S. HAYAKAWA, *Bull. Chem. Soc. Jap.* **54** (1981) 2587.
16. H. K. CHAN and E. DOELKER, *Drug. Dev. Ind. Pharm.* **11** (1985) 315.
17. N. KANENIWA and M. OTSUKA, *Chem. Pharm. Bull.* **33** (1985) 1660.
18. H. NOGAMI, T. NAGAI, E. FUKUOKA and T. YOTSUYANAGI, *ibid.* **17** (1969) 23.
19. T. P. SHAKHTSHNEIDER, *Solid State Ionics* **101–103** (1997) 851.
20. T. P. SHAKHTSHNEIDER, V. A. VASILCHENKO, A. A. POLITOV and V. V. BOLDYREV, *J. Therm. Anal.* **48** (1997) 491.
21. F. VREČER, S. SRČIČ and J. ŠMID-KORBAR, *Int. J. Pharm.* **68** (1991) 35.
22. K. SEKIGUCHI and N. OBI, *Chem. Pharm. Bull.* **9** (1961) 866.
23. Y. NAKAI, E. FUKUOKA, S. NAKAJIMA and K. YAMAMOTO, *ibid.* **25** (1977) 3340.
24. A. M. DUBINSKAYA, *Khim.-Farm. Zhurn.* **23** (1989) 755 (in Russian).
25. T. P. SHAKHTSHNEIDER and V. V. BOLDYREV, in "Reactivity of Molecular Solids," edited by E. Boldyreva and V. Boldyrev (Wiley and Sons, LTD, Chichester, 1999) p. 271.
26. G. AMIDON, in "Techniques of Solubilization of Drugs," edited by S. Yalkowsky (Marcel Dekker, N. Y., 1981) p. 183.
27. H. E. JUNGINGER, *J. Coos Verhoef. PSTT* **1** (1998) 370.

28. A. V. SAVITSKAYA, E. I. KHANTIMUR, L. G. ARTEMOVA and M. L. EZERSKY, *Farmatsia* **39** (1990) 26 (in Russian).
29. K. YAMOMOTO, M. NAKANO, T. ARITA and Y. NAKAI, *J. Pharmakokinet. Biopharm.* **2** (1974) 487.
30. I. NAKAI, Izv. Sib. Otd. AN SSSR, *Ser. Khim. Nauk* **5** (1987) 31 (in Russian).
31. Y. SAWAYANAGI, N. NAMBU and T. NAGAI, *Chem. Pharm. Bull.* **31** (1983) 2064.
32. A. V. DUSHKIN, E. V. NAGOVITSYNA, V. V. BOLDYREV and A. G. DRUGANOV, *Sib. Khim. Zhurn.* **5** (1991) 75 (in Russian).
33. V. P. CHUEV, L. A. LYAGINA, E. YU. IVANOV and V. V. BOLDYREV, *Dokl. Akad. Nauk* **307** (1989) 1429 (in Russian).

*Received 11 September 2003*
*and accepted 27 February 2004*